Evaluation of novel genetic and pharmacogenetic targets in depression

by

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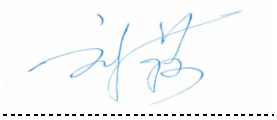
DECLARATION

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university, and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed. 

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LIST OF ABBREVIATIONS

A	Adenine
Actb	Rat actin beta
ACE/*ACE*	Angiotensin I converting enzyme/gene
AMER2	Human APC membrane recruitment protein 2 gene
Amer2	Rat APC membrane recruitment protein 2 gene
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Amph	Amphetamine
ANO8	Human Anoctamin 8 gene
Ano8	Rat Anoctamin 8 gene
ARHGAP8	Human Rho GTPase activating protein 8 gene
*Arhgap*8	Rat Rho GTPase activating protein 8 gene
BCA assay	Bicinchoninic acid assay
BDNF/*BDNF*	Brain-derived neurotrophic factor/gene
BMPR2	Bone morphogenetic protein receptor type 2
C	Cytosine
°C	Celsius
Cm	Centimetres
CASC3	Cancer susceptibility candidate 3
CBT	Cognitive behaviour therapy
CMS	Chronic mild stress
CNTNAP1	Human contactin associated protein 1 gene
Cntnap1	Rat contactin associated protein 1 gene
CLOCK	Clock circadian regulator gene

Con-A	Concanavalin A
CRH	Corticotrophin-releasing hormone
CRS	Chronic Restraint Stress
CSF	Cerebrospinal fluid
Ct	Threshold cycle
CTL	Cytotoxic T lymphocytes
CUMS	Chronic Unpredictable Mild Stress
CWC22	Human CWC22 spliceosome associated protein homolog gene
Cwc22	Rat CWC22 spliceosome associated protein homolog gene
CYP2C8	Cytochrome P450 family 2 subfamily C member 8
CYP2C19	Cytochrome P450 family 2 subfamily C member 19
CYP2D6	Cytochrome P450 family 2 subfamily D member 6
CYP2J2	Cytochrome P450 family 2 subfamily J member 2
DA	Dopamine
DAT	Dopamine active transporter or dopamine transporter
DBH	Dopamine Hydroxylase
DBI	Diffuse brain injury
dbSNP	The Single Nucleotide Polymorphism Database
DNA	Deoxyribonucleic Acid
DOPA	3,4-dihydroxyphenylalanine
ECT	Electroconvulsive Therapy
eIF4A3	Eukaryotic translation initiation factor 4A3EMT Epithelial-mesenchymal transitions
eQTL	Brain Expression Quantitative trait loci

FDA	Food and Drug Administration (US)
FST	Forced swim test
G	Guanidine
Gαs	Gs alpha subunit
Gapdh	Rat glyceraldehyde-3-phosphate dehydrogenase
GBR12935	1-[2-(diphenylmethoxy) ethyl]-4-(3-phenylpropyl) piperazine
Glu	Glutamate Ionotropic Glutamate
GR	Glucocorticoid Receptor
GRIN1	Human glutamate ionotropic receptor NMDA type subunit 1 gene
Grin1	Rat glutamate ionotropic receptor NMDA type subunit 1 gene
GWAS	Genome-wide Association Study
HAMD	Hamilton Depression Rating Scale
HL60	Human promyelocytic leukaemia cells
HLH	Hemophagocytic lymphohistiocytosis
HPA	Hypothalamic-Pituitary-Adrenal
[^{3}H] CGP-39653	D, L-(E)-2-amino-4-propyl-5-phosphono-3-pentenoic acid
5-HT	5-hydroxytryptamine, serotonin
5-HT$_1$	5-hydroxytryptamine receptor 1
5-HT$_{1A}$	5-hydroxytryptamine receptor 1A
5-HT$_3$	5-hydroxytryptamine receptor 3
5-HT$_{3A}$	5-hydroxytryptamine receptor 3A
5-HT$_{3B}$	5-hydroxytryptamine receptor 3B
5-HT$_{3C}$	5-hydroxytryptamine receptor 3C
5-HT$_{3D}$	5-hydroxytryptamine receptor 3D
5-HT$_{3E}$	5-hydroxytryptamine receptor 3E

5-HT_7	5-hydroxytryptamine receptor 7
[^{3}H] MK-801	Izocilpine
HOMER1	Human Homer scaffolding protein 1 gene
HOMER1A	Human Homer scaffolding protein 1A gene
HOMER1B	Human Homer scaffolding protein 1B gene
HOMER1C	Human Homer scaffolding protein 1C gene
HOMER2A	Human Homer scaffolding protein 2A gene
HOMER2B	Human Homer scaffolding protein 2B gene
HOMER3	Human Homer scaffolding protein 3 gene
Homer3	Rat Homer scaffolding protein 3 gene
HPC	Hemangiopericytoma
HRP	Horseradish Peroxidase
HTR1	5-hydroxytryptamine receptor 1 gene
HTR1A	5-hydroxytryptamine receptor 1A gene
HTR2A	5-hydroxytryptamine receptor 2A gene
HTR2C	5-hydroxytryptamine receptor 2C gene
HTR3	5-hydroxytryptamine receptor 3 gene
HTR3A	5-hydroxytryptamine receptor 3A gene
HTR5A	5-hydroxytryptamine receptor 5A gene
HTR6	5-hydroxytryptamine receptor 6 gene
HTR7	5-hydroxytryptamine receptor 7 gene
IL1/*IL1*	Interleukin 1/gene
IL6/ *IL6*	Interleukin 6/gene
IL10/ *IL10*	Interleukin 10/gene
IL1A/ *IL1A*	Interleukin 1 alpha/gene
IP_3	Inositol trisphosphate

IPT	Interpersonal therapy
Jurkat	Human T lymphocyte cells
K562	Human immortalised myelogenous leukaemia cell line
KBCA	Kernel-based adaptive cluster
KCN	Potassium channels
KCNQ1	Potassium voltage-gated channel subfamily Q member 1L Long allele
LH	Learned helplessness
LHPP	Phospholysine phosphohistidine inorganic pyrophosphate phosphatase gene
MAO	Monoamine oxidase
MAOA/*MAOA*	Monoamine oxidase A/gene
MAOI	Monoamine oxidase Inhibitor
MDD	Major depressive disorder
MDMA	3,4-Methylenedioxymethamphetamine
MHV	Mouse hepatitis virus
min	Minutes
mRNA	Messenger ribonucleic acid
Msi1	Musashi RNA binding protein 1
mGluRs	Metabotropic glutamate receptors
MAGOH	Mago homolog, exon junction complex core component
NA	Noradrenaline
NARI	Noradrenaline reuptake inhibitor
NB4	Human acute promyelocytic leukemia cells
NDRI	Norepinephrine-dopamine reuptake inhibitor

NE	Norepinephrine/noradrenaline
NET	Norepinephrine transporter
NEO	Personality inventory
NGF	Nerve growth factor
NK cells	Natural killer cells
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
Nrc3c1	Mouse nuclear receptor subfamily 3 group C member 1 gene
OCD	Obsessive-compulsive disorder
PER3	Period circadian clock 3 gene
PHF21B	Human PHD finger protein 21B gene
Phf21b	Rat PHD finger protein 21B gene
Pmp22	Mouse peripheral myelin protein 22 gene
PRF1	Perforin 1 gene
PRR5	Human Proline rich 5 gene
Prr5	Rat proline rich 5 gene
qPCR	Quantitative reverse transcriptase real-time polymerase chain reaction
QTL	Quantitative trait locus
RAB27A	RAB27A, member RAS oncogene family gene
RBM8A	RNA binding motif protein 8A
RNA	Ribonucleic acid
Rn5s	Rat 5S ribosomal gene
Rn18s	Rat 18S ribosomal gene
Rps18	Rat ribosomal protein S18 gene

RTI-121	(–)-2β-Carboisopropoxy-3β-(4-iodophenyl) tropane
S	Short allele
s	Seconds
SLC6A4	Human solute carrier family 6 member 4 gene/serotonin transporter gene aka HTT; 5HTT; OCD1; SERT; 5-HTT; SERT1; hSERT; 5-HTTLPR
SCL-90	The Symptom Checklist-90
SCN5A	Sodium voltage-gated channel alpha subunit 5
SDS	Social defeat stress
SETGAP	Selectable expression of transient growth-arrest phenotype
SH2D1A	SH2 domain containing 1A gene
SLCO1B1	Solute carrier organic anion transporter family member 1B1
SNP	Single nucleotide polymorphism
SNRI	Serotonin and norepinephrine reuptake inhibitor
SNX14	Human sorting nexin-14 gene
Snx14	Rat sorting nexin-14 gene
SPT	Sucrose preference test
SSRI	Selective serotonin reuptake inhibitor
SIRT1	Sirtuin 1 gene
SIRT2	Sirtuin 2 gene
STX11	Syntaxin 11 gene
STXBP2	Syntaxin binding protein 2 gene
T	Thymine
TBX18	Human T-box gene
Tbx18	Rat T-box gene
TCA	Tricyclic antidepressant

TMS	Transcranial magnetic stimulation
TNF-α	Tumour Necrosis Factor-α
TPH1	Tryptophan Hydroxylase 1
TPQ	Three-dimensional personality questionnaire
TRI	Triple reuptake inhibitor
TRPM2	Human transient receptor potential cation channel subfamily M member 2 gene
Trpm2	Rat transient receptor potential cation channel subfamily M member 2 gene
TRKB	Neurotrophic receptor tyrosine kinase 2 gene
U937	Human leukemic monocyte lymphoma cell line
UNC13D	Human Unc-13 homolog D gene
Unc13d	Rat Unc-13 homolog D gene
UBE2E3	Human ubiquitin conjugating enzyme E2 E3 gene
Ube2e3	Rat ubiquitin conjugating enzyme E2 E3 gene
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UGT2B7	UDP glucuronosyltransferase family 2 member B7
UGT2B15	UDP glucuronosyltransferase family 2 member B15
WIN35,428	β-Carbomethoxy-3-β-(4-fluorophenyl) tropane
XIAP	X-linked inhibitor of apoptosis gene
ZNF34	Human zinc finger protein 34 (*ZNF34)* gene

SUMMARY

Major Depressive Disorder (MDD) is a prevalent multifactorial disorder of unknown aetiology with enormous economic, medical and social impact globally. MDD is also a leading cause of suicide and the third highest fatal disease burden in Australia men. It is treated with antidepressants, which are safe and tolerable drugs. Even though their efficacy in MDD treatment is well proven by double-blind, randomised controlled trials, some patients fail to respond to some antidepressant drugs, which leads to several trials of different medications to obtain clinical improvement. One factor for such variable antidepressant response is genetic variation. Previous work in our lab has aimed at understanding the genetic basis for MDD susceptibility focusing on functional single nucleotide polymorphisms. Our lab has identified several human genetic variations that may be associated with either MDD susceptibility or remission to antidepressant treatment. A variation significantly associated with antidepressant treatment remission has been located in a potential brain DNA immunoprecipitation sequencing site suggesting that it might be involved in epigenetic regulation of neuronal gene expression. Therefore, our research aims were to characterise genes that our group has identified as potentially associated with MDD diagnosis or antidepressant response. In a rodent model of depression, we have studied expression levels of potential risk genes in the rat hippocampus in response to chronic stress. To achieve our goals, we induced depressive-like behaviour using a chronic restraint stress (CRS) paradigm, where the rats were held in a flat-bottom clear acrylic restraint for 6 hours per day for 14 consecutive days. Behavioural tests were performed at baseline and after 14 days of restraint to confirm the presence of

depressive-like behaviour. After completion of behavioural testing, rats were euthanized between 10AM-noon to avoid the confounding effects of circadian rhythms. Quantitative real-time polymerase chain reaction (qPCR) analysis and Western blot analysis were performed in order to study expression levels of potential risk genes in rat hippocampus. In these studies, we identified that mRNA levels for the gene *Phf21b, Argap8, Trpm2* and four other genes were significantly changed in response to chronic restraint stress or social isolation. Additionally, we also have addressed that the relative protein level of PHF21B and ARHGAP8 changed significantly between CRS and control groups. Brain quantitative trait loci analysis revealed that the genes that changed significantly in response to stress or social isolation also have variants that significantly change gene expression in post-mortem brain regions. These findings revealed the involvement of our risk genes in the mechanisms of CRS response, and discovered potential therapeutic targets for the development of novel antidepressants.

CHAPTER 1:
INTRODUCTION

1.1 Major Depressive Disorder

Major depressive disorder (MDD) is a heterogeneous multifactorial disorder of unknown aetiology with enormous medical, social and economic effects globally (Belmaker and Agam, 2008), and potentially affecting people of all ages (Ferrari et al., 2013a). The most widely used diagnostic criteria for MDD are the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM–5; American Psychiatric Association, 2013) and *The World Health Organization's International Statistical Classification of Diseases and Related Health Problems* (10th Revision., ICD-10; World Health Organization, 1992). These criteria mainly encompass symptoms of "(i) depressed mood and anhedonia; (ii) significant weight loss (when not dieting) or weight gain, or a marked increase or decrease in appetite nearly every day; (iii) excessive sleeping or insomnia; (iv) agitation and restlessness; (v) fatigue; (vi) feeling of worthlessness or excessive and inappropriate guilt nearly every day; (vii) diminished ability to think, concentrate or make decisions; and (viii) recurrent thoughts of death or suicide (Figure 1). Five (or more) of the above symptoms need to have been present continuously for a minimum of a two-week period for someone to be classified as having MDD" (aan het Rot et al., 2009, American Psychiatric Association, 2013, Ferrari et al., 2013a).

Based on the above definition, MDD has a high prevalence, affecting more than 12% of men and 20% of women in the United States (US)(Ferrari et al., 2013b, Kessler et al., 2003). Also, more than 45.5% of Australians and up to 20% of the total population around the world (Kessler and Bromet, 2013, Wells et al., 1989) have some experience of mental disorder in their lifetime. Among those populations, females show a significantly higher incidence of MDD during their lives, compared to males (Ferrari et al., 2013b, Brigitta, 2002). Notably, 2% of school children and

5% of teenagers also suffer from MDD, and most go undiagnosed (Charney, 2004). Geographical location, environment and genetic factors are main reasons contribute to the various incidence of MDD in difference areas. MDD was the second cause of disability in the world in 2010, which was an increase of 37.5% since 1990 (Ferrari et al., 2013a). In Australia, MDD is not only one of the leading causes of suicide, but it is also the third highest fatal disease burden among Australian men (Ferrari et al., 2013a, Wadelius et al., 2005).

The total medical costs of MDD have increased significantly from the 1990s to the present (Greenberg et al., 2003). In 2000, the medical cost of MDD was $83.1 billion in the US (Greenberg et al., 2015, Wu et al., 2011). Further, in 2010, depressive disorders were one of the leading causes of this financial burden, which highlights that MDD is the primary concern that threats public health (Ferrari et al., 2013b, Ferrari et al., 2013a). MDD is treated clinically primarily with antidepressant drugs and psychotherapy (Moller et al., 2012, Greenberg et al., 2003). Although the efficacy of antidepressant drugs has been well proven by double-blind randomised controlled trials, 30 to 40% of patients still fail to respond to treatment using first-line antidepressants (O'Leary et al., 2014, O'Reilly et al., 1994, Rapaport et al., 2003, Trivedi et al., 2006). Major problems that affect clinical work and research are the lack of reliable biomarkers for the psychiatric diagnostic procedure (Dworkin 2010) and the lack of understanding of the underlying pathogenesis.

During the last decade, it has become clear that genetic variations contribute to patients' responses to antidepressants and their side effects (O'Leary et al., 2014), which has led to the development of Pharmacogenomics of antidepressants--a research field that seeks to improve the efficacy of treating MDD, guided by genomics (Licinio and Wong, 2011).

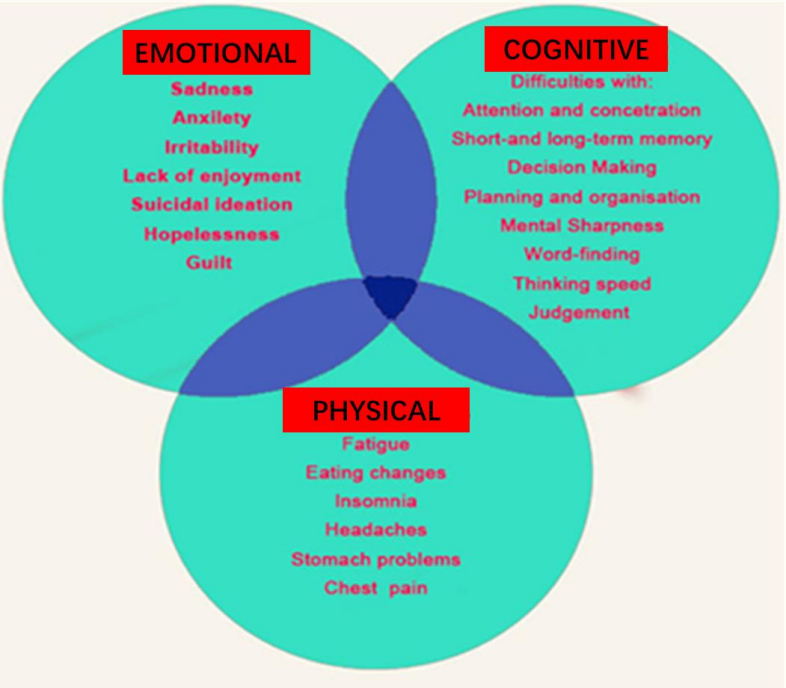


Figure 1: Major depressive disorder syndrome [modified from DSM-5 (American Psychiatric Association, 2013)].

1.2 The Pathogenesis of Major depressive disorder (MDD)

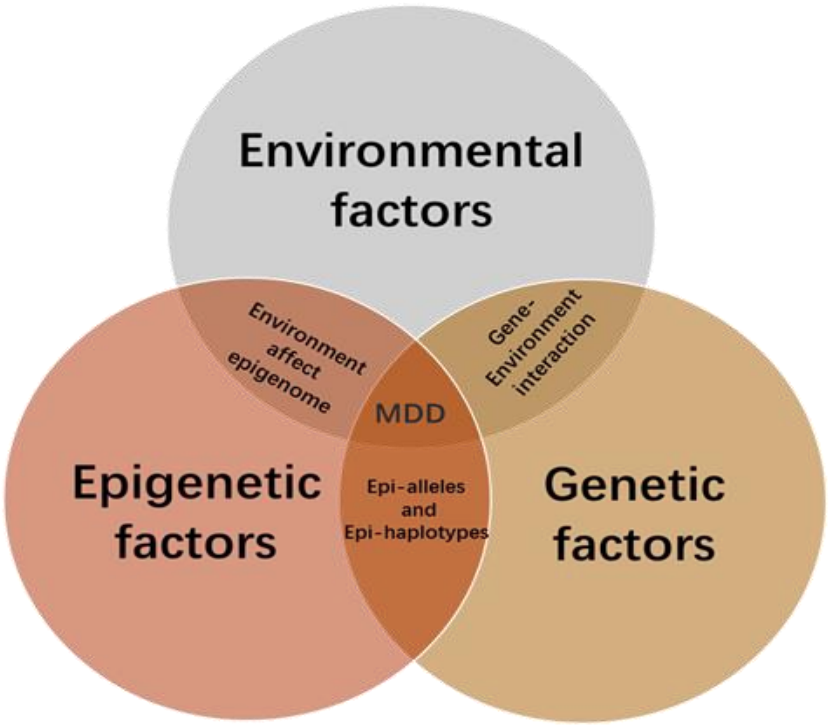


Figure 2: Neurobiological mechanisms of major depressive disorder (MDD).

[Modified from Molecular studies of major depressive disorder: the epigenetic perspective (Mill and Petronis, 2007)].

1.2.1 The Monoamine Hypothesis

MDD is a complex disorder, and the exact mechanism of this disease continues to remain elusive (Figure 2). However, it has been clearly evidenced that the noradrenergic and serotonergic systems, which are dispersed in the entire brain, regulate thinking and feeling (Belmaker and Agam, 2008). The monoamine hypothesis of depression was first illustrated by Schildkraut in 1965 (Jayatissa et al., 2006, Schildkraut et al., 1965) and was based on the fact that the first drug developed to treat depression could boost both norepinephrine (also called noradrenaline; NE) and serotonin (5-HT) levels in synapses, and increase stimulation of postsynaptic neurones by blocking the reuptake of NE and 5-HT (Belmaker and Agam, 2008).

In addition, there is an increase in neurotransmitters as inhibitors of monoamine oxidase enzyme (IMAO) are able to metabolise both NE and 5-HT within the presynaptic neurones. Presynaptic neuron is "a neuron from the axon terminal of which an electrical impulse is transmitted across a synaptic cleft to the cell body or one of more dendrites of a postsynaptic neuron by the release of a chemical neurotransmitter" (medical dictionary, 2012). As a result, both are equally involved in an antidepressant role. (Belmaker and Agam, 2008). This was supported by a study that found a 30% monoamine oxidase (MAO) increase among patients experiencing depression (Meyer et al., 2006). All compounds that seek to inhibit either NE or 5-HT reuptake have been proved to relieve depression in the clinic (Belmaker and Agam, 2008).

There have been a number of studies that have considered monoamine activity in patients with depression (Iversen, 2008). Coppen (1967) showed that people with depression have abnormal levels of NE, 3,4 dihydroxy phenethylamine (Dopamine; DA) and 5-HT. (Figure 3). In the following years, with the development of the gene

knockout technology, the significant increased immobility time in the force swim test was observed in 5-HT-reuptake-transporter knockout mice supports this hypothesis (Ansorge et al., 2004). However, the monoamine hypothesis still fails to explain the altered monoamine activity, their transporters and receptors in most depressed patients and animals. Although many new findings and observations have challenged the monoamine hypothesis, this hypothesis has played a pivotal role in guiding the discovery and development of novel antidepressant drugs during the past 50 years.

1.2.2 Stress and the Hypothalamic-pituitary-adrenal (HPA) Axis

A considerable amount of research has reported that both cortisol and corticotrophin-releasing hormone/factor (CRH) are involved in depression (Belmaker and Agam, 2008, Merali et al., 2004, Upadhyaya et al., 2007). The HPA axis maintains homeostasis via negative feedback regulation. In this regulation, the cortex of the brain can perceive stress and then transmit this stress message to the hypothalamus, which leads to the release of CRH onto pituitary receptors. The effects of the pharmacological response result in the secretion of adrenocorticotropic hormone (ACTH) into plasma and the stimulation of the adrenal cortex corticotrophin receptor. Also, this stimulus promotes the release of cortisol into the blood. At this point, hypothalamic glucocorticoid receptors can decrease the release of CRH if they perceive the alteration of the cortisol level in the blood (Figure 4). However, abnormal cortisol-suppression response has been reported in depressed patients. Alongside cortisol and ACTH concentrations in the plasma, CRH levels in cerebrospinal fluid (CSF) are also elevated or inappropriately normal in depressed patients (Belmaker and Agam, 2008, Wong et al., 2000). Scientists found that mice with specific knockout of the nuclear receptor subfamily 3 group C member 1 (*Nrc3c1*) gene increased HPA axis activity. Moreover, in these animals, both CRH

receptor antagonists and glucocorticoid inhibitors can reverse these abnormalities, which support the HPA axis hypothesis (Boyle et al., 2005, Flores et al., 2006, Louis et al., 2006).

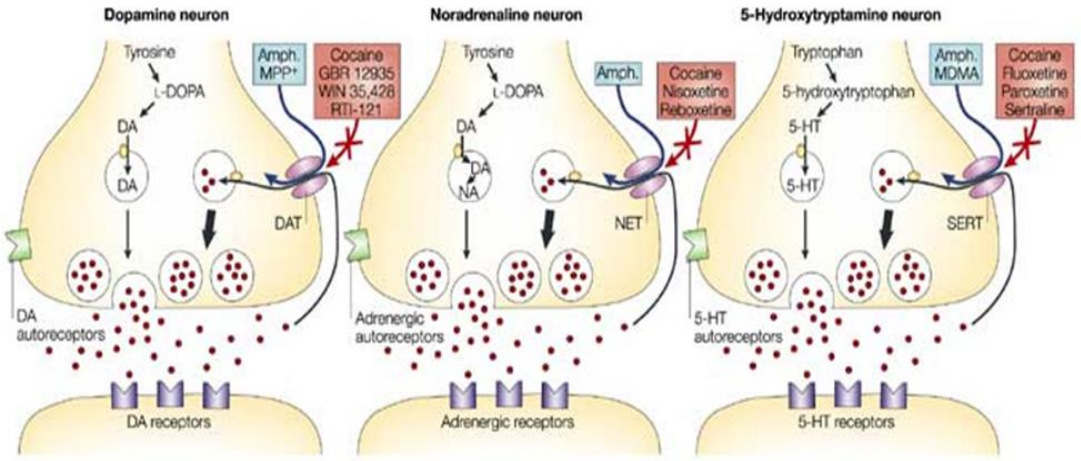


Figure 3: The role of dopamine (DA), noradrenaline (NE), and serotonin (5-HT) in major depression. DOPA, 3,4-dihydroxyphenylalanine; DAT, dopamine active transporter; NET, norepinephrine transporter; SERT, serotonin transporter; Amph, Amphetamine; MDMA, 3,4-Methylenedioxy-methamphetamine; GBR12935, 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine;WIN35,428, β-Carbomethoxy-3-β-(4-fluorophenyl)tropane;RTI-121, (–)-2β-Carboisopropoxy-3β-(4-iodophenyl)tropane; NA, Noradrenaline [Reproduced from websites: http://whyeat.net/forum/entries/7861-Monoamine-theory-of-depression-eating-disorders-and-your-antidepressants-at-work].

1.2.3 The Brain Neurotrophic Factor Hypothesis

Another prevalent hypothesis of depression is related to brain-derived neurotrophic factor (BDNF), which is a member of the neurotrophin family of growth factors. BDNF is active in the hippocampus, cerebral cortex and basal forebrain, where it is important for learning and memory (Yamada & Nabeshima 2003). BDNF also plays a critical role in promoting the survival of existing neurones and supporting the growth of new neurones (Acheson et al., 1995, Huang and Reichardt, 2001) (Figure 5). It is well known to experts in the field that the Flinders rat line fulfils the criteria

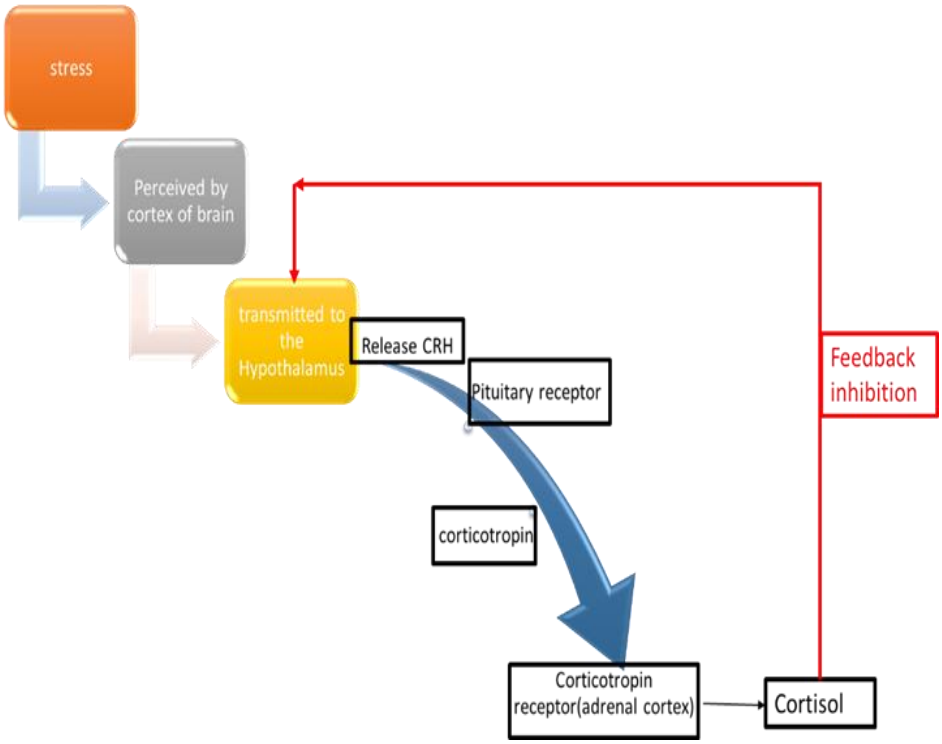


Figure 4: The Hypothalamic-Pituitary-Adrenal axis
[modified from Major Depression Disorder (Belmaker and Agam, 2008)].

of face, construct, and predictive validities; which have been used for over 25 years in depression research. Angelucci, Brene and Mathe (2005) have reported that the Flinders sensitive line depressive model showed the alteration of BDNF and nerve growth factor (NGF) in the prefrontal cortex and hypothalamus in the Flinders sensitive line depressive model, indicating the connection between BDNF, NGF and MDD (Angelucci et al., 2005). Further, a mouse depression model showed that BDNF was downregulated by epigenetic histone methylation (Lv et al., 2013). Meanwhile, patients with MDD and recorded suicide attempts evidenced decreased BDNF level in the hippocampus (Karege et al., 2005). Injecting BDNF directly into the dentate gyrus or midbrain can mimic antidepressant effects (Shirayama et al., 2002). This deficit can be reversed by both antidepressant treatment and electroconvulsive therapy (Chen et al., 2001a).

1.2.4 The Glutamatergic Neurotransmission Hypothesis

The N-methyl-D-aspartate (NMDA) glutamate (Glu) ionotropic receptor (NMDAR) has a strong permeability to Ca^{2+}, which can activate a variety of enzymes inside cells. In turn, complex biochemical and physiological reactions activated. In contrast, if excessive Ca^{2+} passes through the NMDARs channel into neurones, this can cause the massive death of neurones. Antidepressants cannot only change the binding of NMDAR and radioligand but can also change the mRNA expression of encoding NMDAR subunits. According to Nowak *et al*. (1993) after chronic treatment with

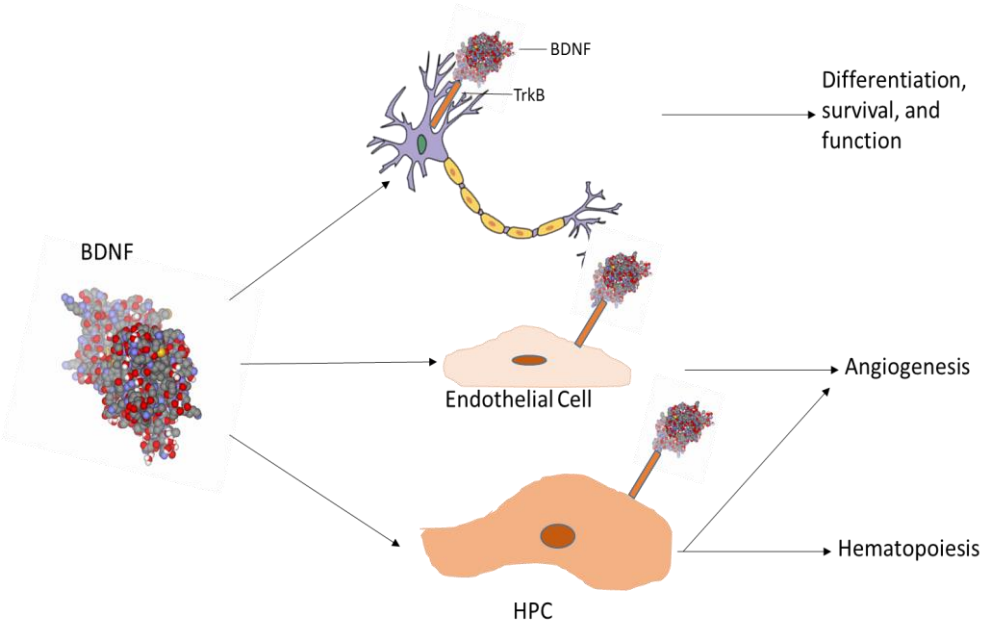


Figure 5: Functional pleiotropy of brain-derived neurotrophic factor (BDNF) extends beyond the nervous system.

TrkB (NTRK2), neurotrophic receptor tyrosine kinase 2; HPC, Hemangiopericytoma [modified from https://www.phoenixpeptide.com/topics/detail/229].

imipramine for 14 days, the non-competitive NMDAR antagonist [^{3}H] MK-801 (also known as dizocilpine/INN) binding of NMDAR sites in the cerebral cortex decreased by 37%. And the ability of glycine to inhibit the combination of [^{3}H] 7-DCKA reduced by 2.6 times, and the binding sites of the NMDAR antagonist radioligand

[^{3}H] CGP-39653 (D, L-(E)-2-amino-4-propyl-5-phosphono-3-pentenoic acid) decreased by 21%, which indicated that chronic antidepressant treatment could lead to the binding alteration of the NMDAR radioligand (Nowak et al., 1993). The NMDAR subunit plays a vital role in determining the affinity of ligand. Also, the fact that antidepressants induce binding changes between NMDAR and its radioligand may reflect the variations of different receptor subunits. Chronic administration of imipramine and citalopram in mice confirmed that antidepressants reduce the mRNA expression of the ε subunit (rat homolog Glu ionotropic receptor NMDA-type subunit 1; *Grin1*) in the cortex and striatum (Boyer et al., 1998). Moreover, chronic stress can increase Glu level significantly in the hippocampus over a long-term period. Followed that, the activation of excessive Glu and its receptors can cause calcium overload inside cells; thereby, inducing cell necrosis (Belanger and Magistretti, 2009, Conrad, 2008, Weber, 2012). In the nervous system, zinc regulates the neurotransmission of excitatory amino acids (mainly Glu).

Studies have confirmed that long-term antidepressant treatment can reduce the activity and function of the Glu-NMDA complex receptor, but can also change the interaction between zinc concentration and this receptor (Szewczyk et al., 2008). After a variety of antidepressant therapies, the number of NMDARs was reduced and their functions were weakened. The change of NMDARs was very slow, and such an adaptive change may be due as the outcome of long-term antidepressant treatment. Indeed, it has been found that NMDAR antagonists have the function of antidepressants. In addition, in rats, both non-competitive NMDAR antagonists MK-801 and competitive antagonists CGP 37849 (DL-(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid) and its corresponding structure CGP 40116 (the competitive NMDAR antagonist

D-(E)-2-amino-4-methyl-5-phosphono-3-pentanoate) could improve the reduction of sugar water intake caused by chronic stress (Papp and Moryl, 1994).

1.2.5 The Neurones and Neuronal Plasticity Hypothesis

Contemporary neuroscience research has confirmed that brain cells can regenerate and undergo apoptosis (Sohur et al., 2006), and the dynamic equilibrium between these two phenomena is a key factor for the maintenance of normal brain functions (Larson et al., 2014). Brain structural and functional imaging research that focuses on investigating the sub-molecule structure of brain cells has found morphology changes in mood-related brain region in depressive patients, especially the hippocampus (Drevets et al., 2008, Sapolsky, 2001). The hippocampus is the primary structural region of neurogenesis in adults. Stress can increase atrophy, reduce regeneration of hippocampal neurones and increase neuronal apoptosis (Leuner and Gould, 2010, Song et al., 2012). Therefore, it has been reported that there is decreased hippocampal volume in depression patients (Frodl et al., 2006). However, hippocampal atrophy can be improved after antidepressant treatment; thereby, relieving the clinical symptoms of depression (Sapolsky, 2001).

1.2.6 The Depression-related Transduction Pathway Hypothesis

Recently, a depression-related signal transduction pathway hypothesis proposed that depressed patients may have an abnormality in their cell signal transduction pathway (Catapano and Manji, 2007, Li et al., 2000, Manji et al., 2003). The signal transduction pathway in the cell can be activated through the intervention of antidepressants, and the signal transmits from the cell membrane into the cell nucleus, and then the phosphorylation is mediated through a cascade reaction (Vaidya and Duman, 2001). Transcription of related genes must depend on the activation of

phosphorylation which further regulates their protein expression levels, thereby playing an antidepressant effect.

Many antidepressants increase the concentration of synapse NE and/or 5-HT.) Furthermore, when adenylate cyclase is activated by the G protein-coupled receptor, there is a corresponding increase in the levels of cAMP. As a result, cAMP-dependent protein kinase A (PKA) is further activated. The nuclear factor, cAMP response element binding protein (CREB), is regulated by PKA phosphorylation. Due to the important role of c AMP, rolipram has become a commonly used antidepressant drug due to its selective phosphodiesterase (PDE) IV inhibitor. Although this kind of drug still has many side effects, this phosphodiesterase inhibitor shows a new anti-depressant action target (Skolnick, 1999, Halene and Siegel, 2007).

Protein phosphorylation is a critical step in the conduction pathway. Antidepressants can activate serine/threonine kinases, PKA and calcium/calmodulin-dependent protein kinases, thereby increasing phosphorylation of the substrate and affecting neurotransmission. Changes in protein phosphorylation caused by long-term antidepressant medications can be used to explain the therapeutic mechanisms of antidepressants, but also suggest a new drug intervention strategy (Popoli et al., 2001). Data suggest that phosphorylation of CREB is a more potent transcription factor when compared to other phosphorylation forms. Chronic antidepressant therapy improves the expression of CREB protein and its mRNA. Therefore, it can be viewed as an effective regulator of gene transcription (Duman et al., 1997).

1.2.7 The Macrophage Hypothesis and Cytokines

The HPA axis is activated by stress factors, resulting in increased glucocorticoid secretion. The excessive production of adrenocortical hormones causes the central glucocorticoid receptor (GR) to become desensitised. However, these receptors are also located on macrophages, so that macrophages are also activated. Three kinds of pro-inflammatory cytokines interleukin (IL) 1, IL6 and tumour necrosis factor-α (TNF) released by macrophages can affect the brain through activating cyclooxygenase, nitric oxide synthase and CRH. Meanwhile, pro-inflammatory cytokines are the potent activator of the HPA axis and glucocorticoids with a higher secretion mutually influenced by cytokines, which eventually leads to NE, 5-HT neuronal conduction disturbances; thereby, causing depressive behaviour (Leonard, 2001). The above theory is the macrophage hypothesis of depression, which extends the biogenic amine hypothesis and fully demonstrates that changes in the endocrine system and immune system play a significant role in depression (Reiche et al., 2004, Miller, 1998).

Depression is often accompanied by increased levels of serum pro-inflammatory factors, which indicates that both psychological stress and mental illness can cause changes in immune function. It was previously known that cytokines might be related to the pathophysiology of depression, somatic symptoms and therapeutic effect of antidepressant medication (Raison et al., 2006, Miller et al., 2009). Depression is also associated with activation of the inflammatory response system. Research on mice suffering from chronic mild stress indicated that a long-term desipramine treatment increased both the level of IL10 (an anti-inflammatory cytokine) and B cell proliferation after lipopolysaccharide stimulation. Also it significantly decreased the numbers of lymphocytes in response to concanavalin A (Con-A) and other antibodies (Kubera et al., 2001). Hypericum is a type of plant

antidepressant, and researchers have found that IL6 might activate the 5-HT system to mediate the therapeutic effect of hypericum, which indicates that IL6 plays a major role in the mechanism of antidepressant action (Calapai et al., 2001). Both cytokines and antidepressants could improve depressive behaviour through the adjustment of glucocorticoid levels.

IL1A inhibits GR translocation and hormone-induced GR-mediated gene expression (Carvalho et al., 2014), thus contributing to the susceptibility of depression. Therefore, the antidepressant desipramine can adjust the neuroendocrine function *in vivo* by improving GR translocation and hormone-induced GR-mediated gene expression (Miller et al., 1999). Although many experiments have indicated that antidepressants have an inhibitory effect on cytokines, there is also evidence to suggest that the immunomodulatory effect of antidepressants changes with the drug used and treatment time (Kubera et al., 2000). Overall, antidepressants significantly reduce variations in the immune system, which seems to imply that inflammatory cytokines and monoamine neurotransmitters occupy the same important position in depression (Leonard, 2001).

1.3 Depression Treatment Modalities

Once depression has been diagnosed, a patient can be treated with three kinds of treatments-psychotherapy, medication or other treatments (Figure 6). Antidepressant medication is the first line of therapy for depression. Psychotherapy-also known as ‘talk therapy'-includes cognitive behavioural therapy (CBT), interpersonal therapy (IBT), Mindfulness-based cognitive therapy (MBCT) and behaviour therapy, which are preferred treatments for adolescents. However, in severe depression, psychotherapy is insufficient for most patients.

According to the *American Psychiatric Association 2010 Practice Guideline for the Treatment of MDD* (Association, 2010), antidepressants should be provided for moderate to severe MDD patients. Antidepressants work mainly on brain neurotransmitters, including 5-HT, NE and DA. The most commonly prescribed antidepressants at present are the selective 5-HT reuptake inhibitors (SSRIs) and the 5-HT and NE reuptake inhibitors (SNRIs). The extensive use of those two classes of antidepressants is because they have fewer side effects than older generation drugs. However, the underlying mechanism of action for these antidepressants remains uncertain.

ECT will not be used unless both psychotherapy and medication are unable to relieve the patient's depression. However, via significant developments and improvements in technique, ECT now provides better outcomes for patients with severe depression. Transcranial magnetic stimulation (TMS) which improves depression symptoms via stimulating nerve cells in the brain by using magnetic fields. TMS, a non-invasive procedure, is normally used when the above treatments prove non-effective (Corthout et al., 2001).

1.3.1 Classes of Antidepressant Drugs (Figure 7)

1.3.1.1 Monoamine Oxidase Inhibitors (MAOIs)

MAOIs, the oldest generation of antidepressant drugs, have distinct effects on atypical depression treatment (Jarrett et al., 1999, Liebowitz et al., 1984). Monoamine oxidase (MAO), including MAOA and MAOB, oxidises neurotransmitters and xenobiotic amines (Patil et al., 2013). Part of the activity of MAO generates hydroxyl radicals, which have been reported to be involved in neurotransmitter degradation (Patil et al., 2013). MAOIs can prevent the breakdown of monoamine neurotransmitters by inhibiting MAO. However, the prescription of

MAOIs is limited due to the potentially lethal interaction between diet and drug. Therefore, MAOIs are used when neither 5-HT reuptake inhibitors nor tricyclic antidepressants can relieve the patient's depression.

1.3.1.2 Tricyclics (TCAs)

TCAs ease depression by blocking the reuptake of neurotransmitters, such as 5-HT and NE (Richelson, 1996, Nemeroff et al., 2002). They were discovered and synthesised in 1959. Imipramine, a dibenzazepine analogue of chlorpromazine, was the first TCA reported in the treatment of depression in 1957 by Swiss psychiatrist Roland Kuhn (Fangmann et al., 2008). In the following years, a series of TCAs—including amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline and trimipramine—were developed by modifying the structure of imipramine. TCAs used to be the gold standard in depression treatment and were widely prescribed in clinics (Storosum et al., 2001). However, because TCAs have many side effects, they were replaced by newer antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs) and selective NE reuptake inhibitors (SNRIs) (Pacher and Kecskemeti, 2004).

1.3.1.3 Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRI antidepressants are currently recommended as first-line treatment drugs in many depression cases (Petersen et al., 2002). This is because SSRIs have comparable treatment efficacy and fewer side effects when compared to other types of antidepressants (Anderson, 2001). Unlike other antidepressants, which alter the balance of more than one neurotransmitter, SSRIs only selectively block the reuptake of 5-HT in the brain. To be more specific, the pharmacological mechanism of SSRIs is the inhibition of the reuptake of presynaptic 5-HT by selectively binding with central nervous system presynaptic 5-HT transporter protein, and eventually

increasing the concentration of 5-HT in the synaptic cleft, which has an antidepressant effect. SSRIs affect almost no other neuroreceptors (such as the histamine, acetylcholine and adrenergic receptors, fast sodium channel, NE reuptake pump and so forth). Also, they have a weak effect on other neurotransmitters and higher selectivity for 5-HT. Therefore, adverse reactions are also relatively mild (Finfgeld, 2004, Masand and Gupta, 2002, Nemeroff and Owens, 2004). SSRIs, compared with the first-generation TCAs, have better tolerance and similar therapeutic effect. Additionally, SSRIs also have high bioavailability, excellent oral absorption, and less dosage of medication is required.

Fluoxetine, citalopram, escitalopram, paroxetine and sertraline are SSRIs that have been approved by the US Food and Drug Administration (FDA) for the treatment of major depressive disorder (Masand and Gupta, 2002). Despite SSRIs being considered safe and efficient antidepressants, there is evidence indicated that depressed patients with polymorphisms in 5-HT transporters display poor response to SSRIs (Arias et al., 2003). Sweating, nausea, headache, dry mouth and drowsiness are the common side effects that patients may have with SSRI treatment. Also, the other major side effects induced by SSRIs are as follows:

1. Sexual dysfunction (post-SSRI sexual dysfunction), with an incidence rate of up to 17 to 41%
2. Cognitive disorder, whereby SSRIs fail to improve the cognitive deficits and impaired cognitive function of depression; cognitive impairment is one of the reasons that patients lose their social ability
3. Suicide risk—SSRIs may increase suicide risk in children and adolescents

4. Taking SSRIs during pregnancy can cause miscarriage, congenital malformations and neonatal pulmonary hypertension, and during lactation can lead to emotional and behavioural disorders for a long period
5. Withdrawal syndrome

These side effects limit the clinical application of SSRIs to a certain extent. Therefore, new antidepressants would be required to overcome those problems.

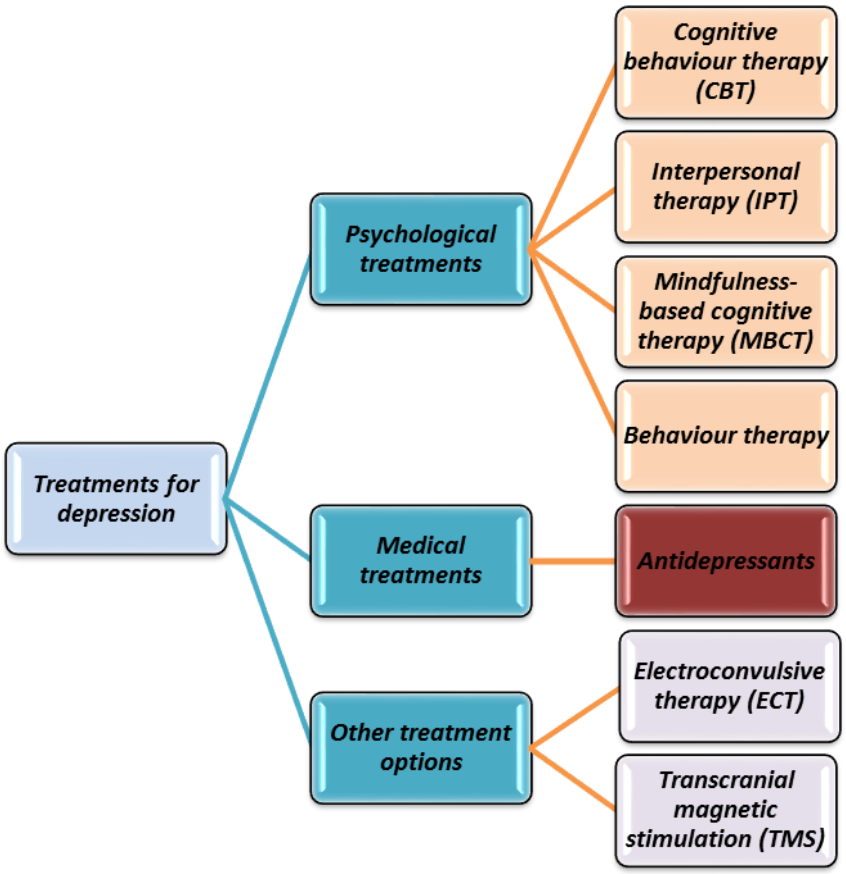


Figure 6: Treatments for depression.

CBT, Cognitive behaviour therapy; IPT, Interpersonal therapy; MBCT, Mindfulness-based cognitive therapy; ECT, Electroconvulsive therapy; Transcranial TMS, magnetic stimulation [reproduced from websites: http://www.webmd.com/depression/symptoms-depressed-anxiety-12/treating-depression?page=1].

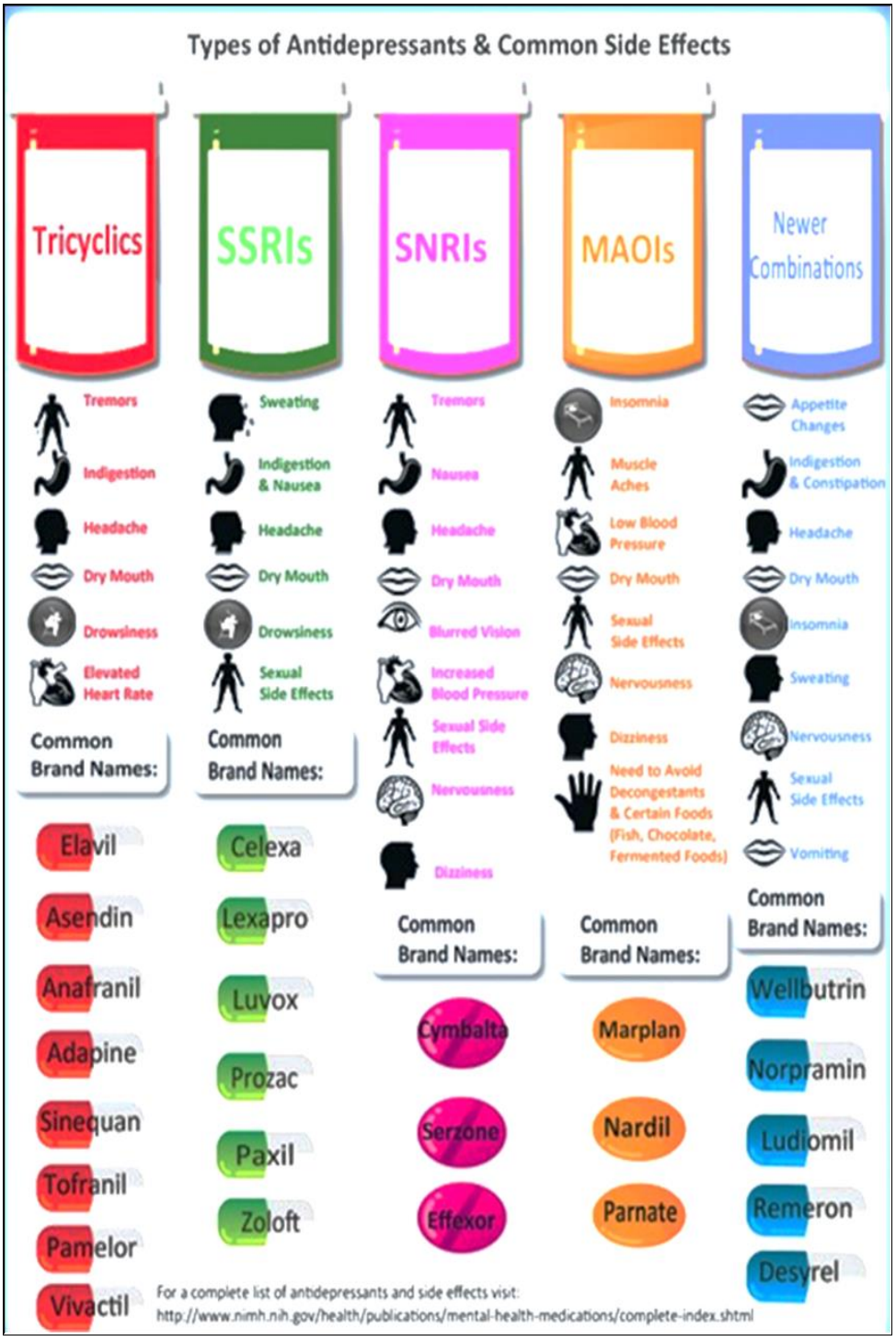


Figure 7: Classes of antidepressant drugs.

SSRIs, Selective Serotonin Reuptake Inhibitors (SSRIs); SNRIs, Serotonin and Norepinephrine Reuptake Inhibitors; MAOIs, Monoamine Oxidase Inhibitors [extracted from http://www.medicaldaily.com/how-antidepressants-work-brain-comprehensive- guide-336250].

1.3.1.4 Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs are widely used antidepressants and representative drugs are venlafaxine, duloxetine, milnacipran and desvenlafaxine. These drugs selectively combine presynaptic membrane 5-HT and NE transporter to significantly inhibit the reuptake of NE and 5-HT, and increase the concentration of these two neurotransmitters in the synaptic cleft to produce an antidepressant effect (Deecher et al., 2006, Bymaster et al., 2001). SNRIs are clinically used for the treatment of depression, various types of attention deficit hyperactivity disorder, anxiety disorders, chronic musculoskeletal pain, neuropathic pain, fibromyalgia syndrome and climacteric syndrome. Clinical studies have indicated that the combination of SSRIs and NE reuptake inhibitors (NARIs) can produce a synergistic effect in improving the therapeutic efficiency and speed (Seth et al., 1992). Also, it has been reported that venlafaxine has a good effect on depression that cannot be relief by SSRIs. As the first-choice drug for the treatment of depression that does not respond to SSRIs, duloxetine has strong ability to inhibit the reuptake of 5-HT and NE, and its antidepressant treatment effect is better than SSRIs (Deecher et al., 2006). Also, the adverse effects of duloxetine are much lower than those of TCAs so that it can be used to treat adults with severe depression. SNRIs and SSRIs may prevent microglial cell inflammatory reaction and offer neuroprotection. SNRIs also increase the level of 5-HT in the brain; thus, their side effects are similar to SSRIs but relatively milder. Adverse reactions likely to be produced by SNRIs include tremors, nausea, headache, dry mouth, blurred vision, increased blood pressure, nervousness, dizziness and sexual side effect.

1.3.1.5 Newer combinations

This class of newer drugs that include drugs with combined mechanism of action.

1.3.1.5.1 Norepinephrine-dopamine Reuptake Inhibitors (NDRIs)

NDRIs are aminoketones, which are novel antidepressants used for the treatment of a variety of depressive conditions, particularly in bipolar disorder (Deecher et al., 2006). It is more effective than other antidepressants and induces less manic episodes; thus, it has become the first choice for the treatment of bipolar disorder. Its primary mechanism is to inhibit the reuptake of NE and DA and thus increase their functions. Adverse effects can include insomnia, xerostomia, nausea, vomiting, headache, epileptic seizure and sexual dysfunction. The representative drug for NDRIs is bupropion, which is a monocycle amine ketone compound that has a moderate inhibition effect on NE reuptake and a weak inhibition effect on DA reuptake but never acts on the 5-HT system. It has roughly the same antidepressant effect as TCAs and has a rapid oral absorption rate that can reach over 80%.

1.3.1.5.2 Noradrenaline/Norepinephrine Reuptake Inhibitors (NARIs)

The pharmacological mechanism of NARIs is to prevent the absorption of the presynaptic membrane to NE, which can effectively enhance the NE function of the central nervous system and does not affect the 5-HT reuptake. These drugs can increase the vigilance of the central nervous system, yet they will not impair cognitive function. Representative drugs are maprotiline, reboxetine and mianserin. The adverse reactions of NARIs include sleep disturbances, anxiety, tachycardia, headache and other anticholinergic effects. Reboxetine was developed by Pharmacia Corporation and listed in 1997 and was the first NARI in a full sense. Its antidepressant effect results from the inhibition of NE reuptake from the presynaptic neurone to enhance NE function in the central nervous system (Kadhe et al., 2003). Tests have indicated that this drug has almost no affinity for other receptors in the brain. As mentioned before, TCAs relief depression syndrome by blocking the

reuptake of both 5-HT and NE. Different from the action of TCAs, NARIs ease the depression without blocking 5-HT reuptake.

1.3.1.5.3 Serotonin antagonist and reuptake inhibitors (SARIs)

Trazodone (also known as Desyrel) is currently the only antidepressant from SARIs. SARIs are the antagonist of alpha1 and alpha2 adrenergic receptors, 5-HT2A and 5-HT2C serotoninergic receptors and H1 histaminergic receptors (Gainsborough et al., 1994{Jarema, 2010 #912, Jarema et al., 2010). The higher doses of SARIs also can block the SERT serotonin transporter (Jarema et al., 2010, Østergaard, 2014). SARIs, compare with other types of antidepressant, induce less unwanted side effects due to its act on the serotoninergic system. Trazodone has been indicated as an effective antidepressant in the treatment of different depression syndromes, including depression with anxiety, depression with insomnia *et al.*(Jarema et al., 2010).

The efficacy of NDRIs, NARIs and SARIs are similar to TCAs and SSRIs. However, they also induce common side effects which including appetite changes, indigestion and constipation, headache, dry mouth, insomnia, nervousness, sexual side effects and vomiting.

1.3.1.6 Other antidepressants

Ketamine, as a non-selective, high-affinity N-methyl-D-aspartate receptor (NMDAR), has attracted researchers' attention in MDD treatment. Compare with prototypical antidepressants that were discussed above; ketamine is able to elevate mood much faster. It also showed positive outcome in the treatment-resistant and bipolar depression (Price et al., 2009, Murrough et al., 2013, Marrannes et al., 1988). However, the underline mechanism of why ketamine can act faster is still unclear. Ketamine could induce severe drug abuse during the process of treatment (aan het Rot et al., 2010, Trujillo et al., 2011, Dotson et al., 1995). Therefore, this side-effect

is a major obstacle that impedes the approval of ketamine for the treatment of MDD by the FDA (Food and Drug Administration, USA).”.

1.3.1.7 Summary

As the first line of treatment in the clinic, antidepressants' proven efficacy has been acknowledged widely. However, because of the lack of reliable diagnostic procedures for MDD and lack of comprehensive understanding of its pathogenesis, there are several problems with antidepressant treatment for MDD. First, several weeks of antidepressant treatment are needed to relieve the clinical symptoms of MDD. Recent evidence indicated that presynaptic desensitisation of 5-HT1A receptors could be detected after a few days of treatment initiation with SSRIs, and the increased number of serotoninergic neurons with desensitised 5-HT1A autoreceptors is one of the key factors that slow the onset of antidepressant action (Le Poul et al., 1995, Invernizzi et al., 1994, Kennett et al., 1987). During this period, patients’ symptoms may worsen. Second, some patients withdraw from antidepressant treatment due to severe side effects. Third, some patients become resistant to antidepressant they have been treated with. Fourth, the urgent situation is that up to 50% of patients fail to respond to one or more antidepressant drugs (O'Leary et al., 2014, Trivedi et al., 2006). The genes involved in pharmacokinetics and pharmacodynamics can contribute to the above problems (O'Brien et al., 2013, Porcelli et al., 2011). Therefore, investigating the pharmacogenetics mechanism of antidepressants may help develop the new guide for individualised treatment.

1.4 Factors Affecting Antidepressants Treatment Outcomes

Many researchers have investigated why different individuals show different responses and side effects after using fluoxetine and other antidepressants. The following details have been shown:

1. Drug metabolic processes *in vivo*: drug metabolism mainly affects the concentration of drug reaching the target organ, thus influencing drug efficacy and side effects. Take fluoxetine as an example: Fluoxetine's therapeutic index is wide, which means that there is a lack of a clear correlation between plasma concentration and therapeutic effect. Most patients using the standard dose of fluoxetine have plasma concentrations that can be higher than a therapeutically effective concentration and lower than the poisoning level. Therefore, the value of plasma therapeutic concentration monitoring in pharmacodynamics studies of the drug is far less than that of a pharmacokinetic study.
2. Differences in pharmacokinetics: Fluoxetine and its transporter, the solute carrier family 6 member 4 (SLC6A4) (also known as serotonin transporter, 5-HTT or serotonin transporter 1, SERT1) have a strong affinity, which is the basis for fluoxetine's antidepressant action and may also be the basis for its side effects. Therefore, the polymorphism of the *SLC6A4* gene among individuals may be a key reason contributing to its diverse therapeutic efficacy and side effects. Fluoxetine also has a week affinity with adrenergic, cholinergic and histamine receptors, which is also associated with its side effects (Mann et al., 2000).
3. Different clinical symptoms: Different sub-phenotypes of depression (such as single and recurrent) showed varied therapeutic responses regarding a antidepressant treatment.
4. Other factors: Various other elements may influence antidepressant treatment outcomes, including social and psychological factors.

The above considerations may cause patients to experience different responses to

antidepressants. In some people, symptoms can remit without adverse effects, while in other people, symptoms do not improve and they experience serious adverse effects. Main reasons for antidepressant response variability include not only psychological and social factors but also pharmacokinetics, pharmacodynamics and clinical features. The last three factors are closely associated with genetic factors. The above problem could be elucidated through pharmacogenetics/pharmacogenomics which can provide new therapeutic targets by studying how genetic polymorphisms affect drug efficacy and side effects. Gene polymorphism of encoding drug metabolising enzymes, drug receptors, neurotransmitter transporters and second messengers are likely to affect the effectiveness and side effects of antidepressants (Owens and Nemeroff, 1994, Mancama and Kerwin, 2003).

1.5 Research and Development of New Types of Antidepressant Drugs

The traditional monoamine theory holds the view that the pathogenesis of depression is associated with a low content of monoamine transmitters, such as 5-HT, NE or DA, in the central nervous system, and the pathogenesis of depression is also related to monoamine transmitters receptors disorder (Han et al., 2012). Currently, available antidepressants include monoamine reuptake inhibitors, MAOIs and monoamine receptor ligand drugs (see below). These drugs have been studied and developed based on the monoamine hypothesis. Compared to the first-generation drugs (such as MAOIs and TCAs), currently commonly used antidepressants (such as SSRIs and NRIs) have high selectivity for receptors and less adverse reactions; however, satisfactory therapeutic effects still cannot be achieved for many depressed patients. The biggest problems are the delayed onset of therapeutic effects, poor efficacy, easy

relapse and need for long-term medication treatment. Since the pathogenesis of depression is complex and involves multiple receptors and neurotransmitters, in recent years, multi-targeted drugs have gradually become the focus of pharmacological research and development.

As part of the investigation and development of multi-target antidepressant drugs, in addition to the SNRIs and NDRIs, the triple reuptake inhibitors (TRIs) or serotonin-norepinephrine-dopamine reuptake inhibitor—which can simultaneously inhibit 5-HT, NE and DA reuptake into the presynaptic membrane—have attracted increasing attention. TRI compounds DOV 216303, DOV 21947, PRC200-SS, PRC025 and PRC050 showed antidepressant effects in preclinical research (Liang et al., 2008, Shaw et al., 2007). Also, Phase II clinical results of DOV 216303 and DOV 219471 developed by Dover Corp were satisfactory (Mathew et al., 2008, Skolnick and Basile, 2007). However, the inhibition of DA reuptake can easily result in adverse reactions; thus, drug safety needs to be evaluated further.

With the in-depth study of the pathogenesis of depression, the new non-monoamines and monoamine receptor modulators have become potential targets for antidepressant drug development. New SLC6A4 modulating drugs—such as HTR1A [5-hydroxytryptamine (serotonin) receptor 1A], HTR2A, HTR2C, HTR3A, HRT5A and HTR7 ligand drugs—have shown antidepressant effects (Bockaert et al., 2006). Non-monoaminergic antidepressants, such as neural plasticity, HPA axis and immune system-related glutamate neurotransmission modulating drugs [mainly NMDA receptor antagonists and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor modulators], neuropeptide receptor modulating drugs, cytokine receptors antidepressants, GR antagonists and other drugs, these new antidepressants have different characteristics, such as a high affinity and a high

specificity (Catena-Dell'Osso et al., 2013). Many compounds are currently being tested in clinical studies (Berton and Nestler, 2006).

With the discovery of new targets and strategies, drug development has become the research focus to achieve a novel, fast and efficient antidepressant with less adverse effects that will enable satisfactory and individualised treatment for patients with depression.

1.6 Genetics of MDD

Based on family studies findings, it is clear that MDD is caused by multiple complex genetic variations (Belmaker and Agam, 2008, Sullivan et al., 2000), although some studies have claimed that heritability contributes only partly to the development of MDD. For example, early-onset, severe and recurrent presentations of this disorder may rely strongly on genetic factors (Kendler et al., 2006). Sullivan, Neale and Kendler (2000) have determined a 37% heritability for MDD based on comparing the concordance rate of MDD between dizygotic and monozygotic twins (Sullivan et al., 2000).

There are more than 350 million people with depression around the world (Paris et al., 2004, Ledford, 2014), with very different symptom severity. In particular, there is a large difference between men and women. As women showed higher risk of first onset of depression, women are twice as likely to develop depression in their lifetime compared with men at the same age (Kessler, 2003). It has also been shown that different expression of the same depression phenotype may exist in different genetic backgrounds (Risch, 2000, Wray et al., 2012). Classical genetic studies have also confirmed the incidence of depression aggregates in families, thereby suggesting that genetic factors play a vital role and may associate with multiple susceptibility genes.

However, this disorder not only has a complex phenotypic character but it may also be the result of the interaction between genes, environment and other non-genetic factors. Thus, phenotypes may be inconsistent with genotypes. According to current views, there may be many candidate gene loci that influence the pathogenesis of depression, including neurotransmitter transporter protein, anabolism enzymes, various receptor subtypes and intracellular signal transduction systems. In past years, scientists have identified candidate genes related to the onset of depression, as discussed below.

1.6.1 Overview of SNP and MDD

The aetiology and pathogenesis of depression remain unclear. Depression is considered a complex disease, with the occurrence and development of depression being affected by a variety of factors, including both internal and external factors. These can include genetic, immune and neuroendocrine, neurochemical, life events and personality factors.

Traditional genetic studies—such as the results of family, twin and adoption studies—have confirmed the important role that genetic factors play in the pathogenesis of depression, with a heritability of about 40 to 70% (Lesch, 2004). With the development of molecular genetics, genetics research exploring depression susceptibility genes or disease genes has been carried out quickly, which have mainly focused on relevant molecules, such as 5-HT, DA, NE and other transporters, receptors and related enzymes. Experts have agreed that depression is a polygenic disease (Lummis, 2012b).

The Human Genome Project is a worldwide collaborative research program aims to decipher the human genome and build a complete database of the entire human

genome sequence. Data from the Human Genome Project shows that genes of different individuals are essentially the same, but the sequence has subtle genetic differences—these differences were named ‘genetic polymorphism’ (Consortium, 2004). On a chromosome, a particular DNA sequence fragment containing polymorphisms is called a ‘genetic marker.' Genetic markers can divide the genome into different regions. The location of disease genes in the chromosome (chr) regions can be obtained via gene linkage and association analysis. Genetic linkage is applied when the alleles have a tendency to be inherited together. When, within a population, the co-occurrence of one or more genotypes with a phenotypic trait happened more often than expected, genetic association analysis may be used. Genetic association analysis aimed to investigate if genotype frequencies and single-locus alleles differ between cases (affected subjects) and controls (healthy subjects). The term single nucleotide polymorphism (SNP) was first proposed by Lander in 1996 for variations of a single nucleotide in DNA sequences (Lander et al., 1996). The Single Nucleotide Polymorphism Database (dbSNP) has a large amount of polymorphism information present in the human genome (Lander et al., 1996). Also, SNPs are easy to detect automatically and analyse.

Other DNA changes include single-base transitions, transversions, insertions and deletions, resulting in chromosome genomic diversity among individuals, which is an important cause of differences in disease susceptibility and drug response. The frequency and type of SNP occurrence maybe different between people from different regions and ethnic origin. In other words, among healthy individuals of a particular ethnic group, different bases may occupy specific nucleotide positions.

SNP loci are unevenly distributed and by definition its lowest allele frequency should not be lower than 1% (Przeworski et al., 2000, Roses, 2002, Wang et al., 1998). In

general, natural selection tends to preserve SNP loci that are most conducive to genetic adaptability (Barreiro et al., 2008). Changes in the human DNA sequence affect disease development and the human body's reactions to drugs and chemicals. The DNA sequence of any two unrelated individuals is 99.9% similar; the other 0.1% is of particular importance because it contains genetic differences that contribute to the susceptibility to different diseases or drug responses. Therefore, SNP is key to personalised medicine and has been applied as a next-generation genetic marker to determine the genetic risk factors for complex diseases. Identifying disease-related SNPs is one of the most important ways to understand human disease caused by complex aetiology (Botstein and Risch, 2003). In the early 2000's, association analysis using the candidate gene SNP had become one of the most important molecular genetic research methods (Botstein and Risch, 2003). The biggest advantage of this approach is its ability to detect the pathogenesis of common human diseases at low cost. A pivotal study found that adjacent SNPs within a given region of chromosomes tend to pass to the next generations as a whole, with only a few combinations. These combinations are named 'haplotypes'. It is possible to identify individual genetic markers associated with disease or phenotype by analysing multiple sites of haploids at the same time (Weiss and Terwilliger, 2000). Researchers are currently seeking to compare affected and non-affected individuals to identify genes that influence susceptibility to different diseases. Therefore, more and more scholars have employed a genome-wide association study (GWAS) strategy in their studies—namely, screening numerous SNPs using SNP arrays in samples from a large number of individuals, including cases and controls, and eventually undertaking a comprehensive disease risk assessment associated with each SNP and haplotype (Yamazaki et al., 2005). The advantages of a genome-wide

research strategy include its ability to assess the function of candidate genes comprehensively in the development of a disease so as to establish the most cost-effective research strategies.

1.6.2 The Candidate Gene Approach

Candidate genes refer to those genes that are assumed to be involved in the development of certain diseases. Those genes may be the structural gene, regulatory gene or genes that influence the expression of character in biochemical pathways (Zhu and Zhao, 2007). The candidate gene approach aims at identifying the correlation between variants in a specific gene of interest and a disease (Tabor et al., 2002). By using the candidate gene approach, the target gene is firstly selected among genes that are associated with a certain phenotype. The existing variants in the target gene are then addressed via sequencing or screening procedures (Malhotra and Goldman, 1999), and variants that result in amino acid changes in the protein may be chosen as the most useful polymorphisms for testing in cases-control studies (Kwon and Goate, 2000). Finally, the results show whether a particular gene variation will bring a real phenotypic variation (Pinheiro et al., 2010). This type of method has a specific goal and good accuracy, and reduces research expenditure (Zhu and Zhao, 2007). Therefore, the candidate gene approach has been extensively used to investigate various complex diseases.

1.6.3 Candidate Gene Studies

In the recent year, by applying candidate gene approach, Buttenschøn has identified four variants within the angiotensin I converting enzyme (ACE) gene that is associated with depression using data from 408 depressed patients and 289 controls (Buttenschøn et al., 2016). As increasing evidence indicate increased DNA damage in depression, Czarny's team found that SNPs within genes involved in base-excision

repair modulated the level of DNA damage repair, which significantly lower in depressed patients (Czarny et al., 2016). Also, genetic polymorphisms in the human clock circadian regulator (CLOCK，also known as bHLHe8, KAT13D, KIAA0334) and human period circadian clock 3 (PER3) circadian genes play a role in the development of depression, but in sex- and stress-dependent manner (Shi et al., 2016).

1.6.4 5-HT system

In recent years, molecular genetic studies of depression have demonstrated increasing evidence to support a close association between 5-HT and depression. Dysfunction of the 5-HT system is closely related to depressed mood, loss of appetite, sleep disturbances, anxiety, decreased activity, sexual dysfunction and endocrine hormone disorder. Therefore, those genes involved in the 5-HT system synthesis, metabolism, release and uptake, and those genes affecting 5-HT receptors activities, are important candidate genes in the study of depression. 5-HT activity is adjusted by a variety of receptors. Currently, at least seven types of receptors have been identified—5-HT_1 to 5-HT_7 receptors. Till present, among those 7 serotonin receptors, the 5-HT3 receptors have been extensively investigated. 5-HT_3 receptors are the only ligand-gated cation channel, other types of receptors are G protein-coupled receptors (Hannon and Hoyer, 2008). Studies have shown that 5-HT_3 receptors are associated with many complex functional disorders, including mental illness, cognitive disorders, irritable bowel syndrome and drug abuse (Bearcroft et al., 1998, Walstab et al., 2010). Abnormal expression of 5-HT_3 receptors may affect the release of 5-HT, DA, gamma-aminobutyric acid, substance P and acetylcholine (Kumar et al., 2007, Li et al., 2009, Smoller and Finn, 2003, Tsai et al., 2009). The distribution of 5-HT_3 receptors are non-uniform; these receptors are widely distributed in the peripheral

and central nervous systems, including area postrema and nucleus tractus solitarius in the brainstem (Lummis, 2012a, Pires et al., 1998), hippocampus, and spinal cord dorsal horn, after the trigeminal nucleus, forebrain, amygdala, nucleus accumbens, putamen, and caudate nucleus. Distinct parts of the 5-HT_3 receptors may play different functions. For example, 5-HT_3 receptors located in the limbic system is associated with depression, anxiety, and other mental disorders (Barnes et al., 1989, Parker et al., 1996). At present, five 5-HT_3 receptors subunits have been identified: 5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E} receptor. The *HRT3A* gene was first cloned by Maricq et al. (1991) from the hybrid cell lines NCB20 of hamster embryo brain cells and mouse neuroblastoma, this gene spans approximately 15 kb, containing nine sizes between 45 and 845 bp exons. Moreover, *HTR3A* encodes a 478 amino acid protein (Belelli et al., 1995, Frank et al., 2004). The 5-HT_{3A} receptor can form functional homology receptors and can be co-expressed with 5-HT_{3B}, 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E} receptors to create different polymer composites with various functions that show different physiological and pharmacological properties (Yaakob et al.). Barrera's study found that the *HTR3A* gene is located on Chr 11q23 (Barrera et al., 2005). Through family studies, a depression-susceptible gene located on Chr 11q23 has been indicated. Therefore, *HTR3A* is considered one of the most important candidate genes contributing to depression aetiology and pathogenesis (Davies et al., 1999, Maziade et al., 1995, Weiss et al., 1995, Yamada et al., 2006). Correlation analysis of *HTR3A* conducted by Niesler in 2001 revealed that a polymorphism in *HTR3A* is associated with MDD and bipolar disorder (Niesler et al., 2001). Yamada et al. (2006) recruited 99 patients with bipolar affective disorder and 81 patients with unipolar depression in the central region of Japan and determined a total of 29 polymorphic loci in *HTR3A* and *HTR3B*. This study found

that *HTR3A* gene polymorphism is associated with bipolar disorder in the Japanese population (Yamada et al., 2006). Niesler et al. (2001) found that the missense mutation of SNP c.-42C (cytosine) > T (thymine) (= C178T: rs1062613) located in the cis-regulatory region of *HTR3A* is associated with the Germanic bipolar disorder. The *HTR3A* variation located upstream of the open reading frame region changed the *HTR3A* transcription level, which further resulted in an exchange of prediction of amino acids (C178T; rs1062613; Pro16Ser) (Niesler et al., 2001). Morris and Geballe's (2000) study attained the same result: mutations located upstream of the open reading frame played an role in the regulation of gene expression via reducing the translation of downstream genes (Morris and Geballe, 2000). In 2008, Kapeller *et al.* (2008) selected the 5-HT_3 receptor antagonist [^{3}H] GR65630 to undertake a radioligand binding assay on HEK293 transfected cell membranes and confirmed that c. -42 C > T alleles increased the 5-HT_{3A} receptor expression on the cell surface (Kapeller et al., 2008). Melke *et al.* (2003) conducted two independent analytic case-control studies in the Swedish population and confirmed that polymorphism is associated with female body harm avoidance. Furthermore, this polymorphism reduced the activities of the amygdala and prefrontal cortex, and Iidaka *et al.* (2005) reported similar findings. Along these lines, the clinical symptoms of depression reflect the diversity of cognitive, psychomotor and affective processes disorder. In addition to the core symptoms and accompanying (mental and physical) symptoms of depression, cognitive dysfunction is also a fundamental feature of depression and might be one of the primary symptoms of depression (Holden, 2000; Koetsier et al., 2002b; Koetsier et al., 2002a; Von Korff et al., 1996). Meanwhile, the clinical characteristics and severity of depressive individuals vary. These differences may be closely associated with genetic heterogeneity. A study

conducted by Caspi *et al.* (2003) first mentioned that the modification of genes might affect individual susceptibility to environmental damage. This research also clarified the effect of genetic factors on the severity of depression at a molecular biology level. Therefore, another trend in contemporary research is to select the symptom or symptom group and explore the pathological mechanism of depression. In 2011, Misuhiro and colleagues (Kamata et al., 2011) undertook correlation analysis of the clinical symptoms of 132 Japanese unipolar depression patients with *HTR2A* gene and 5HTTLPR polymorphism. This study found that those gene polymorphisms are associated with some factors in the Montgomery Depression Rating Scale (Kamata et al., 2011). In the same year, Klengel *et al*. (Klengel et al., 2011) published their findings that *HTR2A* polymorphism is associated with physical symptoms in depression.

1.6.5 Solute carrier family 6 member 4 (SLC6A4) gene

The human *SLC6A4* (also known as serotonin transporter, *5-HTT;* serotonin transporter 1, *SERT1)* gene is located on Chr 17q11.1–12. At the 5' end of its promoter region, there is a 44 base pair deletion/insertion that form the functional polymorphism of short (S) or long (L) alleles, respectively, and they constitute three kinds of genotypes—L/L, L/S and S/S—which are also referred as 5-HTTLPR genotypes (Lesch et al., 1996). The messenger ribonucleic acid (mRNA) level generated by S/S homozygote cells is higher than that of heterozygote cells, and the intake of 5-HT also increases. Thus, individuals with different 5-HTTLPR genotypes may have different 5-HT uptake; thereby, affecting their susceptibility to anxiety-depression disorder and adaptation to environmental stress (Bellivier et al., 2000). Research on patients with depression has also indicated a higher frequency of the S/S genotype and the S allele, which suggests that people with these genotypes

may have susceptibility to depression (Smeraldi et al., 2002). When affected by stressful life events, the depression prevalence rate among people who are S homozygous is higher than that of people who are L homozygous, and they can also exhibit more depressive symptoms and higher suicide risk (Caspi et al., 2003). Previous studies have also shown that depression reflects the combination of prevalence risk genes, environment and other non-genetic factors. However, because the role of *SLC6A4* polymorphism in the pathogenesis of depression has not been conclusive; to solve this, it might be necessary to undertake an in-depth analysis of the variation of this gene regulatory sequence, with the help of emerging and new genetic approaches.

1.6.6 Tryptophan hydroxylase 1 (*TPH1*) and Tryptophan hydroxylase 2 (*TPH2*) gene

Tryptophan hydroxylase 1 (TPH1, also known as TPH, TPRH) is the rate-limiting enzyme in 5-HT biosynthesis. A change in the level of TPH1 can cause a metabolic disorder of 5-HT in the brain (Nielsen et al., 1994). The alteration of TPH1 is also associated with behavioural abnormalities (such as suicide) and psychiatric disorders. The human *TPH1* gene is located in Chr 11p15.3–p14. Several different SNPs have been described in its intron 7. Relevant research between this gene and depression has indicated that 218A (adenine)/C (rs1800532), 1067G (guanine)/A (rs684302) and 347T/A (rs623580) are three SNPs in close linkage disequilibrium. Among these three SNPs, the frequency of 218A/C, which is located in a non-coding region and the modification changes after protein translation, is significantly associated with depression (Zill et al., 2002). The presence of 218A/A in a depressed patient is associated with the higher somatic anxiety scores (Du et al., 2001). Otherwise, this polymorphic site is a potential binding site of the GATA1 (GATA binding protein 1) transcription factor, which may affect the expression of the *TPH1* gene. *TPH2*, the

rate-limiting enzyme for brain serotonin in the synthetic pathway. *TPH2* plays a crucial role in supporting normal serotonin transmission in the central nervous system. Despite some studies highlighting the relationship between TPH2 and MDD, many contradictory studies have also been published (Zill et al., 2004, Illi et al., 2009, Gao et al., 2012, Garriock et al., 2005).

1.6.7 5-hydroxytryptamine receptor 1A (*HTR1A)* gene

The effect of 5-HT is mediated by 14 different receptors, among which the HTR1A (also known as 5-HT1A) is a subtype most expressed in the central nervous system. Also, it has a negative feedback inhibition effect on the 5-HT system and simultaneously works as presynaptic autoreceptor and postsynaptic receptor (Albert and Lemonde, 2004). The human *HTR1A* gene is located in Chr 5q12.3, and there is a C (-1019) G SNP (rs6295) in its upstream regulatory region which has been studied. The frequency of homozygous G allele in rs6295 is higher in patients with depression, comparing with the control population. Moreover, the homozygous G (-1019) allele is found as much as four times greater among suicidal patients than in the healthy population (Lemonde et al., 2003). A previous study found that the scores of the Personality Inventory (NEO) and three-dimensional Personality Questionnaire (TPQ) of people who carried the G allele were much higher than those people who carried the C allele. Moreover, individuals who carried the G allele also showed a high TPQ damage avoidance index (Strobel et al., 2003). Therefore, the functional SNP in the transcriptional regulatory region C (-1019) G in the *HTR1A* gene may be involved in the pathogenesis of depression.

1.6.8 5-hydroxytryptamine receptor 2A (*HTR2A*) gene

The role of HTR2A is opposite to the HTR1A. It is involved in regulating the activities of a variety of psychotropic drugs. The human *HTR2A* gene, located on Chr

13q14-21, contains a large number of SNPs. Among those SNPs, the T102C SNP (rs6313) is one of the most investigated SNP that is associated with variation in emotionality, activity, sociability, as well as schizophrenia (Golimbet et al., 2004, Abdolmaleky et al., 2004). The A1/A2 [A1 and A2 are two alleles of the autosomal locus A (Griffiths, 2002)] is a genotype of -1438G/A SNP (rs6311) in the *HTR2A* promoter region. The frequency of A1/A2 genotype was found to be significantly reduced among patients with depression. Also, it was significantly reduced among the affective disorder patients who had recorded suicide attempts or suicidal behaviours (Sato et al., 2002). However, there are still contradictions in this study's results as two studies reported no association of *HTR2A* with suicidality or general psychopathology (Chen et al., 2001b, Ertugrul et al., 2004), which may be associated with the strong or weak linkage disequilibrium that existed in some functional variants and rs6313. Therefore, follow-up studies and larger sample size are needed to help further clarify the relationship between affective disorders and SNPs in this gene.

1.6.9 Monoamine Oxidase A (*MAOA*) Gene

Monoamine oxidase—which is classified into A and B subtypes—has a catalytic effect on the degradation of monoamines. The human *MAOA* gene is located on Chr Xp 11.23–p11.4, and there are two polymorphic sites on the *MAOA* gene that have been investigated: EcoRV and uVNTR. The EcoRV2–uVNTR1 haploid had a higher frequency among male patients with depression. Also, the score of the Hamilton Depression Rating Scale (HAMD) for sleep disorders of male patients who carried the EcoRV2 allele was significantly increased (Du et al., 2004). However, Du's research could not reach a conclusion regarding the results for this gene. Future research focused on clinical disease classification (such as comparing early-onset and

late-onset depression, or comparing bipolar disorder combined with and without symptoms of schizophrenia) is needed to help clarify the relationship between the *MAOA* gene and affective disorders. This may also enable further examination of new ways to explore and discuss depression aetiology.

1.6.10 Dopamine (DA) beta-hydroxylase (*DBH*) gene

DA beta-hydroxylase (DBH) is the key enzyme that generates NE. Reducing its activity may increase the risk of psychotic depression. The human *DBH* gene, located on Chr 9q34, its SNP (G444A; rs1108580) in exon 2 has been associated with the activity of body fluids DBH. Patients with depression with the GG genotype had low scores of interpersonal sensitivity and delusional ideas in the Symptom Checklist-90 (SCL-90). Thus, this genotype may create protective factors that prevents patients from developing psychotic symptoms (Wood et al., 2002). Due to the relatively limited research on the *DBH* gene and depression, and the positive result of the link between *DBH* gene and depression has been difficult to replicate. Therefore, a large multi-centre experiment needs be conducted to draw definitive conclusions.

1.6.11 G protein subunit beta 3 (*GNB3*) C825T SNP

G Protein consists of three kinds of subunits: Gα, Gβ and Gγ. The SNP C825T (rs5443) exists on the tenth exon of the *GNB3* gene. The heterogenesis of this fragment could suggest that the GNB3 lacks 41 amino acids, thereby generating a variation (Siffert et al., 1995). This polymorphism may be one of the factors that increase the susceptibility of depression. Meanwhile, considering this polymorphism's role in the signal transduction process, it is also related to antidepressant treatment (Zill et al., 2000). The study of *GNB3* polymorphisms is still

at a preliminary stage and requires further exploration of its specific mechanism in the pathogenesis of depression.

1.6.12 Other candidate gene studies

Candidate gene approach has been criticised not only because the results are difficult to replicate, but also because it lacks the ability to consider all possible disease-related genes or/and polymorphisms (Zhu and Zhao, 2007, Tabor et al., 2002). Therefore, other approaches have been used. For example, variants within the zinc finger protein 34 (*ZNF34*) gene also may contribute to susceptibility to MDD via whole-exome analyse using a family-based approach (Subaran et al., 2016).

1.6.13 The Genome-Wide Study (GWAS) Approach

A detailed map of the human genome symbolised that the development of modern medicine has gradually entered the era of genomic medicine. The focus of human functional genomics is to study human genes and their encoded proteins, thus revealing the secrets of life as comprehensively as possible (Celniker et al., 2009). This approach has been established based on the whole genome sequence. Currently, genomic medicine has just begun to have a major effect on disease diagnosis, malignant tumours, organ transplantation, mental diseases, cardiovascular diseases, pharmacy, medical ethics and gene therapy. Also, the human genome has provided a new source for drug development (Hamburg and Collins, 2010).

Genetic factors and the interaction between environmental and genetic factors are involved in the development processes of almost all human diseases (McClellan and King, 2010). Based on the number of disease-causing genes, diseases in which genetic factors are involved could traditionally divide into monogenic diseases and complex diseases. Monogenic diseases refer to those caused by the variant of a single

gene (Ng et al., 2010). During the past 20 years, researchers have discovered many single gene mutation that contribute to the develop of cystic fibrosis, Huntington's disease and other monogenic diseases, through the positional cloning method of family-based linkage analysis (Koboldt et al., 2013, Elliott et al., 2009). Variations in these genes cause changes in amino acid sequence or in the production of the corresponding coding proteins, thereby generating the disease phenotype that conforms to Mendelian inheritance (Klein et al., 2005, Plomin et al., 2013). However, for complex diseases, the role of linkage analysis is very limited.

Complex diseases refer to those caused by a combination of environmental factors and genetic factors. However, it has been difficult to identify genetic variations that affect complex diseases. In recent years, alongside the implementation of the Human Genome Project and the International HapMap Project, researchers have begun to explore the genetic features that influence the formation of humans characteristics and the emergence of complex diseases, which will provide valuable clues for further understanding and control the genetic characteristics of human complex disease occurrence (Bodmer and McKie, 1997).

Following the completion of the Human Genome Project, international research on the human genome has entered a new stage. The GWAS is a new approach that has been significantly innovated, popularised and applied to greatly promote the development of genomic medicine. The GWAS is a type of study that focuses on common genetic variations within the scope of the whole genome—this method uses SNP data to conduct an overall correlation analysis (Moskvina et al., 2009). GWAS involves choosing the genetic variations and performing genotyping within the whole genetic sequence. The genomic difference between controls and cases is compared next. Moreover, calculating the correlation strength between the variation and

disease to choose the most suitable variation for validation, and finally confirming that the result is associated with the disease (Moskvina et al., 2009).

In 2005, the *Science* journal reported for the first time GWAS results of age-related retinal macular degeneration, which created a sensation in the medical and genetic fields (Edwards et al., 2005). Following this, a series of GWAS studies undertook. In 2006, the medical schools of Boston and Harvard Universities and other research organisations reported GWAS findings in obesity (Llewellyn et al., 2013, Saxena et al., 2012, Yang et al., 2009). In 2007, Saxena *et al*. (2007) and other research institutions described multiple alleles associated with type-2 diabetes. In 2008, Barrett *et al.* (2008) found more than 30 susceptibility gene loci linked to Crohn's disease through GWAS. While Elliott *et al.* (2009) published genes correlated to coronary heart disease (Deloukas et al., 2013, Elliott et al., 2009). In the same year, Weiss *et al.* (2009) identified chromosomal regions that have high heredity with autism, a neurodevelopment disease, using GWAS. Chinese scholars found five lupus erythematosus susceptibility genes by GWAS, using a cohort of Han nationality patients (4199) and controls (9255). Also, four new susceptibility loci were also determined to be closely associated with lupus erythematosus (Han et al., 2009). Up to the present time, the genes and related SNPs associated with human height, weight, blood pressure and other main phenotypes have been identified using GWAS. Furthermore, GWAS also identified variants associated with macula lutea, breast cancer, prostate cancer, leukaemia, coronary heart disease, obesity, diabetes, schizophrenia, rheumatic arthritis and other dozens of common diseases that posed a threat to human health.

The research method that GWAS adopts is consistent with the traditional candidate gene case-control association analysis—namely if some SNPs associated with a

particular kind of disease, the allele frequency of the related SNPs in patients with this disease should theoretically be higher than that of healthy people (Neale et al., 2010). Initially, the GWAS was divided into single-phase, two-stage or multistage designs (Witte, 2010, Cantor et al., 2010, Korte and Farlow, 2013). The single gene stage selects sufficient cases and contrast samples and conducts genotyping of the chosen SNPs in all participants. Following this, the correlation of each SNP with the disease is analysed, and correlation strength is calculated. However, this approach was mainly adopted in the initial stages of GWAS usage. Currently, GWAS utilises mostly the two-stage or the multistage design. The case-control analysis conducted through SNP, which encompasses the scope of the whole genome in the first stage and fewer number of positive SNPs are selected for the second phase based on statistical analysis. Otherwise, it can adopt larger sample cases and compare them with the control group to conduct genotyping in the next multi-stage, and then the analysis is carried out in combination with the results of the two-stage or multistage analysis. This type of design is needed to ensure that the sensitivity and specificity of the disease associated SNPs of the first stage are screened to minimise the occurrence of false positives and negatives, and a larger sample size is applied in the second stage. It is also necessary to replicate the result in different cohorts.

Although GWAS results have significantly increased understanding of the genetic mechanism of the disease molecule, they also present significant limitations (Korte and Farlow, 2013). First, there is a certain degree of difficulty in determining the functional loci associated with specific characteristics and complex diseases through statistical analysis of their relationship. Many SNP loci are out of the protein-encoding open reading frame, which causes difficulties in explaining the relationship between SNP loci, phenotypes and complex diseases. However, since

the symptoms of complex diseases are mostly determined by quantitative characteristics, SNP loci may have a slight influence on these quantitative markers through affecting the expression level of the genes (for example, a genetic variation in the insulin gene promoter, which increases the risk of type-1 diabetes, plays a significant role in the transcription or translation efficiency of RNA, having a short-term and spatial effect on gene expression, stimulating and regulating the expression and transcription of genes, or affecting RNA splicing patterns (Korte and Farlow, 2013). Thus, researchers should note the importance of locus variation in the coding and regulatory regions when they discover disease-associated variations.

Second, the allele structure (number, type, effect size and susceptibility variation frequency) may have different characteristics in different phenotypes/diseases (Stringer et al., 2011). For example, age-dependent macular degeneration (Edwards et al., 2005), which is the most common eye-related disease, is caused by a few common genetic variations with a large effect. However, although it has been found that more genetic variations associated with many other diseases, such as Crohn's disease, only some of these cases can be explained by these genetic variations (Barrett et al. 2008). Another example is research that found that at least 40 SNP loci were related to human height (heritability of about 80%) through studying thousands of subjects; however, these SNP loci only explained about 5% of the variations in height phenotype (Gudbjartsson et al., 2008). Thus, the most common genetic variations may slightly increase the occurrence risk of disease by single or combined action; however, these variations can only explain the phenotypic variation caused by inheritance in part of populations.

With the constant advance of contemporary genetics, genomics and medical research, the understanding of gene functions have also increased. After the initial completion

of the Human Genome Project, the GWAS strategy started a new prologue of investigation and within a few years discovered many previously unknown loci and chromosomal regions associated with phenotypes or diseases, which have provided more clues to understand the molecular pathogenesis of complex human diseases.

1.6.14 GWAS Studies

As early as 2011, Japanese researchers had already found that the expression of *sirtuin 1* (*SIRT1),* and *sirtuin 2 (SIRT2)* decreased within the peripheral blood leukocytes of severe depression and bipolar depression patients. That study suggested that the expression level of *SIRT1* in peripheral blood could be used as a kind of index to screen depression (Abe et al., 2011). Jonathan Flint cooperated with the psychiatrist Kenneth Kendler (Cai et al., 2015) from the Virginia Commonwealth University to collect samples from depression patients in China, where there is a relatively high occurrence of depression. To reduce confounding, they narrowed the scope of their research to include only female patients with severe depression and Chinese Han nationality. In 2014, Flint, Kendler and their team (Cai et al., 2015) completed an analysis of the DNA sequences of 5,303 depressed and 5,337 control Han Chinese women. Their results indicated two depression-related variation sites located on chromosome 10. One mutation located near *SIRT1*, which is an essential protease inside the mitochondria (Cai et al., 2015), and the another variation was located in an intron of the phospholysine phosphohistidine inorganic pyrophosphate phosphatase (*LHPP)* gene, which encoded a kind of protease whose function is not currently entirely understood. These associations were replicated using data from another 3,000 depressed patients and 3,000 control subjects of Han Chinese descent. In another study, a variant within the intron of the *LHPP* gene has also been suggested to be associated with the aetiology of MDD by using QTL (Quantitative

trait locus)-specific association analysis of 1221 Mexican–American individuals (Knowles et al., 2016). In early 2016, Hyde's team identified 15 genetic loci associated with the risk of depression by studying the self-reported data of a European descent cohort (Hyde et al., 2016). The variants of another two genes- the RAR related orphan receptor A (*RORA*) gene, involved in circadian rhythm, and the glutamate metabotropic receptor type 8 (*GRM8*) gene also showed strong association with depression trait by meta-analysis (Terracciano et al., 2010).

1.6.15 Summary

As it can be seen from the studies mentioned above, there is still a lack of consistent and clear conclusions regarding the specific role of the central relevant genes associated with depression in its pathogenetic process. Also, the replication rate of positive results has not been high. The reasons for these results may include the following. Firstly, depression is a type of complex disorder that results from genetic, physiological and psychological factors. Also, its genetic patterns do not match Mendelian genetics. Instead, it may be subject to the control of multiple susceptibility genes, in which one or a few genetic variations can cause similar clinical symptoms. The interaction between multiple genes exists, yet the role of each gene is relatively small. Secondly, depression has genetic heterogeneity, and patients from different regions, races and ethnicities have different genetic backgrounds; therefore, the gene that triggers depression may differ in different ethnicities/regions.

Again, depression is a mental illness with complex and diverse symptoms. Currently, its diagnosis depends largely on clinical presentation and psychiatric examination, with a lack of effective biological quantitative indicators. Also, some characteristics of the enrolled subjects—such as the discordance in age, the severity of illness and

family history—may have caused statistical confounding that reduced the reliability of the results.

Therefore, future research should focus on multi-gene research and ensure the homogeneity of enrolled cohort. For example, more family genetic studies could be conducted to exclude the inconsistency of the genetic background and avoid false negatives and the stratification phenomenon of group structure (Mynett-Johnson et al., 2000). If conditions permit, the combined research of large sample and multiple centres should be undertaken. Improving the reliability of the inclusion criteria by using the latest methods of assessments, such as functional magnetic resonance imaging, to conduct disease diagnosis on blood flow in the cerebral cortex and the change of metabolic rate (Mildner et al., 2005) could be very helpful.

1.7 Overview of Pharmacogenetics

Pharmacogenetics originated in the late nineteenth and early twentieth centuries. British physician Archibald Garrod first discovered and proposed that drug reactions have ‘innate decisive' (Löwy and Gaudillière, 2001). In the 1950s and 1960s, three milestone experiments confirmed this theory. In 1956, Carson discovered that haemolysis induced after using primaquine due to the genetic defects of erythrocyte glucose-6-phosphate dehydrogenase (G6PD). In 1957, Kalow confirmed that succinylcholine resulted in apnea was closely associated with the genetic defects of serum cholinesterase. In 1960, Evans reported that genetic differences affect the metabolic rate of isoniazid. In 1959, Motulsky and Vogel officially presented genetic pharmacology as a branch of pharmacology and named it as "pharmacogenetics" for the first time. Since then, pharmacogenetics has become an independent discipline (Motulsky, 1978). The term ‘pharmacogenetics' is a combination of ‘pharmaco' and

‘genetics.' The broad definition of pharmacogenetics is a discipline that studies any living species' abnormal response to exogenous substances due to natural genetic variations. The narrow definition is the research field that investigates how genetic variation affects drug response (Kalow, 1967, Meyer, 2000, Nebert, 1999) (Figure 8). Modern medical research has indicated that certain subpopulations suffer from a high incidence of severe side effects or treatment failures due to their significantly different genetic backgrounds. This is important because different drug responses induced by genetic variations may lead to increased pain, death or medical costs (Bernard et al., 2006). Until present, at least 10 drugs have been withdrawal from the market due to the sides effects induced by gene variants (Figure 9). Through the study of pharmacogenetics, it will be possible to use contemporary technology to predict medication response in advance and to eventually provide patients with a safer, and more efficient and economical drug regime. Additionally, it is well known that new drug development is a time-consuming process that costs an enormous amount of resources (Figure 10), therefore, pharmacogenetics studies also provides the fundamental theory to save costs on the development of a novel effective drugMultiple reports have revealed differences in the efficacy of personalised medicine and sped up the rapid development of pharmacogenetics in the past years. The ever-changing technology of genetic testing—especially the completion of the Human Genome Project—has had a huge effect on the clinical medicine model. After undergoing experience-based medicine and evidence-based medicine, the clinical medicine model is now progressing into a new stage: personalised medicine, which is guided by pharmacogenetics. Pharmacogenetics is focused on extensive research, including the understanding that different patients have ethnic and regional variations in drug metabolism enzymes, drug transport capacity, and drug sensitivity (Mancinelli et al.,

2000). Among these topics, most research has focused on how genetic factors influence drug metabolism and drug response. Pharmacogenetics accordingly aims to determine specific proteins or common/rare polymorphisms that have functional significance and play a vital role in individual drug response. It also seeks to investigate the genetics and molecular biology of epidemiological, family, patient, and population studies through *in vitro*, *in vivo* and computer models. Regarding this procedure, pharmacogenetics clarifies the role of genetics in individual differences regarding drug response and adverse effects occurrence. Such an emphasis will ultimately lead to the selection of appropriate drugs and suitable dosages and may even prevent the occurrence of illnesses according to each patient's particular metabolism, elimination, and reaction. Finally, this methodology may achieve truly individualised treatment. The rapid development of contemporary science and technology has accelerated the progress of pharmacogenetics and personalised medicine. At present, researchers can identify drug response-related genes through clinical observation, genotyping and genetic analyses. They can also screen drugs and adjust their dosages to improve therapeutic effects after detecting drug response-related genes. Drug reactions can be affected by many factors; however, the genetic factor is a relatively stable determinant in human lives. Thus, if the relationship between unusual drug reactions and all kinds of genotype clusters is clear, following the pharmacogenetic information so as to choose safer and efficient drugs with the precise dosage for each may be possible (Mancinelli et al., 2000). At present, pharmacogenetic studies have shown high potential for psychotic drugs, anti-epileptics, anti-hypertensives, hypoglycemic agents, rheumatism drugs, and antineoplastic drugs, among others. However, a certain gap remains for achieving truly clinical medication guided by pharmacogenetics. Until now, published

pharmacogenetic studies have mainly focused on a single gene or single drug metabolic pathway-related gene; thus, the practical usability of their results needs to be strengthened. The genetic difference in drug metabolism can regulate by a series of proteins and enzymes involved in the drug metabolic pathway, and these are likely to affect drug efficacy and safety. Therefore, determining the clinical value of using the combined detection of multiple gene targets by screening candidate genes or genomes with gene chips could significantly improve the prediction accuracy and clinical utility of drug efficacy. Drug reaction is a complex process affected by multiple factors *in vivo* and *in vitro*. In addition to differences in pharmacological action resulting from gene mutation, the mutual induction between different drugs may also influence the process of drug tolerance, efficacy, and elimination. Moreover, the environment, age and pathophysiology of the patient are important factors to ensure a holistic explanation and prediction of drug safety and effects. National drug research institutions and relevant state departments have given high priority to the development of pharmacogenetics. The US Food and Drug Administration (FDA) has encouraged pharmaceutical companies to provide pharmacogenetic evidence when developing new drugs. Also, US and Japanese pharmaceutical companies may be required to retain genetic information of all specimens during the process of new drug development to track genetic variations if any severe adverse drug reactions occur (Mancinelli et al., 2000).

Multiple international organisation–based pharmacogenetic studies have been published in recent years. Moreover, those institutions have developed and established bioinformatics resources, and provided an excellent foundation for multi-disciplinary and multi-research centre collaboration, which have significantly promoted the development of pharmacogenetics. In summary, through

pharmacogenetic studies, it is hoped that it will be possible to not only select the most appropriate drug for a given patient through genetic testing but also determine the safest and most efficient dose to reduce possible adverse effects. The application of pharmacogenetics in the field of drug development can also help screen the most useful indication and most suitable patients of a certain drug to improve the therapeutic effect. It will even be possible to maximise the rationalisation of treatment by developing related drugs that act on the genetic material and specific genotypes.

1.8 Antidepressant Pharmacogenetics

The gene associates with antidepressant treatment response and side effects are essential for the adoption of personalised medicine. In the past years, antidepressant pharmacogenetic studies have identified genetic variants of cytochrome P450 (CYP) (Zackrisson et al., 2009, David et al., 2007, Suzuki et al., 2006), P-glycoprotein (Kato et al., 2008, Uhr et al., 2008), *TPH1* and *TPH2* (Tsai et al., 2009b, Tzvetkov et al., 2008, Serretti et al., 2001b, Serretti et al., 2001a), *COMT* (Tsai et al., 2009a, Arias et al., 2006, Baune et al., 2008), *MAOA* (Tzeng et al., 2009, Domschke et al., 2008, Younger et al., 2005), *5-HT$_{1A}$* (Lemonde et al., 2003, Kato et al., 2009), *5-HT$_{2A}$* (Minov et al., 2001, Choi et al., 2005), *β1* adrenoceptor (Crowley et al., 2006) *et al.* are associated with antidepressant treatment response. Below I have focused on the 5-HTTLPR polymorphism in the *SLC6A4* gene.

1.8.1 Pharmacogenetics of Response to SSRI Antidepressants

The transcription of the *SLC6A4* gene could be affected by 5-HTTLPR, thereby affecting the concentration of SLC6A4 and 5-HT uptake. Ultimately, drug efficacy depends on the combination of drug and receptors. SSRIs have a direct effect on SLC6A4. Since the L allele has high transcription efficiency, it allows for an increase

in the expression of SLC6A4 that combines with SSRIs, which indicates that SSRIs will have a better therapeutic effect. Several studies have already found a relationship between 5-HTTLPR and antidepressant efficacy. Smeraldi, Benedetti, and Zanardi (2002) found that among patients with the genotype S/S, fluvoxamine took effect more slowly than in patients with the genotype S/L or L/L. Previous research has also found that paroxetine takes effect slowly in hospitalised depressed patients who carry the S allele and have no delusional disorder (Benedetti et al., 1998). Similarly, Pollock *et al.* (2000) described that paroxetine takes effect slowly in patients with late-onset depression who carry the genotype S/S. Research by Arias and colleagues indicated that the genotype S/S was poorly associated with citalopram efficacy (Arias et al., 2005). Also, the incidence of poor efficacy of citalopram is three times higher in patients with the S/S genotype than patients with other genotypes (Arias et al., 2005).

The L allele was associated with antidepressant efficacy. Benedetti *et al.* (2004) reported that drugs had a better therapeutic effect on symptoms of sleep loss among genotype L/L patients with depression or bipolar disorder. Yu *et al.* (2002) also reported that depressed genotype L/L patients treated with fluoxetine could achieve a more satisfactory result than S/S genotype patients. Finally, when Pollock *et al.* (2000) treated elderly depressed patients, they found that the HAMD scores of patients with the genotype L/L decreased faster than those with S/L or S/S genotypes during fluoxetine treatment. Also, they had a more rapid response to the drugs. However, this type of result was not observed in nortriptyline treatment.

The efficacy of medications critically depends on the affinity between drugs and SLC6A4—briefly, the effectiveness of the drug is better if the affinity is strong. Rausch *et al.* (2002) showed that the genotype, initial affinity, and steady drug dose

have a significant effect on fluoxetine efficacy. They speculated that L genotype individuals have a high affinity for the drugs, thereby obtaining satisfactory results. In contrast, the results of Nobile *et al.* showed that the polymorphism of *SLC6A4* (L/L, L/S or S/S) have no effect on the combination of paroxetine with blood platelets or the affinity of 5-HT or paroxetine with SLC6A4 (1999).

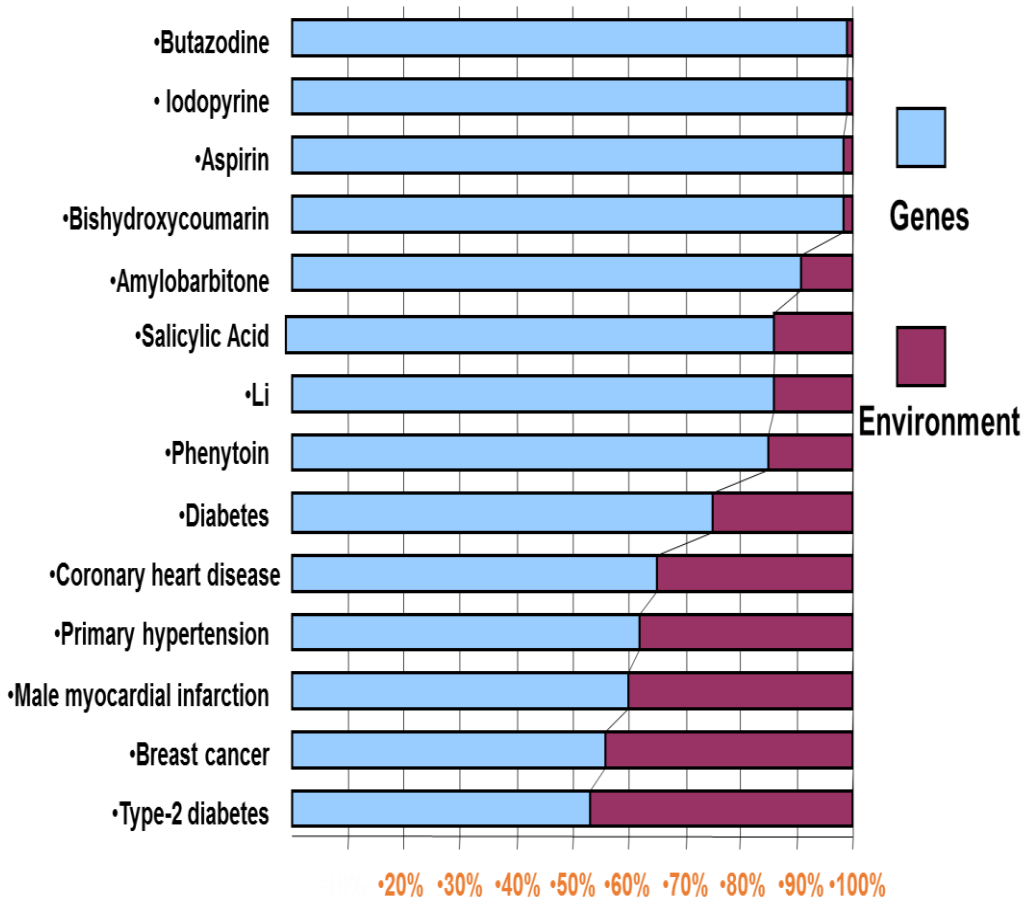


Figure 8: Genetic and non-genetic factors in the role of drug metabolism and susceptibility to disease. [modified from Progress and promise in understanding the genetic basis of common diseases (Price et al., 2015)].

Drugs have been withdrawn from the market	Application	Toxicity	The relevant gene mutation
Alosetron	Bowel syndrome	Ischemic colitis	SLC6A4
Astemizole	Allergic reaction	QT extended	CYP2J2,
Cerivastin	Hyperlipidemia	Rhabdomyolysis	CYP2C8, SLCO1B1
Cisapride	Gastric duodenal reflux	QT extended	SCN5A, KCNQ1
Dexfenfluramine	obesity	Pulmonary arterial hypertension	CYP2D6, BMPR2
Rofecoxib, Vioxx	pain	Cardiovascular toxicity	UDP - glucoside acid transferase: UGT2B7, UGT2B15
Terfenadine	Allergic reaction	QT, Reverse sexual type of ventricular tachycardia	KCNQ1
Dilevalol	hypertension	hepatotoxicity	UGT (2001, UK)
Sertindole	schizophrenia	QT, Reverse sexual type of ventricular tachycardia	KCN (1998, UK)
Terodiline	uracratia	Reverse type of ventricular tachycardia	CYP2C19 (1991, UK)

Figure 9: Drugs withdrawn from the market due to toxicity caused by gene polymorphisms since 1990.

SLC6A4, Solute carrier family 6 member 4; CYP2J2, Cytochrome P450 family 2 subfamily J member 2; CYP2C8, Cytochrome P450 family 2 subfamily C member 8; SLCO1B1, Solute carrier organic anion transporter family member 1B1; SCN5A, Sodium voltage-gated channel alpha subunit 5; KCNQ1, Potassium voltage-gated channel subfamily Q member 1; CYP2D6, Cytochrome P450 family 2 subfamily D member 6; BMPR2, Bone morphogenetic protein receptor type 2; UGT2B7, UDP glucuronosyltransferase family 2 member B7; UGT2B15, UDP glucuronosyltransferase family 2 member B15; UGT, Uridine 5'-diphospho-glucuronosyltransferase; KCN, Potassium channels; CYP2C19, cytochrome P450 family 2 subfamily C member 19 [modified from Recent advances in the pharmacological management of substance use disorders (Sharma and Kar, 2015)].

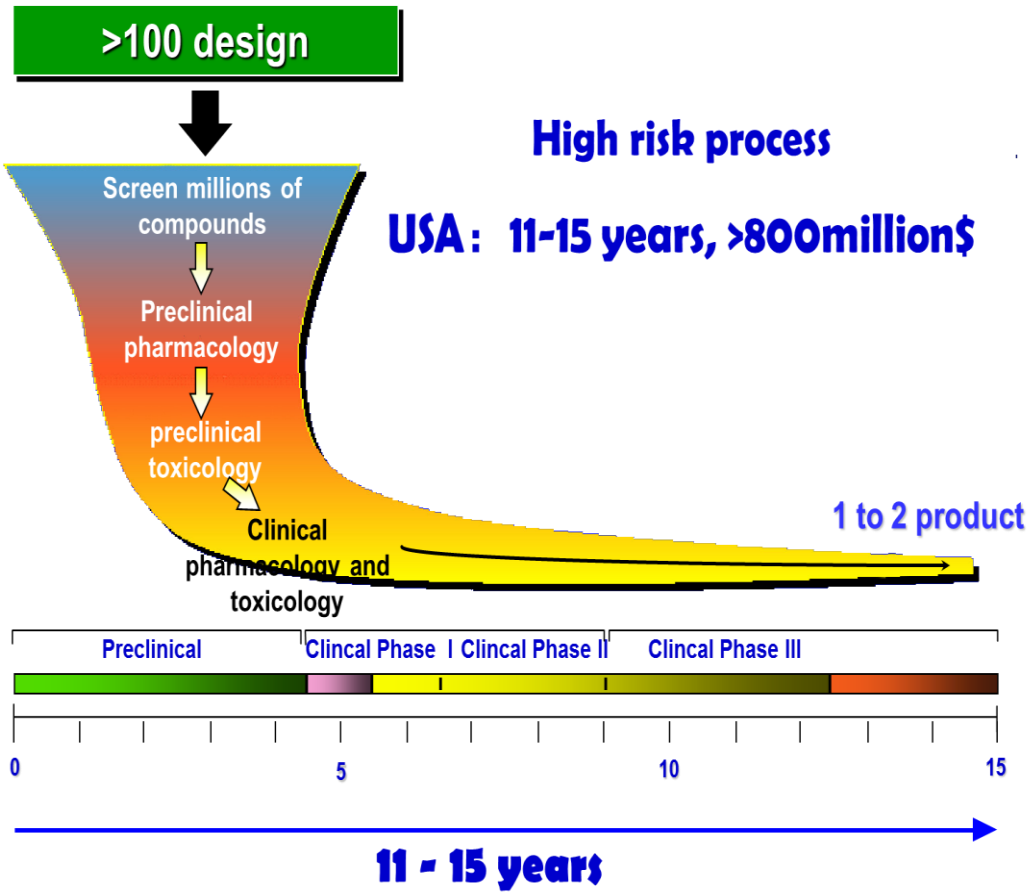


Figure 10: Medical costs to develop a new drug

[modified from Regulatory Explainer: Everything You Need to Know About US Food and Drug Administration (FDA)'s Priority Review Vouchers (Price et al., 2015)].

The presence of the 5-HTTLPR polymorphism in the *SLC6A4* gene results in differences in SLC6A4 binding specificity. Research has found that the genotype L/L is associated with an increase of prolactin secretion. Whale *et al.* (2000) illustrated that healthy women with the genotype L/L had more prolactin secretion when treated with clomipramine.

There are two explanations for this. Firstly, as individuals who have the L/L genotype would have a larger chromosome locus, it is hypothesised that there would be an increase in nerve conduction regulation as a result of the SSRIs. The increased

level of drug-induced prolactin secretion may reflect the degree to which the functions of 5-HT can be strengthened. Secondly, S/S genotype individuals may have little reabsorption of 5-HT. Clomipramine increased extracellular 5-HT so that more 5-HT exerted an effect on the inhibitory 5-HT_{1A} auto-receptor. Therefore, the activation of 5-HT cells was strongly inhibited, which undermined the fact that clomipramine enhanced 5-HT neurotransmission.

As a result, an increase in prolactin secretion caused a low response in S/S genotype individuals. Corresponding with the interpretation of Whale *et al.* (2000), Reist *et al.* (2001) demonstrated that genotype S/S individuals experienced a relatively slow prolactin secretion rate during fenfluramine use. However, there are opposing views regarding whether genotype S/S people are prone to side effects. For example, Perlis *et al.* indicated that genotype S/S individuals treated with paroxetine were prone to side effects, including insomnia and agitation (Perlis et al., 2010). Furthermore, studies have found that an increased prolactin secretion level was associated with drug efficacy. For example, Anderson *et al.* concluded that 5-HT function would be enhanced if clomipramine could cause an increase in prolactin secretion (Anderson and Cowen, 1986). Thus, they believed that the level at which the drugs increased prolactin secretion could reflect the degree to which 5-HT function can be enhanced. Briefly, a drug-induced prolactin secretion increase could lead to satisfactory antidepressant efficacy. The satisfactory antidepressant effectiveness of SSRIs has been positively correlated with increased prolactin caused by fenfluramine (New et al., 1999, Cleare et al., 1998, Siever et al., 1999).

Studies have shown that the S allele is related to the enhancement of the therapeutic effect of SSRIs. Whale *et al.* (Whale et al., 2000) predicted that since the 5-HT function enhancement of the S/ S genotype was blocked due to an excessive

activation of auto-receptors, blocking HTR1A auto-receptors would enhance the role of synaptic terminals. Weizman and Weizman (2000) reported that, regardless of whether the efficacy of SSRIs is improved by pindolol, the L allele corresponds with SSRIs satisfaction and the increased speed of antidepressant efficacy. However, patients who carried the S allele had a rapid onset when the effectiveness of fluoxetine was boosted by pindolol. Moreover, its effectiveness was similar to that of L homozygous patients who were treated with SSRIs. Indeed, the S allele was associated with accelerated SSRI efficacy. However, Smeraldi, Benedetti, and Zanardi (2002) had a different opinion—they found that the efficiency of all genotypes was similar when treated with a combination of citalopram and pindolol.

The S or L allele also affected the efficacy of SSRIs in treating other mental disorders. Studies on obsessive compulsive disorder (OCD) found that affected individuals who inherited the L allele from heterozygous parents and were treated with SSRIs had 3.33 times higher measurements compared to those who inherited the S allele from heterozygous parents (McDougle et al., 1998). This suggests that SSRI effectiveness is decreased in L allele patients compared to S allele patients. However, another OCD study found that the 5-HTTLPR genotype showed no difference in SSRIs treatment effectiveness between 57 patients with good efficacy and 21 patientswho had poor treatment efficacy (Billett et al., 1997). Furthermore, although the research of Di Bella *et al*. (2002) reported that this genotype made no statistically significant difference in efficacy, out of the 156 OCD patients in the study, the females who had a poor treatment efficacy lacked the S/S genotype, which implies that their results may have some bias.

The above findings suggest that 5-HTTLPR influences efficacy of SSRIs and their side effects. These outcomes may also affect which drug should be used to strengthen efficiency.

SSRIs have been widely used to treat depression, obsessive-compulsive disorder, and other compulsive disorders. The effectiveness of SSRIs may be different among individuals. In the past, the research found that the reasons for this difference were mainly at the pharmacokinetic level. However, in recent years, with the development of genetics and pharmacology, researchers have turned from pharmacokinetics ("the study of the time-course of drug absorption, distribution, metabolism and excretion") to pharmacodynamics ("the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of their actions and effects with their chemical structure")(Tozer and Rowland, 2006, Rowland and Tozer, 1995, Glass et al., 1999). Understanding the differences between individuals with the 5-HTTLPR polymorphism in the SCL6A4 gene was a hot topic in the early 2000's. As stated above, the S allele is associated with poor antidepressant efficacy while the L genotype is linked with satisfactory antidepressant efficacy. The L genotype was strongly linked to drug receptor binding strength. Studies focused on the polymorphism of the *SLC6A4* gene are continuing, yet most research on both 5-HTTLPR polymorphism and SSRI efficacy has focused on Western populations. Although research began to examine the relevance of 5-HTTLRP polymorphisms, depression, and antidepressant treatment effect many years ago, consistent results have not always been achieved; thus, the debate continues as research progresses. However, overall, the genetic mechanism regarding the efficacy difference of SSRIs offers a path for individualised depression treatment.

1.8.2 Summary

Although antidepressants have good efficiency, one-third of patients still experience poor outcomes (Henter et al., 2016). Many factors affecting drugs' therapeutic effect have been studied, yet there remain difficulties in determining which factors influence antidepressant efficacy. Many factors influence the effects of drug treatment. Rausch *et al.* (Rausch et al., 2002) suggested that fundamental differences in drug binding sites might determine differences in antidepressant efficacy. *SLC6A4* is believed to be involved in human emotion regulation and SSRI action. Relevant conditions that affect SLC6A4 initial transport capacity include the original receptor affinity (Km), number of receptors and the genotype of proteins that regulate mood and drug efficacy can affect SSRIs treatment efficiency. The polymorphism of the *SLC6A4* promoter region plays a significant role in regulating its transport capacity. Therefore, it is reasonable to assume that 5-HTTLPR is likely to affect the SSRI efficacy.

Besides, a possible reason is that 5-HT concentrations in the extracellular synaptic gap will increase over SSRI treatment course. Moreover, 5-HTTLPR has a feedback regulation mechanism that involves dynamic 5-HT changes as L alleles make this system more sensitive and efficient. Therefore, in the process of SSRI drug treatment, patients with the L allele will attain better therapeutic effect (Glatz et al., 2003). Other studies have supported this conclusion (Hu et al., 2006, Seeger et al., 2001, Benedetti et al., 1998, ISHIGURO et al., 1997, Fumeron et al., 2002). Current drug treatment for depression is empirical and lacks individualised drug treatment. As such, patients may be switched to different drugs after four to six weeks of ineffective treatment, which delays the symptom relief. Thus, the above conclusion is important both to better understand the efficacy of antidepressant therapy and to seek individualised regimens for antidepressant treatment.

1.9 Animal Models of Depression

In many areas of medical research, human experimental research is largely limited by ethics, science and technology conditions. Thus, research using animal models has been widely employed and developed. Currently, more than 20 different types of animal models are used to study depression (Table 1). According to various modelling approaches, these animal models can be divided into stress, transgenic, neural biochemical function change and isolation animal models. Stress-induced depression animal models are the most commonly used experimental model, which is further divided into a variety of types, such as the chronic unpredictable mild stress (CUMS), chronic mild stress (CMS) depression, learned helpless depression and behavioural despair depression models (Krishnan and Nestler, 2011). Many scholars believe that the ideal CMS animal model should have the following characteristics (Redei et al., 2001). Firstly, it should have behavioural simulations—namely, consistency between the animal model and the disease symptom to be studied. Secondly, it should have a reasonable theory basis—that is, a clear link between the modelling approach and the causes of disease to be studied. Thirdly, the pathophysiology changes inside the chronic stress animal model should have some similarities with the disease to be considered. Fourth, the corresponding drug therapy should be effective, while behaviour changes caused by animal models must last long enough to satisfy the long-term use of the drugs.

Predictive validity, face validity, and constructs validity are three criteria to evaluate a successful animal model of depression (Willner and Mitchell, 2002, Krishnan and Nestler, 2011). Predictive validity requires any manipulations to reflect the same pathological state in the animal models. Face validity guarantees that a similar phenomenon is present in the animal model and diseased modelled. Also, the animal

model needs to demonstrate theoretical rationale (Willner and Mitchell, 2002). The depressive-like behaviour rat model used in this study showed good predictive validity, face validity, and constructed validity during the procedure (Willner, 1997). Therefore, after it was established, this depressive-like behaviour animal model could be used to address many problems that other models have found difficult to address.

Since the CUMS or CMS essentially meet the above requirements, chronic stress depression models have been widely used to study depression behaviour, neurobiology and psychopharmacology evaluation as CUMS or CMS have advantages over other animal depression models (Redei et al., 2001). The CUMS animal model was developed by Willner *et al.* (Willner et al., 1987) based on Katz's (Katz and Sibel, 1982) modelling methods. Two changes have been made to Katz's modelling methods. First, the stimulation intensity of stress factors was significantly reduced. Second, anhedonia detection (the core symptom of depression) was used as a key element to evaluate the modelling success. Its theory based on the notion that the occurrence and development of human depression are associated with chronic and low-level stimulation, while the core symptom of depression is anhedonia. Also, this model simulated many symptoms of depression, such as decreased exercise capacity, social communication and exploratory behaviour. The abnormal behaviours mediated by chronic stimulation can be maintained for a few months. Long-term treatment with antidepressants can reverse this abnormal behaviour. Although animal models have these advantages, they also have some shortcomings, such as a heavy workload, long experimental duration, and poor stability.

J.S. Richardson's (Richardson, 1991) review of animal models of depression indicated that young animals that were submitted to infancy maternal separation

presented a status of despair after a few months, and noted increased prostration time. Also, those young, isolated animals showed reducing the exploration and staying alone time. Rats submitted to infancy maternal separation have significantly decreased total distance, central distance, rearing counts and mean velocity in the open field test and decreased sucrose preference (SPT) when compared to controls rats (Shu et al., 2015).

In the current project, a depressive-like behaviour rat model induced by chronic restraint stress (CRS) was used. In this CRS model, rats were restrained in flat-bottom clear acrylic containers for a stress session of six hours each day for 14 consecutive days. This restraint model of six hours per day was based on the previously published work of Pham *et al.* (2003), where he used two different restraint paradigms (six hours of daily restraint for three weeks and six weeks) to elicit decreased hippocampal neurogenesis (Pham et al., 2003). The outcome of his model is associated with reduced hippocampal volume observed in depressed patients (Fuchs et al., 2004, Sheline et al., 1999). Therefore, the current study used a refined Pham's experimental paradigm by performing six hours of daily stress for two weeks. Thus, this study used the CRS model to induce depressive-like behaviour in rats to understand the interactions between stress, and genes potentially implicated in MDD diagnosis or antidepressant treatment remission and methylation changes in the rat hippocampus.

1.9.1 Sucrose Preference Test (SPT) and Anhedonia

Due to the variety of clinical manifestations of depression, it is hard to choose an experimental animal that mimics all symptoms of depression. However, anhedonia is a subjective symptom, and ways to successfully simulate social anhedonia in an animal model is a key point for successful depression research. CMS-induced

depression is a sophisticated model that has been widely used in basic research of depression (Nestler et al., 2002) and pharmacological research of antidepressants.

Many studies have shown that the CMS model of depression in rodents can better simulate some of the major symptoms of depression, and the use of the SPT to evaluate rodents' reward response has been widely accepted (Forbes et al., 1996, Gronli et al., 2005, Willner et al., 1987). Rodents are sensitive to sweet solutions (commonly sucrose). Therefore, a sweet solution is a sufficient reward for them. Regarding this, the total amount of sweet solution consumed and the percentage of sucrose consumed are used to evaluate the degree of anhedonia. Most scholars believe that stress can reduce the consumption of sucrose solution and sucrose preference; thus, sucrose preference reduction is the core symptom of a depression rat model (Forbes et al., 1996). CMS can induce anhedonia in rodents, as measured by the SPT. Specifically stressed rodents significantly reduce their preference for sucrose solution, compared with the non-stressed animals. This change is a critical indicator to evaluate the success of the depressive-like behaviour model.

1.9.2 Behaviour Despair Forced Swim Test (FST)

The FST was first applied by Porsolt, Le Pichon and Jalfre (Porsolt et al., 1977) in 1977 to screen antidepressants, and became a useful animal model to evaluate the efficacy of antidepressants. This experimental method is a type of behavioural despair method. The fundamental principle is that when a rat or a mouse is placed in a limited space filled with water to force them to swim, they try to escape at the beginning and then quickly turn to a floating state (do not move), in which it only expose their nostrils outside the water surface in order to keep breathing. During this floating period, their limbs occasionally paddle to maintain its body balanced to avoid sinking. This state is called behavioural despair, in which the animal abandons

the hope of escaping. It is believed that this behavioural despair (rat or mice immobility during forced swimming) is similar to human depressive symptoms (Dar and Khatoon, 2000, Takeda et al., 2002). Clinically effective antidepressant treatment can shorten the rat or mouse immobility time, while the drug that induces depression in rodent will increase their immobility time (Porsolt et al., 1977).

The standard FST is performed over two days. On the first day, a rat or mouse is forced to swim in ~ 25℃ deep water for 15 minutes. After drying, they are returned to the home cage. The next day, the rodent is forced to swim under the same conditions for five minutes, and the immobility time is recorded. The water temperature, water depth, animal and season are four factors that can affect experiment results. Kitada *et al*. (Kitada et al., 1981) illustrated that a water temperature below 20℃ would shorten the duration of immobility. Therefore, the water temperature is controlled between 25 to 30℃. Usually, the water depth for rats is 17 to 33 cm, and for mice is about 10 cm. If the water is too deep, it is difficult for rodents to maintain a floating state by using their forepaws and tails. Therefore, they will be swimming and climbing. In contrast, if the water is too shallow, rodents can balance their bodies easily, which will affect the results. Also, different strains of animals have varied sensitivities to antidepressants. For example, Wistar-Kyoto rats are more likely to remain immobile during FST compared to other strains (Marti and Armario, 1996). Finally, FST results are also affected by season. The immobility time of animals is extended in winter and shortened in summer (Abel, 1995). However, during the same day the FST result is the same at any hour of the day it is tested.

Table 1: Animal models of depression.

Stress model types	Stress models	Rationale	Advantage	Disadvantage
Adult stress models	Learned helplessness (LH)	animals develop deficits in escape, cognitive and rewarded behaviors when subjected to repeated unavoidable and uncontrollable shocks	Replicated	Requires very strong stressors to induce the behavioral phenotypes
	Chronic mild stress(CMS)	long lasting changes of behavioural, neurochemical, neuroimmune, and neuroendocrinological variables resembling reward functions including decreased intracranial self-stimulation, reflecting anhedonia that is reversed by chronic but not acute antidepressant treatment	Good predictive validity Good face validity Good construct validity	Practical difficulty (labor intensive, space long duration. Besides, difficult to be established and data can be hardly replicated)
	Social defeat stress(SDS)	The consequent behaviour changes in the subject caused by SDS, like decreased social interaction or lacking of interesting, are similar to some parts of human depression, and behavioural treatment and antidepressants can reverse these changes in SDS model	Good predictive validity Good face validity Good construct validity	Long duration
Early life stress models	Maternal deprivation	increased anxiety and depression-like behaviours and increased HPA response in adulthood		
Other models	Olfactory bulbectomy	disruption of the limbic-hypothalamic axis with the consequence of behavioural, neurochemical, neuroendocrine and neuroimmune changes	high predictive validity	
	Psychostimulant withdrawal (amphetamine, cocaine)	Rodents display behavioural changes that are highly similar to some aspects of depression in humans, such as anhedonia, and behaviours opposite to those seen after treatment with antidepressant drugs		
	Genetically engineered mice			
	Forward genetics		Behavioural changes that are highly similar to some aspects of depression in humans, such as anhedonia, and behaviours opposite to those seen after treatment with antidepressant drugs	

Abbreviation: LH, Learned helplessness; CMS, Chronic mild stress; SDS, Social defeat stress; [Reproduced from The validity of animal models of depression (Willner, 1997) and Learned helplessness and animal models of depression (Maier, 1984)].

Detke, Rickels and Lucki (Detke et al., 1995) divided the forced swim test into four phases:

- swimming-animals swim around in the water
- climbing-animal's paws paddling the water and touching the cylinder wall
- diving-animal's entire body sinks under the water
- immobile-animal's limbs floating on the water and the animal does not move, with only the head or nose above water to breathe.

It has been reported that different antidepressants affect different phases of the FST. For example, in rats desipramine and maprotiline (NE reuptake inhibitors) selectively increase climbing behaviour, while fluoxetine (5-HT reuptake inhibitor) selectivity enhances swimming behaviour (Detke et al., 1995). The FST as a despair animal model can effectively screen and assess antidepressant effects. The establishment of the FST meets the animal model requirements by indicating good face validity, construct or etiological validity, and pharmacological validity. Although the FST has many shortcomings, it remains a successful animal model that is widely used in research.

1.10 Hypothesis and Aims

1.10.1 Hypothesis 1 and aim 1: Candidate gene expression is modulated by chronic restraint stress.

Hypothesis 1

Recent studies performed at the South Australian Health and Medical Research Mind & Brain Theme (Wong et al., 2016a) have identified 44 common and rare variants associated with MDD via analysing whole exome genotyping (Illumina® HumanExome BeadChip-12v1_A) data of 196 controls and 203 MDD patients in a

Los Angeles Mexican-American cohort (Wong et al., 2016a). Our lab used an expanded replication strategy that includes the adjacent 30 kb sequence to the SNPs/genes that were significantly associated with MDD in the Mexican-American cohort, and have replicated the *PHF21B* gene in a European-ancestry cohort (499 controls and 473 MDD). Among variations significantly associated with MDD in Mexican-Americans, 19 common SNPs in 18 genes were identified by GWAS analysis and 27 genes were identified by rare variant analysis (using the kernel-based adaptive cluster (KBCA) method) (Wong et al., 2016a) (Table 2). There is currently a limited amount of information regarding the relationship of these genes and MDD; therefore, to understand whether stress changed the gene expression of the above genes in the hippocampus, which is an important brain region to the stress response, we used a rodent chronic restraint stress model, which has already been previously used in both rats and mice in our lab (Mastronardi et al., 2011, Wong et al., 2016b).

Aim 1

To compare mRNA level in the rat hippocampus for the genes of interest (*Phf21b, Arhgap8, Prr5, Trpm2, Cntnap1, Ano8, Homer3, Unc13d* and *Amer2*) between the CRS and the control groups (Chapter 4).

1.10.2 Hypothesis 2 and aim 2: Genes that may be associated with antidepressant remission may be related to stress response.

Hypothesis 2

A previous pharmacogenetic study conducted to compare the effectiveness of different types of antidepressants on first-generation Mexico-American depressed patients has identified several genetic variations that are potentially associated with antidepressants response (Wong et al., 2014b). Analysis of whole-exome genotyping data identified that exm-rs1321744 achieved exome-wide significance for antidepressant remission. Nine other common gene variants were listed amongst the

top variants that could also be related to antidepressants treatment remission. Many of those variations were located in brain methylated DNA immunoprecipitation sequencing sites suggesting that they might be involved in altering neuronal gene expression (Wong et al., 2014b). Therefore, our hypothesis is genetic variations our lab has identified might be associated with gene expression level alteration in the hippocampus in response to stress.

To present day, there is a dearth of studies that consider the relationship between neighbouring genes and MDD. To investigate this hypothesis, the expression levels of neighbouring genes near intergenic SNPs of interest (exm-rs1321744, exm-rs16867321) and the nonsynonymous coding SNP (ANXA10; Table 3) [Neighbouring gene selection (UCSC) APPENDICES: Table 22] were investigated using a depressive-like behaviour rat model. The expression levels of the adjacent genes and nonsynonymous coding SNPs in the rat hippocampus were determined by qPCR. If expression level of any of our candidate genes is altered by stress, our plan is to investigate the change of methylation status in the nearby methylation sites in the same brain region in the future.

Aim 2

To compare the selected neighbouring genes *Tbx18, Nt5e, Snx14, Syncrip, Cwc22, Ube2e3* and the Anxa*10* gene (Table 3) expression levels in the rat hippocampus between chronic restraint stress (CRS) and control (non-CRS) groups (Chapter 5).

1.10.3 Hypothesis 3 and aim 3: PHF21B, ARHGAP8 and PRR5 protein level changes in response to CRS

Hypothesis 3

According to previous findings, *PHF21B,* and its neighbouring genes: *ARHGAP8* and *PRR5* are three genes that potentially confer susceptibility of MDD in a Los Angeles Mexican-American cohort.. The contribution of mRNA's transcription level might affect PHF21B, ARGHAP8 and PRR5 total protein level in the rat hippocampus.

Aim 3

To investigate whether the protein level of PHF21B, ARHGAP8 or PRR5 change in response to CRS or social isolation stress (Chapter 6). Because the association of PHF21B has been replicated in a European ancestry cohort, we have focused on the protein changes of PHF21B, ARHGAP8 and PRR5 to address further assess their relevance to the stress response.

1.10.4 Hypothesis 4 and aim 4: Brain quantitative trait loci (eQTL) analysis

Hypothesis 4

Variants in the genes studied in Aims 1-2 might contribute to changing their respective mRNA level in different brain regions

Aim 4

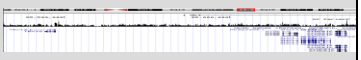
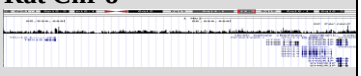
Aim 4 focused on obtaining brain quantitative trait loci (eQTL) analysis primarily in the hippocampus, as ten brain areas have been compiled in the UK Brain Expression Consortium, those areas were also included here. To Therefore, in our studies we investigated whether gene variants of *Tbx18, Nt5e, Snx14, Syncrip, Cwc22, Ube2e3,* Anxa*10, Phf21b, Arhgap8, Prr5, Trpm2, Cntnap1, Ano8, Homer3, Unc13d Cwc22* and *Amer2* significantly change eQTL in brain hippocampus (Chapter 7) and in ten listed brain areas (APPENDICES: table 23~36).

Table 2: Genes of interest that were tested in chronic restraint stress experiments based on recently published findings from our lab.

Target gene name	rs ID	Chr	Position	Major Allele
ARHGAP8-PRR5	rs140395831	22	45,152,408	A
PHF21B	rs1003851 rs117160508 rs118154683 rs75806917 rs8138025 rs5765490 rs62228464	22	44,782,265 45,442,461 45,442,465 45,442,547 45,974,757 45,974,913 45,113,754	
TRPM2	rs142151549	21	45,860,766	T
ANO8	rs143696449	18	17,435,651	G
AMER2 (FAM123A)		16	25,742,672	
CNTNAP1	rs142029931	17	40,843,980	G
HOMER3	rs200520741	19	19,042,434	C
UNC13D	rs150952348	17	73,824,159	T

Abbreviations: rs, reference SNP; Chr, chromosome; *PHF21B*, PHD finger protein 21B; *ARHGAP8*, Rho GTPase activating protein 8; *PRR5*, Proline rich 5; *TRPM2*, Transient receptor potential cation channel subfamily M member 2; ANO8, Anoctamin 8; *CNTNAP1*, Contactin associated protein 1; *HOMER3*, Homer scaffolding protein 3;*UNC13D*, Unc-13 homolog D; *AMER2* (*FAM123A*), APC membrane recruitment protein 2 (Wong et al., 2016a).

Table 3: Single nucleotide polymorphisms (SNPs) and their neighbouring genes selected from our lab's pharmacogenetic work (UCSC neighbouring gene selection figure: APPENDICES table 22).

SNPS	rs ID	Position	Major Allele	Ref/Alt Allele	Neighbouring gene	Neighbouring gene selection (UCSC)
exm-rs1321744[a,b] Intergenic	rs132174 4	Chr6: 85,891,744	C	T/C	*TBX18/ Tbx18* *NT5E/ Nt5e* *SNX14/ Snx14* *SYNCRIP/ Syncrip*	Human Chr 6  Rat Chr 8 
exm-rs16867321[b] Intergenic	rs16867321	Chr2: 181,362,379	C	C/T	*CWC22/ Cwc22* *UBE2E3/Ube2e3*	Human chr2  Rat Chr 3 
exm433050[$] (Coding Nonsynonymous)	rs683699 4	Chr4: 169,083,694	A	A/C	*ANXA10/Anxa10*	Human Chr 4  Rat Chr 16 

Abbreviations: Chr, chromosome; rs, reference SNP; Ref, reference; alt, alternate; USCS, University of California Santa Cruz; *TBX18/Tbx18*, human/rat T-box 18 gene; *NT5E/Nt5e*, human/rat 5'-nucleotidase ecto gene; *SNX14/Snx14*, human/rat Sorting nexin 14; *SYNCRIP/Syncrip*, human/rat synaptotagmin binding cytoplasmic RNA interacting protein; *CWC22/Cwc22*, human/rat CWC22 spliceosome associated protein homolog; *UBE2E3/Ube2e3*, human/rat ubiquitin conjugating enzyme E2 E3; *ANXA10/Anxa10*, human/rat Annexin A10 (Wong et al., 2014a).

CHAPTER 2:
METHODOLOGY AND MATERIALS

2.1 Animal

Animal procedures were conducted in accordance with the Australian Code for the Care and Use of Animals for Scientific Purposes (8th edition, 2013) and local regulations, and were approved by the Animal Ethics Committees at Flinders University and the South Australian Health and Medical Research Institute (SAHMRI). Sexually mature male Sprague-Dawley rats (weight between 150-200 g, aged six weeks) were imported from Animal Resources Centre Charles River (UK) or bred in house by SAHMRI Bioresources. All rats were housed in Green Line IVC Sealsafe PLUS cages (Tecniplast, Varese, Italy) under standard conditions. Lights were on from 7:00 am to 7:00 pm, and cage temperature was 22 $\pm$ 1°C, in a stress-free and specific pathogen-free environment with assess to water and standard regular chow *ad libitum* 24 hours a day.

2.2 Chronic restraint stress (CRS) model (Figure 11)

All rats were allowed to habituate for one week before the onset of experiment. After behavioural baseline tests, rats were randomly assigned CRS and non-CRS groups. Experiment 1 (Exp1) animals were imported from the UK, and were used to examine only one gene (*Phf21b*), as we determined that some of these animals displayed depressive-like behaviour at baseline. All other genes of interest were assessed with animals from Experiment 2 (Exp2). In. Exp1: rats were assigned to 2 groups: CRS, (n=27) and control group which were single-housed (n=10). In Exp2 rats were assigned to 3 groups: CRS, (n=15), Control 1 (single-housed without CRS, n=10) and Control 2 (group-housed without CRS, n=16). The CRS groups, rats were restrained in rodent restrainers, 3.25"x8", flat bottom (Catalog # PLAS544-RR； LabGear；Lansing, MI, USA; Figure 11) for a daily stress session of 6 hours (between 9：00 am to 16:00 pm) for 14 consecutive days. After each daily stress

session, rats were unrestrained and returned their home cages. The CRS and non-CRS control groups were submitted to the same behavioural testing schedule.

Figure 11: Animal restrained using a 3.25"x 8" flat bottom rodent restrainer.

2.3 Forced swim test (FST, Figure 12)

All rats were habituated to the test room 60 min before the test and FST was performed between 9:00 am to 12:00 pm using the EthoVision XT video tracking system (Noldus Information Technology). A training session was conducted 24 hours before the FST. During the training session, rats were allowed to swim for 10 min. Two rats were tested at the same time in separate glass cylinders (45 cm height and 30 cm diameter), and a blackboard was set between two cylinders to avoid that rats interfered with each other. The water depth was 30 cm to avoid that the rat tail reach the cylinder's floor. Water was autoclaved one day before the test and maintained at room temperature. FST was conducted for 5 min, and the EthoVision XT video tracking software automatically measured and collected activity data (highly mobile/struggling: >18.5% of distance moved; mobile/swimming: <18.5% and >12.5% of distance moved; immobile/floating: <12% of distance moved) (Figure

13). After the test, rats were dried and placed in a 30 °C Thermacage (Bio Services BV; Uden; Netherlands) for approximately 10 to 15 min. FST was performed at baseline and after two weeks of CRS.

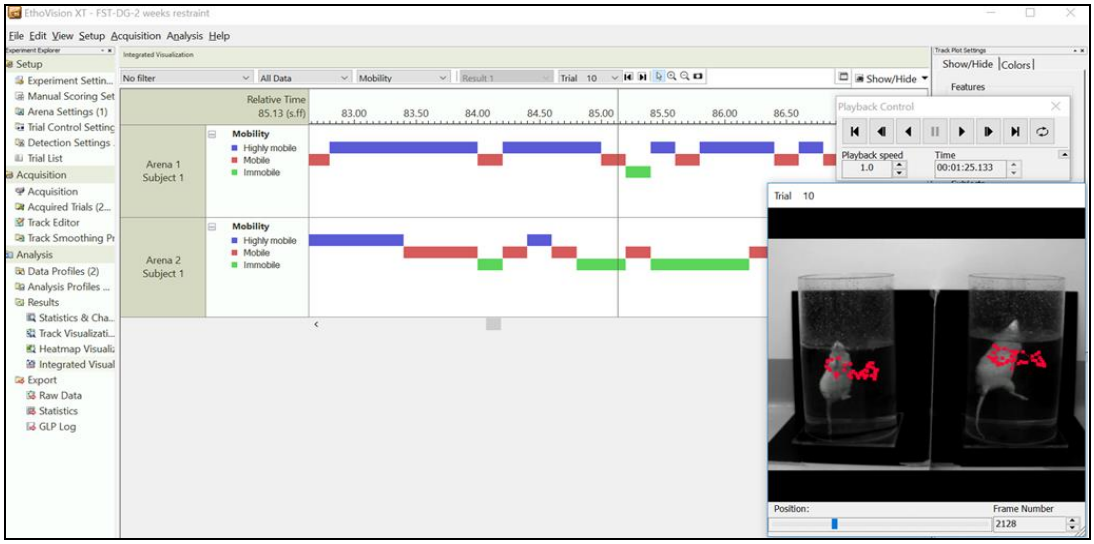


Figure 12: Forced swim test [EthoVision, Noldus Information Technology, Wageningen, The Netherlands].

2.4 Sucrose preference test (SPT)

No previous food or water deprivation was performed prior to SPT. Before the SPT, rats were given four days training to decrease the variability in sucrose consumption during the SPT. For the first and second day of training, rats were given two bottles of 2% sucrose water. In the third-day animals were allowed to freely choose to drink from two bottles, one containing either 2% sucrose solution and the other one containing autoclaved tap water. The position of those two bottles was switched on the fourth day to minimise side preferences. After a 4-day training period, rats were given 24 hours (from 4:00 pm to 4:00 pm) of free choice between two bottles, one with sucrose solution (1%) and another with autoclaved tap water. The test started 3 hours before the active phase cycle of rats, and in order to avoid the effects of side preference in drinking behaviour, the position of the bottles was switched twice in 24

hours. To decrease liquid leakage during the SPT, bottles were filled and kept at room temperature in the up-side-down position for at least 24 hours before testing.

2.5 Animal tissue collection

Rats were allowed to rest for at least five days after the last behavioural test (FST) was performed before they were euthanized with a guillotine between 10:00 AM to 12:00 PM in order to avoid the confounding effects of circadian rhythms. After being removed from the skull, the whole brain was submerged in RNAlater solution (25mM Na citrate; 10mM EDTA; 5.3M ammonium sulfate; pH=5.2) and stored at 4℃ for at least 48 hours. Our pre-test experiment conducted on difference rat and mice tissues confirmed the RNAlater treated samples can be stored at room temperature (25ºC) for up to one week, at 4ºC for up to one month. Intact protein can be recovered from RNAlater stabilised samples for use in downstream applications such as Western blotting or 2D gel analysis. After being removed from the skull, the whole brain was submerged in RNAlater solution and stored at 4℃ for at least 48 hours. Brains then were dissected on a cold plastic surface after being removed from the RNAlater solution. Whole hippocampus dissection was performed following protocols described by Spijker S (Spijker, 2011) and then stored at -80℃.

2.6 Two-step Real-time PCR (qPCR) SYBR Green assay to determine gene expression

The final goal of the gene expression detection technology is to determine the absolute RNA expression quantity of any tissue or cell line, and in order to achieve this, real-time PCR was performed to quantify a small amount of PCR products. The basic principle of real-time PCR is built on the detection of the fluorescence produced by a reporter molecule which increases, as the reaction proceeds. Two common methods are generally used to detect the PCR products in real-time PCR: (1)

non-specific fluorescent dyes that intercalate with any double-stranded DNA; (2) sequence-specific DNA probes labelled with a fluorescent reporter which could only be detected only after hybridization of the probe with its complementary sequence (Dorak, 2007). However, the relationship between the amount of a particular gene expression with its respective hybridised signal strength is complex and depends on many factors including labelling method, hybridization conditions, and the sequence of the gene of interest. The most important feature of gene expression is to understand the expression differences between samples (including temporal expression and spatial characteristics). There are several other ways to detect gene expression. With the progress of macromolecular separation technology, it became possible to identify and isolate specific gene products or proteins. With the use of recombinant DNA technology, it is now possible to detect and analyse any gene transcript products. There are several methods widely used to study specific RNA molecules, for example, *in situ* hybridization, Northern blot, S - 1 nucleic acid enzyme analysis and Protective RNA enzymes. In this thesis, we used the real-time PCR method to detect gene expression level.

2.6.1 Total RNA isolation

Total RNA from the rat hippocampus was extracted using a PureLink® RNA Mini Kit (Catalog # 12183018A; Life technologies; Mulgrave, VIC, Australia), and DNase digestion was performed to remove genomic DNA using the Purelink DNase set (Catalog #12185010; Life Technologies; Mulgrave, VIC, Australia). The extraction process was done in accordance with the manufacturer's instructions. Total RNA was quantified by measuring the absorbance at 260nm (A260) using a NanoDrop™ 2000 spectrophotometer (Thermo Scientific, Scoresby, VIC, Australia) its purity was estimated via the 260/280 absorbance ratio (A260/A280>2.0 for pure RNA) and a

denaturing agarose gel electrophoresis of RNA was performed to confirm that the RNA was not degraded.

2.6.2 cDNA synthesis

For each sample, 500 ng RNA was reverse transcribed using 4 µl of iScript RT supermix (Catalog # 170-8841; BioRad; CA, USA), and H_2O was added so that the total volume was 20 µl. The reaction was incubated for 5 min at 25℃, 20 min at 46℃ and 1 min at 95℃, and the cDNA was stored at -20℃ until use.

2.6.3 Quantitative reverse transcriptase real-time polymerase chain reaction (qPCR)

This technique was developed to determine gene expression level alteration. We used SYBR Green as a DNA-intercalating dye, which binds to the double-strand DNA PCR product. As the reaction cycle progresses the increase in fluorescence is recorded. One of the advantages of this method is that it takes only a few days for primer design and validation (Figure 13).

2.6.3.1 Primer Specificity and PCR efficiency

Primers for the genes of interest (Table 4) were designed using the primer Premier 5 software (Premier Biosoft International, Palo Alto, CA, USA) or the IDT primerQuest tool (Integrated DNA Technologies Pte Ltd, Baulkham Hills, NSW, Australia) (Table 4). Primers were then tested, and PCR efficiency was determined for each primer pair. Serial dilutions of cDNA (1:2; 1:4; 1:8; 1:16; 1:32; 1:64 dilution) were prepared for the standard curve. The qPCR reactions and cycle were set according to the manufacturer's protocol. Standard curves were analysed, and a PCR efficiency of 90%-110% (standard curve slope from -3.6 to -3.1) was accepted. In addition, qPCR primers specificity was determined by two ways: (1) a default melting program was ran on qPCR instruments at the end of the cycling program and

the dissociation curves (first derivatives of the melting curves) contained a single peak with no shoulders; (2) agarose gel revealed a single corresponding band size.

2.6.3.2 Reference/Housekeeping genes selection

Reference genes, also known as housekeeping genes, are frequently used to normalise mRNA levels in qPCR. However, the expression level of these genes may differ between tissues or under certain circumstances. Thus, the selection of stable housekeeping genes is critical for gene expression studies. In our studies, we selected 5 reference genes reported to be stable in the rat hippocampus, namely: Glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*), ribosomal protein S18 (*Rps18*), 18S ribosomal RNA (*Rn18s*), 5S ribosomal RNA (*Rn5s*) and actin beta (*Actb*) (Bonefeld et al., 2008, Roceri et al., 2004, Cruz-Muros et al., 2007, van der Doelen et al., 2014)*;* their gene expression level were tested in all samples after having validated their primer efficiency and specificity. BestKeeper© Software and geNorm were used to select the two most stable reference genes out of the 5 genes tested. BestKeeper© Software calculated two crucial values that evaluate the reference genes stability: standard deviation [SD: ±Ct (threshold cycle)] and coefficient of variation (CV: %Ct) (Mehta et al., 2010). Therefore, SD of Ct values must be as low as possible (Taïhi et al. 2015). In our studies reactions with SD >0.3 were excluded. Then we used GeNorm to determine the stability value (M) of each reference gene. The lowest the M value the most stable the reference gene; thus, reference genes with M values >1.5 were considered as not stable (Taïhi et al. 2015, Vandesompele et al. 2002).

2.6.3.3 Real-Time PCR

Quantitative real-time PCR reactions (qPCR) were performed employing SYBR® Green PCR Master Mix (Applied Biosystems; cat 4309155) and using the

QuantStudioTM 7 Flex Real-Time PCR system (Thermo Fisher Scientific, Waltham, MA, USA) following the manufacturer's instructions. Reactions were carried out under the following conditions: 95°C for 10 minutes and PCR cycles 95°C for 15 seconds, 60°C for 60 seconds for 40 cycles. A melting curve was obtained to confirm the specificity of products, which were also visualised using 1% agarose gel electrophoresis with Gel Red staining. Each assay was ran in triplicate. PCR controls were generated using RNase-free water as template. The geometric mean of two housekeeping genes' CT values was used to calculate the results (Vandesompele et al., 2002). Related RNA levels were normalised to corresponding control by using the delta-delta CT methods (ΔΔCt) (Hellemans et al., 2007, Bustin et al., 2010).

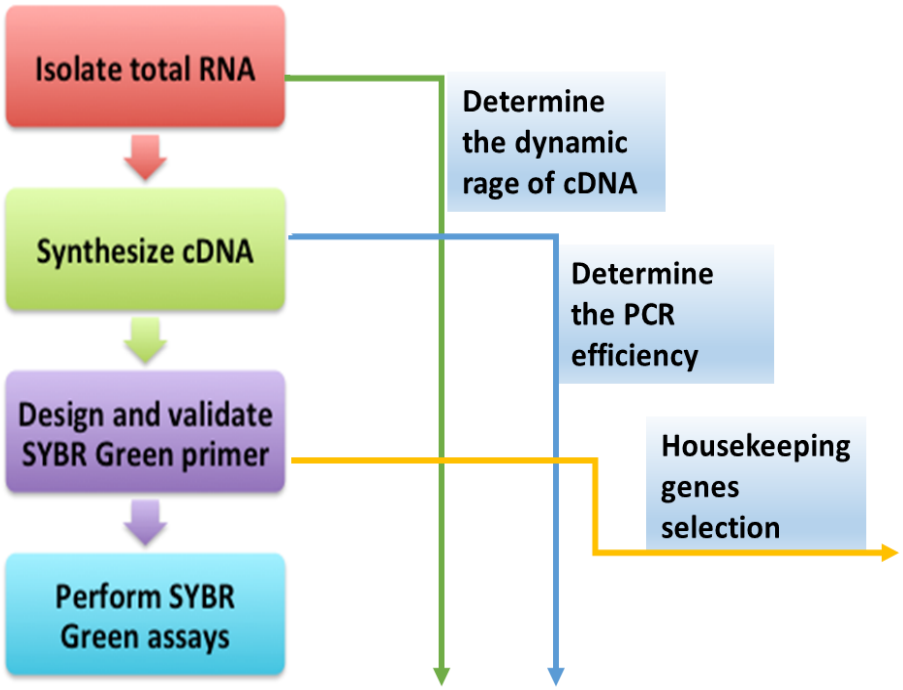


Figure 13: Typical workflow for designing and implementing Real-time PCR assay (SYBR Green).

Table 4: qPCR primer design details.

Gene	Primer name	Primer sequence (5'-3')	Amplicon Length	Design tool
Rps18	*Rps18-F*	TTCAGCACATCCTGCGAGTA	135	premier 5 software
	Rps18-R	TTGGTGAGGTCAATGTCTGC		
Gapdh	*Gapdh-F*	CCATT CTTCC ACCTT TGATG CT	76	premier 5 software
	Gapdh-R	TGTCA TACCA GGAAA TGAGC TTCA		
Phf21b	*Phf21b-F*	CAGCGGAAGGCCTTAAAGAA	87	IDT primerQuest
	Phf21b-R	CACTGTCTTGTGGGTGACATAG		
Arhgap8	*Arhgap8-F*	CAGCATGTGGAGAACGACTATAC	111	IDT primerQuest
	Arhgap8-R	CTTCCGGTCAAACTCCTTGTAG		
Prr5	*Prr5-F*	CGAGACATTGATCCAGAAGGTAG	92	IDT primerQuest
	Prr5-R	CAAGGATACAGGAATGGGTACAG		
Trpm2	*Trmp2-F*	CGAGTGCTACAGAAAGGATGAG	129	IDT primerQuest
	Trmp2-R	CCTCCGTGAGACACGAATTT		
Cntnap1	*Cntnap1-F*	AACCCCAGGAGAAAAGCTGG	135	IDT primerQuest
	Cntnap1-R	ATTGCAGCCATAGTAGCCCC		
Cwc22	*Cwc22-F*	ATACGGTGACGTGTGGAGAC	74	IDT primerQuest
	Cwc22-R	AGGACTGTTTCATGTGTGCCA		
Amer2	*Amer2-F*	ACATGAGGCCCTTCCAAATC	121	IDT primerQuest
	Amer2-R	GAACAACCAGTGTGGGTAACT		
Ano8	*Ano8-F*	CGGGAGACAGAAGAGACATAAC	172	IDT primerQuest
	Ano8-R	AGAGGAGAAGAGGACCACATAG		
Homer3	*Homer3-F*	AGGGAACAGCCAATCTTCAG	129	IDT primerQuest
	Homer3-R	CACATTTCGGGTTGCATCATAG		
Tbx18	*Tbx18-F*	TCAGCAGATTACTCGCCTGAAG	123	IDT primerQuest
	Tbx18-R	AGTGATGGCCTCCAGAATGC		

Nt5e	*Nt5e-F*	GCACCATTCGTGAAGATGCAG	117	premier 5 software
	Nt5e-R	AGACGATGGTTCTCCCGAGT		
Snx14	*Snx14-F*	CACTGGGACTGTGAGAACATT	145	premier 5 software
	Snx14-R	CTGCTCCTCTAGCACCTTTATC		
Syncrip	*Syncrip-F*	AGCCC ATGGA TACTA CTTCA GC	122	premier 5 software
	Syncrip-R	TTCCT CTGAC CTGCA ACGTA A		
Ube2e3	*Ube2e3--F*	CGGGA TGAAA GACAA CTGGA GTCCC G	102	premier 5 software
	Ube2e3-R	TCGTG TTCTG CTCTG TTGGT CA		
Unc13D	*Unc13D-F*	TCTGGGACGAGACCTTTATCT	120	premier 5 software
	Unc13D-R	AAAGTCGTCCTGGCCTTTATC		

2.7 Protein extraction

2.7.1 Monolayer cells protein extraction

Cells were lysed in RIPA buffer [50 mM Tris-HCl, pH 7.5, 1% NP-40, 0.5% Na-deoxycholate, 0.1% SDS, 150 mM NaCl, 25 mM EDTA, 1×Protease Inhibitor Cocktail (Sigma-Aldrich; Australia) add freshly]. Cells were washed twice in pre-cold PBS and lysed in pre-cold RIPA lysis buffer for 30 min on ice. Lysates were centrifuged for 10 min, 13 000 rpm, at 4℃, and protein concentrations of the cleared supernatant were determined by the bicinchoninic acid (BCA) protein assay kit assay; Catalog # PIE23255; Thermo Fisher Scientific, Waltham, MA, USA).

2.7.2 Tissue protein extraction

Rat hippocampus was weighted and cut with a blade into small pieces. In order to prevent protein degradation, all above processes were done on the dry ice. Rat hippocampus (50-60 mg tissue) were individually homogenised in protein extraction RIPA buffer with freshly added a protease inhibitor cocktail (30 µl lysis buffer/mg tissue), and lysate was centrifuged for 15 min at 10 000 rpm, at 4℃. Supernatant

were collected and protein concentration was determined using the BCA protein assay kit assay; Catalog # PIE23255; Thermo Fisher Scientific, Waltham, MA, USA).

2.8 Western blot

Samples were mixed with 4 x Laemmli sample buffer (Table 5) with 3:1 ratio and incubated at 95° C for 10 min. Whole cell lysate or tissue lysate (30~50µg) of each sample was loaded on Criterion gels 4-20% pre-cast gel (Catalog #3450412; BioRad; CA, USA), depending on the size of the protein of interest. Following electrophoresis, SDS-PAGE gels were transferred to nitrocellulose membranes (Catalog # 10600002; Amersham Protran 0.45 NC, GE Healthcare; Australia) using transfer buffer at 100 V for 1h, after which membranes were washed in TBS-T and then blocked with 5% non-fat milk extract in TBS-T for 1h. Membranes were incubated with the primary antibody overnight at 4° C using a rotating platform. Blots were then washed two to three times for 10 min with TBS-T (Table 6), and incubated with the secondary antibody for 1 hr at room temperature in a rotating platform. Blots were washed twice for 10 min with TBS-T and ECL (SuperSignal™ West Pico Chemiluminescent Substrate; Catalog # 34077; or SuperSignal^{R} West Femto Maximum Sensitivity substrate; Catalog #34094; Thermo Fisher Scientific, Waltham, MA, USA) was used according to the manufacturer's instructions. The blot was directly imaged using ChemiDoc™ MP (Biorad; CA, USA) and protein expressions were normalised with Image Lab Software V5.1 (Biorad; CA, USA). If necessary, the blot was stripped with stripping buffer (Table 6) for 1 hr and re-probed.

Primary antibodies used in Western blots:

All primary antibodies were used at a 1:1000 dilution in 5% milk/TBS-T (Table 5) unless indicated otherwise. Primary antibody was incubated overnight at 4°C in a rotating platform.

Anti-Phf21b: Rabbit anti PHF21B (Catalog # NBP2-30660; In Vitro Technologies (Hyclone); USA).

Anti-Prr5: Rabbit PRR5 antibody (Catalog # TA319960; Diagnostic Technology; USA).

Anti-Arhgap8: Rabbit anti-ARHGAP8 antibody (Catalog # TA337735; Diagnostic Technology; USA).

Secondary antibodies used in Western blots:

Secondary antibodies [Catalog#: 31460; Goat anti-Rabbit IgG (H+L) Secondary Antibody, Horseradish Peroxidase (HRP)] were obtained from Thermo Fisher Scientific (Waltham, MA, USA) and were used in a 1: 5000 dilutions in 5% milk/TBS-T (Table 5). The secondary antibody was incubated with the blot for 1 hr at room temperature.

2.9 Brain Expression Quantitative trait loci (eQTL) Analyses

The UK Brain Expression Consortium (UKBEC) web based server Braineac (Brain eQTL Almanac, http://www.braineac.org/) was used to investigate whether genetic polymorphisms of our candidate genes have significant associations with transcription level change (expression quantitative trait loci, eQTL) in ten brain regions (cerebellum; frontal cortex; hippocampus; medulla; occipital cortex; putamen; substantia nigra; temporal cortex; thalamus; and central white matter) (Ramasamy et al., 2014).

2.10 Power Analysis and Statistical Analysis

We performed a power analysis calculation using G*Power 3.0.10 (Franz Faul, Universitat Kiel, Germany)(Button et al., 2013, Festing and Altman, 2002) to justify the appropriate sample size to achieve 85% power for our gene expression test result (Table 6). Since we planned to use one-way ANOVA (3 groups) to analysis the real-time PCR results, the data was reassessed through a power analysis with an alpha err probability of 0.2, effect size f of 0.5 (large), and power (1-beta err probability) of 0.85. The total sample size should be 30 rats and 10 rats/group.

All statistical analyses were performed with GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA) and data were expressed as mean + S.E.M. Data was log transformed when necessary in order to ensure homogeneity of variance, although non-transformed data are shown in all figures and table. In Exp1 and Exp2, we have two and three groups respectively with different sample size in each group. The animal behaviour test data we collected were not normally distributed. Additionally, we have noticed the significant individual variances among animals even without interference. Thus, our data did not meet the requirement for analysis using Two-Way ANOVA. Therefore, after consultation with a statistician (Dr. Pawel Skuza, Statistical Consultant, Flinders University) and a mathematician and bioinformatician (Dr. Chenglong Yu, Research Fellow Mind and Brain Theme at the South Australian Health and Medical Research Institute), animal behaviour tests of Exp1 were analysed by Student paired t- test and Exp2 behaviour tests were analysed using mixed one-way ANOVA (Friedman test) with Dunn's multiple comparisons post-hoc test. qPCR data were analysed by One-way ANOVA with Tukey's multiple comparisons or nonparametric ANOVA (Kruskal-Wallis test) with Dunn's multiple

comparisons post-hoc analysis to assess expression difference between CRS and non-CRS groups and $P < 0.05$ was considered statistically significant.

Table 5: Buffers used for Western blotting.

Buffers used for Western blotting		
2x Laemmli sample buffer (loading buffer) **2.4 ml 1 M Tris pH 6.8** **0.8 g SDS stock** **4 ml 100% glycerol** **0.01% bromophenol blue.** **(Final Concentration is 0.02%)** **1 ml ß-mercaptoethanol (electrophoresis grade)** **2.8 ml water** **(goes off even at -20ºC)** **Aliquot and store at -20ºC**	100ml lysis buffer 0.5 ml 1M TRIS (pH 7.5) 0.5 ml 100 mM EDTA 1.5 ml 1M NaCl 1 ml NP-40 5ml 10% sodium deoxycholate 1ml 10% SDS AdH2O 84 ml add protease inhibitors freshly: For 10 ml lysis buffer add 0.1 ml protease inhibitor cocktail	100 ml stripping buffer 140 µl β-mercaptoethanol 6.25 ml 1M Tris pH 6.8 10 ml 10% SDS 83 ml H2O Incubate for 1 hr at 60°C
10X Running buffer **122g Tris base** **576 g Glycine** **200ml 20% SDS** **dH2O to 4 L**	1 X Running buffer 100 ml 10 x Running buffer add 1000 ml H2O	100 ml 5% milk (blocking solution) 5 g dry milk fill up to 100 ml with 1xTBS-T
Naphthol Blue Black **(This dye is also used in rapid staining of protein bands on nitrocellulose membranes such as Western blots)**	10X Transfer Buffer 576 g Glycine (48 mM final) 121.1 g Tris-base (39 mM final) dH2O to 4 L	1X Transfer buffer: 100 mL 10 X Base Transfer Buffer 700 mL dH2O 200 mL Methanol Store at +4 ˚C
20x TBS, for 4 L **193.6 g Tris base** **640 g NaCl** **Bring up the volume to 3.2 L with ddH2O Adjust the pH to 7.6 with concentrated HCl** **Bring up the volume to 4 L with ddH2O**	20x TBST, for 100 mL Add 2 mL Tween-20 to 100 mL of 20x TBS	

Table 6: Power analysis.

F tests - ANOVA: Fixed effects, omnibus, one-way		
Analysis:	A priori: Compute required sample size	
Input:	Effect size f	0.5
	α err prob	0.2
	Power (1-β err prob	0.85
	Number of groups	3
Output:	Noncentrality parameter λ	7.500000
	Critical F	1.709303
	Numerator df	2
	Denominator df	27
	Total sample size	30
	Actual power	0.864398

CHAPTER 3:
ANIMAL DEPRESSIVE-LIKE BEHAVIOUR MODEL

In this project, we used a depressive-like behaviour rat model induced by CRS; we restrained rats was six hours each day for 14 days. Two behaviour tests: The forced swimming and sucrose preference test were performed at baseline and post-CRS to evaluate if the rat displayed depressive-like behaviour.

3.1 Forced Swim Test (FST) results

To understand whether mild stress induced changes in expression level of genes of interest in the hippocampus, non-restraint control groups were set along with the CRS groups. In order to compare the behaviour changes between the CRS groups and control (non-CRS) groups, student paired *t*-test analysis was used to compare baseline and 14 days later (which was post-CRS) data. Highly mobile time decreased in the CRS and control groups between baseline and post-CRS (Highly-baseline-CRS vs. Highly-post-CRS: P=0.0002; Highly-baseline-control vs. Highly-post-CRS-control: P=0.0084), mobile time increased in the CRS and control groups between baseline and post-CRS (Mobile-baseline-CRS vs Mobile-post-CRS : P<0.0001; Mobile-baseline-control vs Mobile -post-CRS-control : P=0.010) and immobility time significantly decreased between baseline and post-CRS only in the CRS group (Immobile-baseline-CRS vs Immobile-post-CRS : P=0.0036; Immobile-baseline-control vs Immobile -post-CRS- control : P = 0.076; Figure 14 a-c).

Exp1 rats were transported from Charles River (UK) to South Australia. , CRS rats were house individually during the whole experiment period because previous experiments showed that single-housed rats displayed depressive-like behaviour more consistently. As some of the animals displayed depressive-like behaviour at baseline in the FST and needed to be excluded from the analyses, we conducted

Exp2. Three groups were used in Exp2, the same 2 groups from Exp1 and one additional group-housed rat was used as the control group 2. Experiment 2 was not sub-divided in resilient and non-resilient groups, as this sub-analysis was beyond the scope of the proposed work. Mixed one-way ANOVA (Friedman test) followed by the Dunn's multiple comparisons Tukey's multiple comparisons post-hoc test was used to understand the changes in the FST. Mixed One-way ANOVA indicated significant difference among three groups (P=0.0008), only highly mobile-CRS showed a significant decrease in compared to highly mobile-baseline (P=0.002). Mobile time also showed difference among the three groups with P=0.0011. The post-hoc test showed the mobile time increased significantly in Control 1 and Control 2 group (P=0.035 and P=0.035 respectively). Moreover, similar to the previous experiment, CRS significantly increased the immobility time, while the two control groups were not different (P=0.0016) (Figure 15: a, b, c).

3.2 Sucrose preference test (SPT) results

In Experiment 1 (Exp1) sucrose preference data were obtained in control (individually housed) and CRS groups at baseline and three weeks afterwards, at which time the CRS paradigm had ended. A significant increase in the percentage of sucrose solution intake was found in non-stressed animals using the Student paired *t*-test (baseline-control vs. none-CRS, P=0.0057; Figure 16 a), and a significant decrease in sucrose solution intake was shown post-CRS (baseline-CRS vs. post-CRS: P=0.0042; Figure 16 b).

To understand if social isolation stress (individual housing rat) induces mild stress, a repeated chronic restraint stress experiment, Experiment 2 (Exp2), was performed. Behavioural testing of single-housed control (control 1), group-housed control

(control 2), and CRS groups was performed. A significant difference was found using mixed one-way ANOVA (Friedman test) (*P*=0.0001) and the Dunn's multiple comparisons post-hoc test indicated that the post-CRS had significantly decreased sucrose solution intake when compared to CRS-baseline (*P*=0.017; Figure 17).

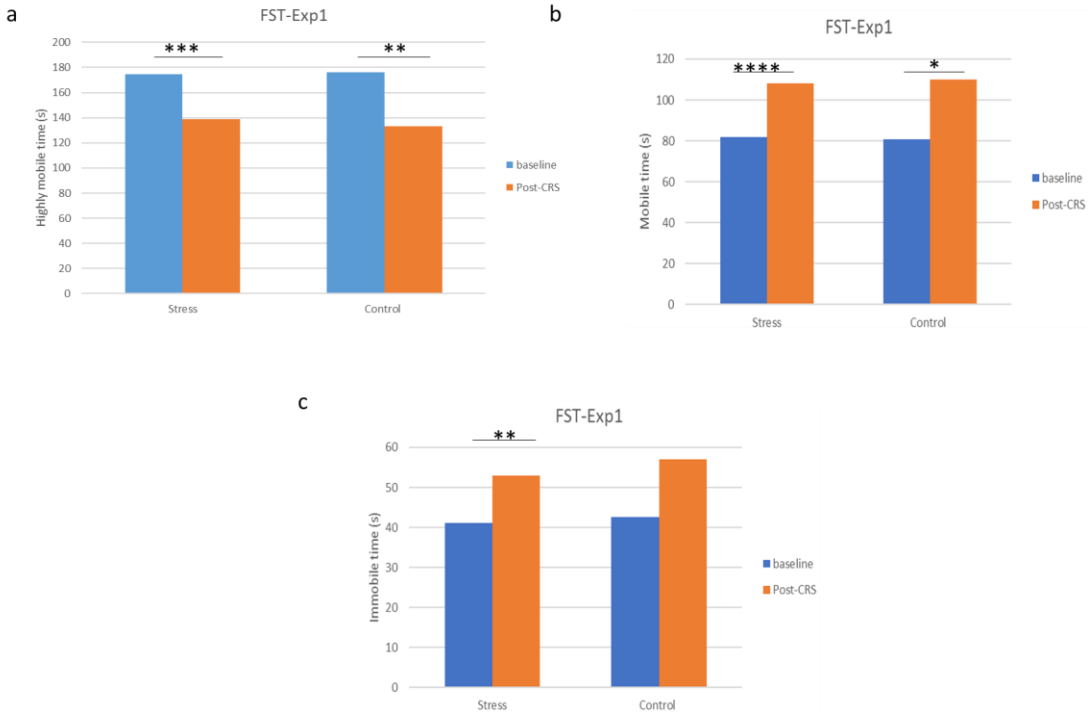


Figure 14: Experiment 1 (Exp1) forced swim test (FST) results.

Means of highly mobile time, mobile time and immobility time in Sprague-Dawley rats at baseline and post-CRS, two weeks after the conclusion of chronic restraint stress) were used to ascertain that rats showed behaviour despair. All data are represented as mean ± SEM (CRS n=27, Non-CRS n=10). Data were analysed using Student paired-t test. (a) A significant decrease in highly mobile time was shown in the CRS and the non-CRS groups (*P*=0.0002 and *P*=0.0084). (b) A significant increase in mobile time was shown in the CRS and in the non-CRS groups (*P*<0.0001 and *P*=0.010). (c) A significant increase in immobility time was only indicated in the CRS group (*P*=0.0036). *=*P* ≤ 0.05 **=*P*≤ 0.01; *=*P*≤ 0.001; ****=*P*≤ 0.0001.**

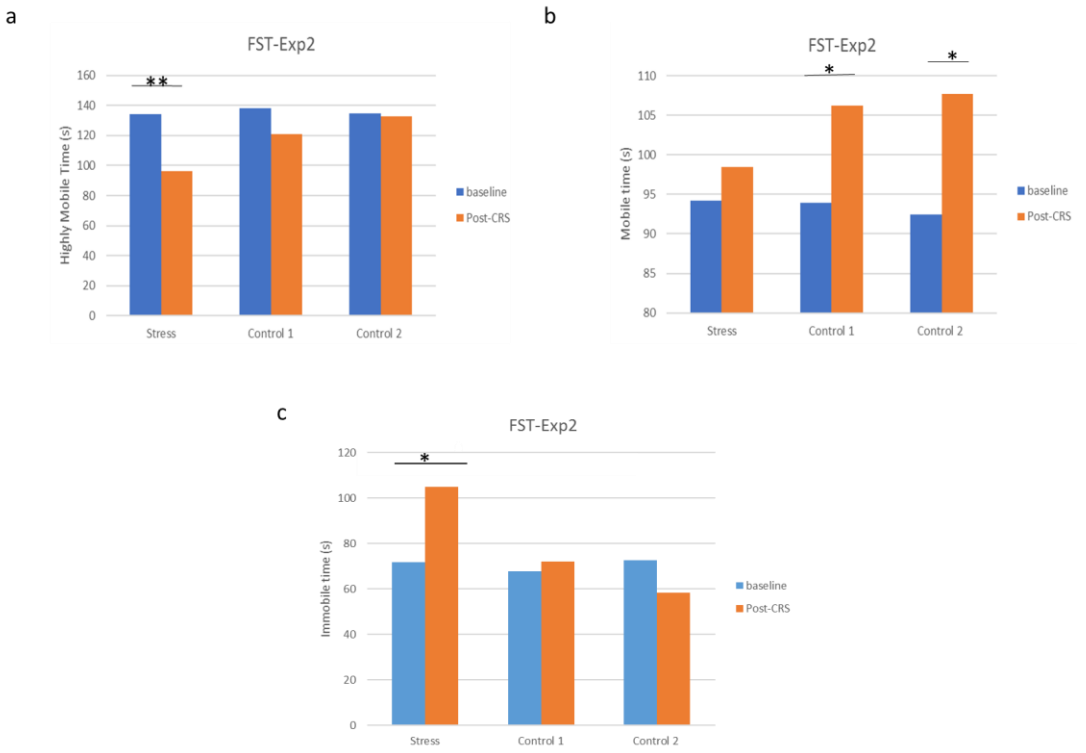


Figure 15: Experiment 2 (Exp2) forced swim test (FST) results.

Means of highly mobile time, mobile time and immobility time for Sprague-Dawley rats at baseline and post-CRS repeated (after two weeks of chronic restraint) to ascertain that rats showed behaviour despair. Control 1 represented non-CRS single-housed rats; control 2 represented non-CRS group-housed rats. All data are represented as mean ± SEM (CRS n=15, Control 1 n=10, Control 2 n=16). Data were analysed using mixed one-way ANOVA (Friedman test) followed by the Dunn's multiple comparisons post-hoc test. (a) CRS significantly decreased the highly mobile time in comparison to baseline measure (*P*=0.002). (b) The mean of total mobile time also showed difference among the group with *P*=0.0011; and the post-hoc test indicated the mobile time increased significantly in two control groups with *P*=0.035 and *P*=0.035 respectively. (c) CRS significantly increased the total immobility time (*P*=0.0016), and compared with immobile-CRS in control 2, immobility time-CRS increased significantly (*P*=0.0004). *=*P* ≤ 0.05 **=*P*≤ 0.01; *=*P*≤ 0.001.**

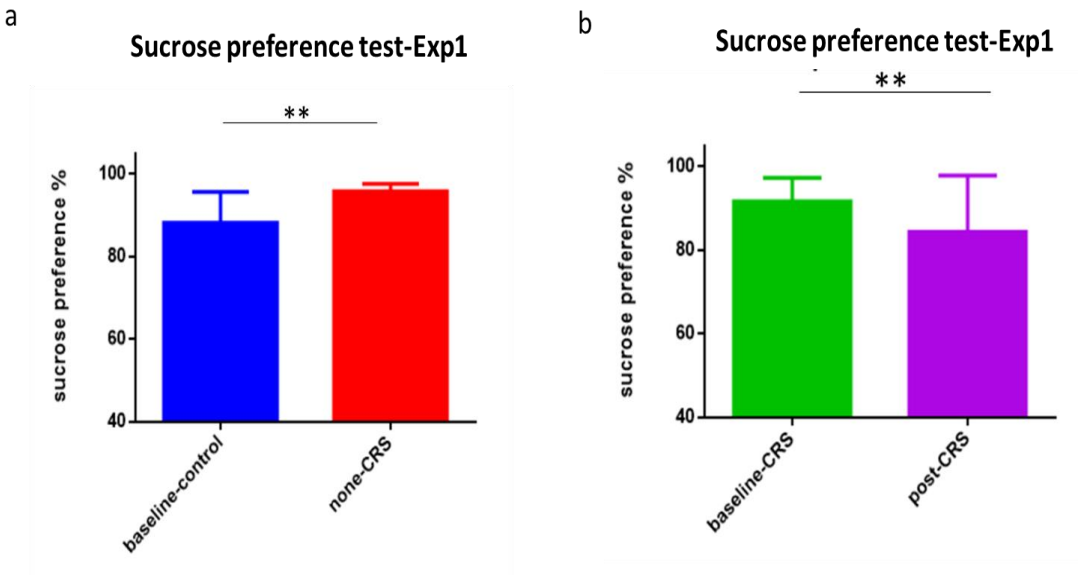


Figure 16: Sucrose preference test in experiment 1 (Exp1).

Mean consumption of 1% sucrose water at baseline and three weeks later (which was after the termination of chronic restraint stress (CRS) paradigm to assess anhedonia in Exp1. All data are represented as mean ± SEM. Data were analysed using Student paired t-test (a) Mean consumption of 1% sucrose solution in the control group. SPT was increased in week three (none-CRS) in relation to baseline consumption (baseline-control; n=10, *P*=0.0057). (b) Mean consumption of 1% sucrose solution in the CRS group was decreased after CRS (post-CRS) in comparison to baseline measures (baseline-CRS; n=27, *P*=0.0042). **=*P*≤ 0.01.

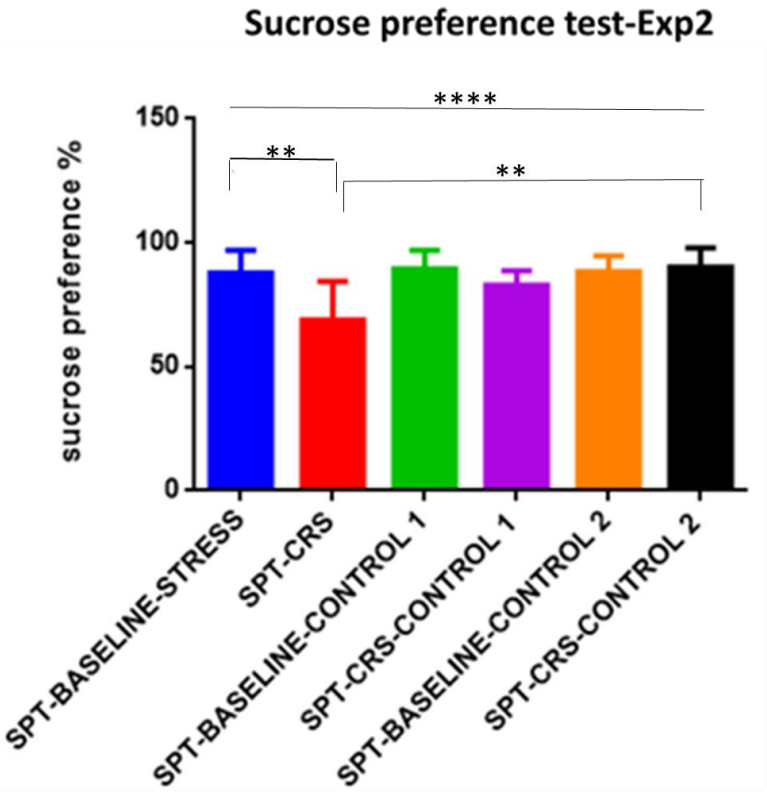


Figure 17: Sucrose preference test (SPT) in experiment 2 (Exp2).

Mean consumption of 1% sucrose water at baseline and post-chronic restraint stress (CRS), which was performed 2 weeks after termination of the CRS paradigm to show that rats displayed post-CRS anhedonia in Exp2. Control groups 1 and 2 were not submitted to CRS; control 1 rats were single-housed and control 2 animals were group-housed (3 to 4 rats/cage). All data are represented as mean ± SEM (CRS n=15, Control 1 n=10 and Control 2 n=16). Data were analysed using mixed one-way ANOVA (Friedman test). The Dunn's multiple comparisons post-hoc test indicated that the post-CRS group (SPT-CRS) had significantly decreased 1% sucrose solution intake when compare to the CRS-baseline-stress group (*P*=0.017) and SPT-CRS vs. SPT-CRS-control 2 (*P*=0.0012). **=*P*≤ 0.01; **=*P*≤ 0.0001.**

CHAPTER 4:
GENE EXPRESSION CHANGES IN THE RAT HIPPOCAMPUS IN RESPONSE TO CRS OR SOCIAL ISOLATION STRESS

Although, the progress has been achieved in understanding the pathogenesis of depression in regards to the genetic factors. A large number of genes have been reported that are associated with depression's onset, prevention and treatment remission. We have discussed those genes in details in the introduction chapter. However, there is still a lack of consistent and clear conclusion regarding the role of the central relevant genes associated with depression in its pathogenetic process. Furthermore, the gene that triggers depression may differ in different ethnicities. Previous studies from SAHMRI Mind and Brain Theme identified forty-four common and rare functional variants potentially associated with MDD in Mexican-Americans and several SNPs closely related with antidepressant treatment remission through pharmacogenetic studies. These genes and SNPs may also be relevant to stress response (Wong et al., 2016, Wong et al., 2014b). And *PHF21B* has been replicated in both a Los Angeles Mexican-American cohort and a European ancestry cohort; thus, here, we investigate and verify those finding using rodent depressive-like behaviour models.

4.1 The rat PHD finger protein 21B (*Phf21b*) gene

Ph21b mRNA abundance showed a significant change between the CRS group and the control (non-CRS) group (Figure 18 a-c). In Exp1, we excluded rats that showed high immobility time at baseline in CRS group (immobility time at baseline > the average of post-CRS immobility time). In addition, we also excluded rats that showed increased immobility time at the second FST in the non-CRS control group (immobility time at the second FST > the average of post-CRS immobility time). The main reason for doing this was that we had to consider the confounding effects of single housing (social isolation) and long-distance transportation (from the UK to Australia) may have caused significant stress that increased depressive-like

behaviours at baseline in those animals. We found that CRS significant decreased *Phf21b* mRNA level in the rat hippocampus when compared to control animals (Student unpaired *t*-test *P*=0.011; figure 18 a). We further classified the CRS group into two subgroups based on the FST data, namely CRS resilient (below average baseline and post-CRS floating times) and CRS non-resilient, and found that CRS resulted in significantly decreased *Phf21b* mRNA in CRS resilient animals when compared to the control group, but not in the CRS non-resilient ones (*P*=0.0021; figure 18 b)(Wong et al., 2016a). To ascertain whether social isolation itself increased depressive-like behaviours, we conducted Exp2 with rats bred in house, and set-up an additional control group: group-housed animals (Control 2). CRS significantly decreased *Phf21b* mRNA level in rat hippocampus when compared to the control 2 group (*P*=0.031; figure 18 c).

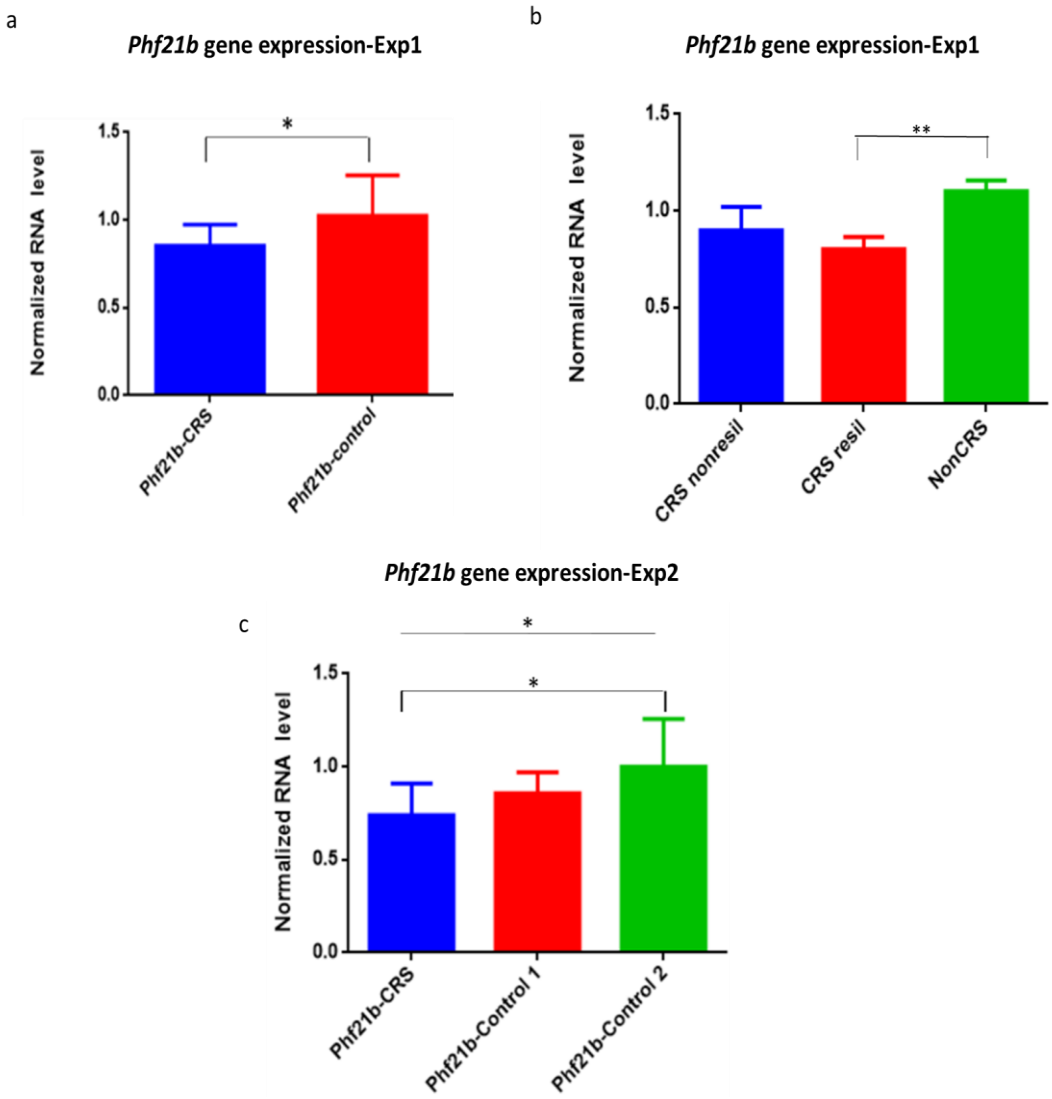


Figure 18: *Phf21b* gene expression in the rat hippocampus after chronic restraint stress (CRS)

Gene expression was assessed by qPCR and data were analysed via ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. (a) Experiment 1 (Exp1) data showed that indicated that Phf21b mRNA level significantly decreased after chronic restrain stress (CRS) when compared to the non-CRS group (Unpaired t-test, *P*=0.0109). (b) Exp1 data showed that hippocampal *Phf21b* gene expression significantly diminished in the CRS resil (resilient) group (n=11) but not in the CRS nonresil (non-resilient) group (n=8) comparing with the non-CRS group (n=6) (one-way ANOVA, *P*=0.0021; Figure 19b was reproduced from (Wong et al., 2016); (c) Experiment 2 (Exp2) data showed that *Phf21b* gene expression in the rat hippocampus significantly decreased after CRS when compared to control 2 (*P*=0.031) using Kruskal-Wallis test followed by the Dunn's multiple comparison post-hoc test. *=$P \leq 0.05$; **=$P \leq 0.01$.

4.2 The Rat Rho GTPase activating protein 8 (*Arhgap8*) gene

The *ARHGAP8* gene, which is next to the *PHF21B* gene, was also significantly associated with MDD in the Mexican-American cohort; however, it was not replicated in the European-ancestry cohort. Therefore, we performed qPCR to investigate *Arhgap8* gene expression alteration in the rat hippocampus in response to CRS. *Arhgap8* mRNA level was significantly increased by CRS in comparison to the control 1 and control 2 groups (with P=0.0057 and P<0.0001 respectively); *Arhgap8* gene expression level between the two control groups was not significantly different (Figure 19).

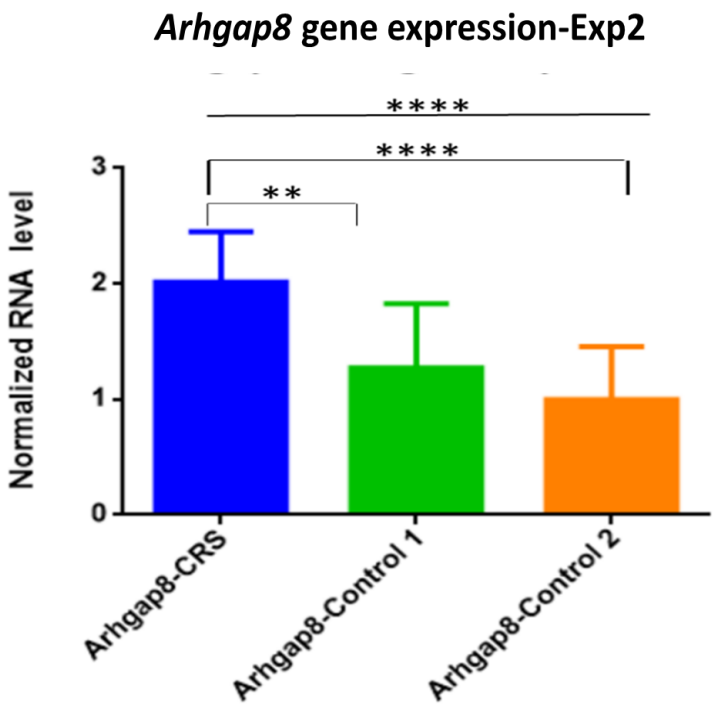


Figure 19: *Arhgap8* gene expression in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by real-time qPCR and analysed via the ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. *Arhgap8* expression level significantly increased in the CRS group when compared to the control 1 group and the control 2 group (P=0.0057 and P<0.0001 respectively) Data were analysed using one-way ANOVA followed by the Tukey's multiple comparisons post-hoc test. **=$P\leq$ 0.01; ****=$P\leq$ 0.0001.

4.3 The rat proline rich 5 (*Prr5*) gene

The *PRR5* gene is located near the *PHF21B* and the *ARHAGAP8* genes. Therefore, as *Phf21b* and *Arhgap8* gene expression level were modulated by CRS, we were also interested in understanding whether *Prr5* gene expression changed in response to CRS. Our qPCR data showed that *Prr5* gene expression was not changed by CRS (Figure 20).

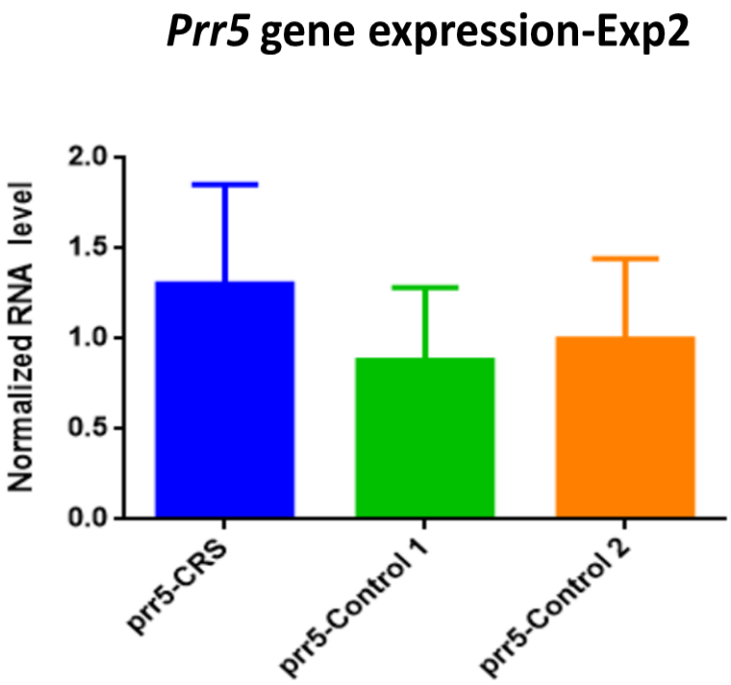


Figure 20: *Prr5* gene expression in rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by real-time qPCR and analysed via the ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. There was no difference in *Prr5* gene expression between the three groups using one-way ANOVA (*P*=ns).

4.4 The rat transient receptor potential cation channel subfamily M member 2 (*Trpm2*) gene

The *TRPM2* gene was associated with MDD in the Mexican-American cohort by haplotype analysis (Wong et al., 2016). The nonparametric Kruskal-Wallis test indicated a significant difference in *Trpm2* mRNA level between the three groups (*P*=0.020) and the Dunn's multiple comparisons post-hoc analysis revealed that CRS significantly increased *Trpm2* mRNA level when compared to the control 2 group (*P*=0.018; Figure 21).

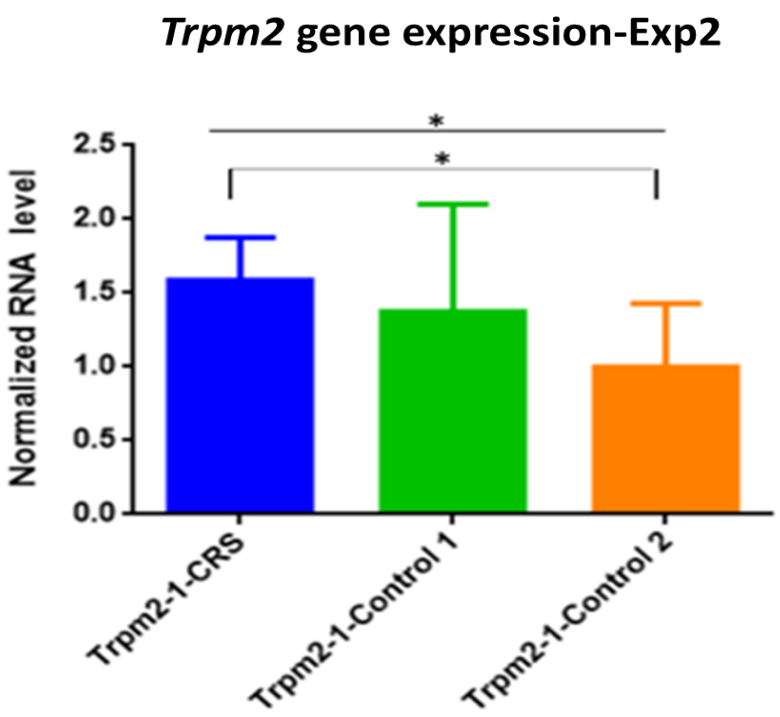


Figure 21: *Trpm2* gene expression in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by real-time qPCR and analysed via the ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. Significant differences between the three groups were found using the nonparametric Kruskal-Wallis test at *P*=0.020. The Dunn's multiple comparisons post-hoc test showed that *Trpm2* expression level was significantly increased by CRS in comparison to the control 2 group (*P*=0.018). *=*P* ≤ 0.05.

4.5 The rat contactin associated protein 1 (*Cntnap1*) gene

To search for other antidepressant drug response or/and CRS-response genes, the changes in mRNA abundant of *Cntnap1* gene were validated by the same method in Exp2 samples. The CRS group had significantly increased *Cntnap1* gene expression level in comparison to control 1 (*P*=0.021) and control 2 (*P*=0.018; Figure 22) groups.

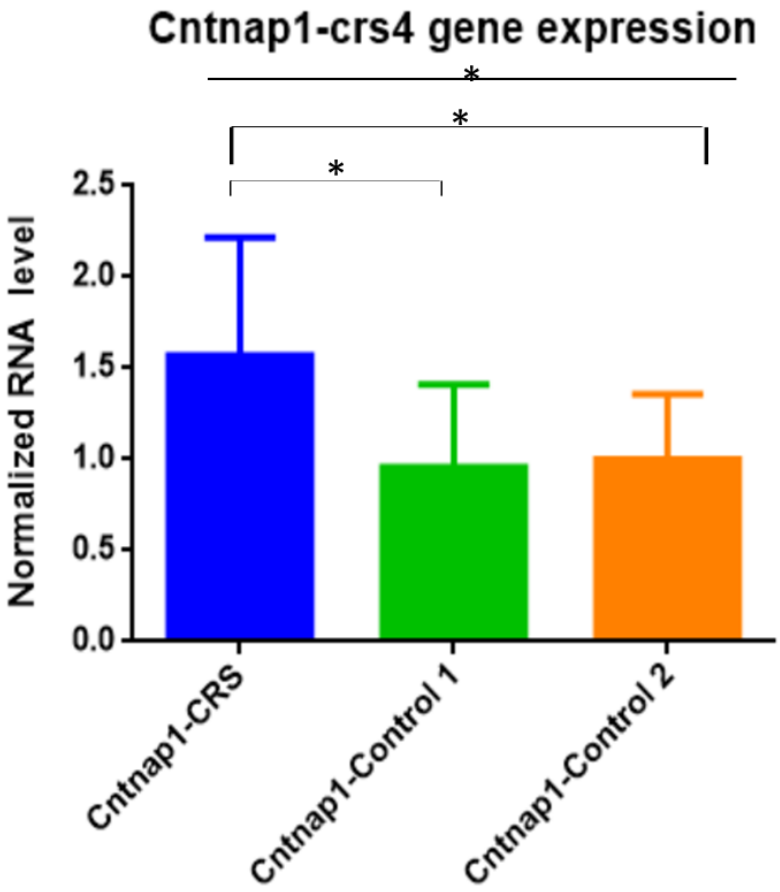


Figure 22: *Cntnap1* gene expression in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by qPCR and data were analysed via the ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. Significant difference between the three groups was found using one-way ANOVA at *P*=0.0111 and the Tukey's multiple comparisons post-hoc test showed that CRS significantly increased *Cntnap1* expression level when compared to the control 1 (*P*=0.021) and control 2 (*P*=0.018) groups. *=$P \leq 0.05$.

4.6 The rat APC membrane recruitment protein 2 (*Amer2*)/FAM123A gene

The *AMER2/FAM123A* gene was amongst the genes with possible association to MDD in recently publication (Wong et al., 2016). Therefore, *Amer2* gene expression level was examined in our studies. *Amer2* mRNA level was not altered by CRS (Figure 23), as there was no significant difference between the CRS and the two control groups.

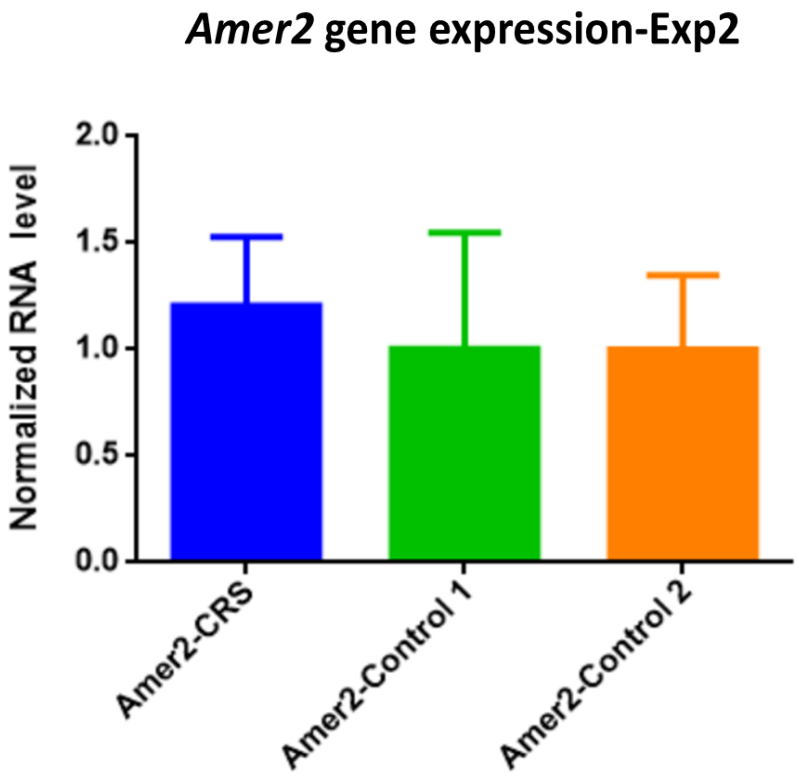


Figure 23: *Amer2* gene expression in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by qPCR and data were analysed via ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. No significant difference was found between the CRS group and the 2 control groups by one-way ANOVA (*P*=ns).

4.7 The rat unc-13 homolog D (*Unc13d*), anoctamin 8 (*Ano8*) and Homer scaffolding protein 3 (*Homer3*) genes

Functional SNPs harboured in the *UNC13D, ANO8, HOMER3* genes were significantly associated with MDD in common and rare variants analyses in Mexican-Americans (Wong et al., 2016a). In the rat hippocampus, social isolation significantly decreased *Unc13d* gene expression level, as mRNA level was decreased in the single-housed control 1 group in comparison to the group-housed control 2 group (*P=0.024*). However, no significant differences were found between the CRS and the control groups (Figure 27 a). In additionally, neither *Ano8* nor *Homer3* gene showed any difference in mRNA level in the rat hippocampus in response to CRS or social isolation (Figure 24 b-c).

4.8 Summary of results

In these studies, we investigated rat hippocampal expression changes of several candidate genes in response to CRS. To achieve this purpose, we firstly established a depressive-like behaviour model induced by CRS in rats. Two behavioural tests: FST and SPT, were performed to confirm the successful implementation of this animal depression model. Then, mRNA levels for different genes were assessed by qPCR in the rat hippocampus. We analysed qPCR via the ΔΔCt method using *Gapdh* and *Rps18* as reference genes. According to our studies, the mRNA level of 6 genes, namely the *Phf1b, Arhgap8, Trpm2, Cntnap1 and Unc13d* genes (Table 7) have changed significantly in response to CRS or social isolation stress.

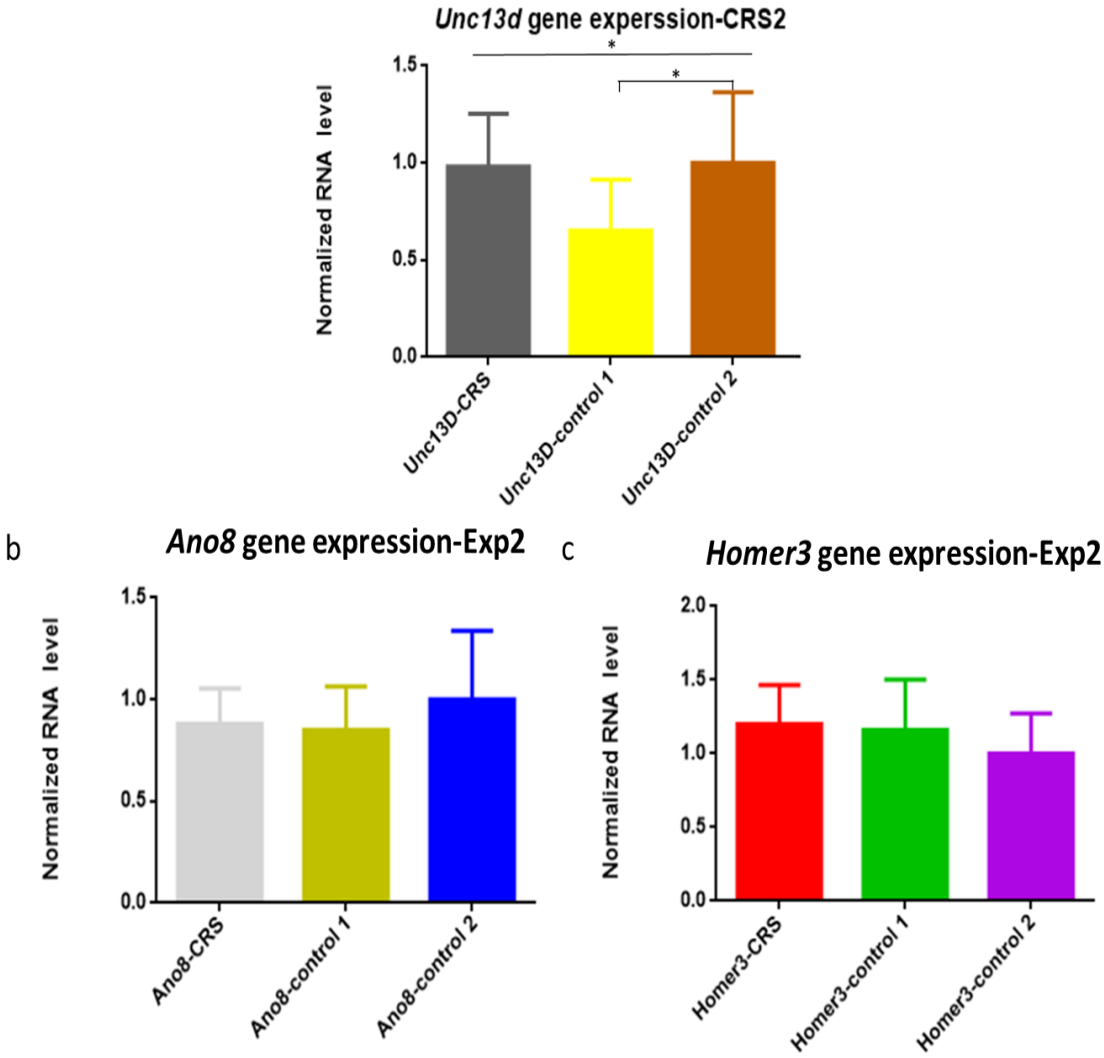


Figure 24: Expression of the *Unc13d*, *Ano8* and *Homer3* genes in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by qPCR and data were analysed via the ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. (a) A significant difference in *Unc13d* gene expression level between the three groups was found using the Kruskal-Wallis test, *P*=0.024, and the Tukey's multiple comparisons post-hoc test showed that the *Unc13d* mRNA level in the control 1 group was significantly decreased in comparison to the control 2 group (*P*=0.026). (b) and (c) *Ano8* and *Homer3* gene expression showed no significant differences between the three groups. *=*P* ≤ 0.05.

Table 7: Summary of gene expression results

Gene	CRS	Control 1	Control 2	Significant
***Phf21b* (Exp1)**	0.87 ± 0.024, n=20	13.50 ± 7.87, n=6		CRS: *P*=0.0032*
***Phf21b* (Exp2)**	0.74 ± 0.17, n=15	0.86 ± 0.11, n=10	1 ± 0.26, n=16	*P*=0.035^ CRS vs. control 1: ns^ CRS vs. control 2: *P*=0.030^
***Arhgap8* (Exp 2)**	2.01 ± 0.43, n=15	1.27 ± 0.55, n=10	1 ± 0.46, n=16	*P*<0.0001# CRS vs. control 1: *P*= 0.0057# CRS vs. control 2: *P*<0.0001#
***Trpm2* (Exp 2)**	1.59 ± 0.29, n=150	1.37 ± 0.73, n=10	1 ± 0.43, n=16	*P*=0.020^ CRS vs. control 1: ns^ CRS vs. control 2: *P*=0.018^
***Cntnap1* (Exp 2)**	1.57 ± 0.65, n=15	0.959 ± 0.45, n=10	1 ± 0.36, n=16	*P*=0.011# CRS vs. control 1: *P*= 0.0213# CRS vs. control 2: *P*=0.018#
***Unc13d* (Exp 2)**	0.98 ± 0.27, n=15	0.650 ± 0.27, n=10	1 ± 0.36, n=16	*P*=0.024# CRS vs. control 1: ns# CRS vs. control 2: ns# Control1 vs control 2: *P*=0.026#

Values are presented as mean ± SEM (standard error of the mean); Exp1, chronic restraint stress experiment 1; Exp2, chronic restraint stress experiment 2; control 1, single-housed non-CRS group; control 2, group-housed non-CRS group; * = unpaired t-test, # = one-way ANOVA followed by the Tukey's multiple comparisons post-hoc test, ^ = Kruskal-Wallis test followed by the Dunn's multiple comparisons post-hoc test; significant was set at *P*<0.05.

CHAPTER 5:
GENES SELECTED FROM PHARMACOGENETIC STUDY ARE ASSOCIATED WITH ANTIDEPRESSANT REMISSION

5.1 The rat T-box 18 (*Tbx18*) gene

The SNP exm-rs1321744 achieved exome-wide significance in response to antidepressant treatment. This SNP is located in a methylated DNA immunoprecipitation sequencing site, which suggests that this SNP may alter the expression of its adjacent genes via epigenetic regulation (Wong et al., 2014a). The *TBX18* gene was selected as a candidate gene as it neighbours the exm-rs1321744 intergenic variation (Wong et al., 2014b). Data obtained by qPCR showed that *Tbx18* mRNA level was not altered by CRS or social isolation (Figure 25).

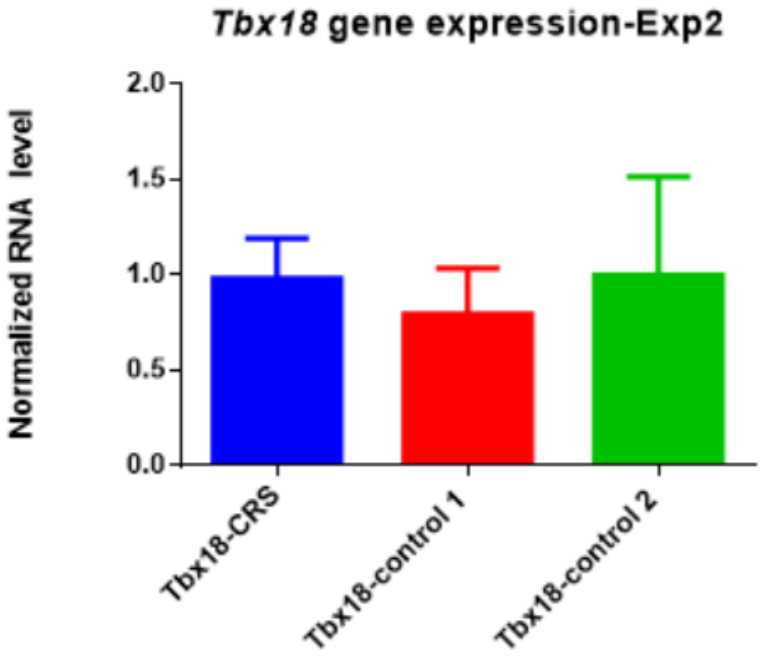


Figure 25: *Tbx18* gene expression in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by qPCR and data were analysed via ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. No significant difference was found between the three groups (*P*=ns) using the Kruskal-Wallis non-parametric test.

5.2 The rat 5'-nucleotidase ecto (*Nt5e*) gene

The *NT5E* gene was selected as candidate gene as it also neighbours the exm-rs1321744 intergenic variation (Wong et al., 2014b). Therefore, *Nt5e* gene expression level was tested to understand the relationship between *Nt5e* and CRS. However, no significant change in *Nt5e* mRNA level of was found in response to CRS in the hippocampus (Figure 26).

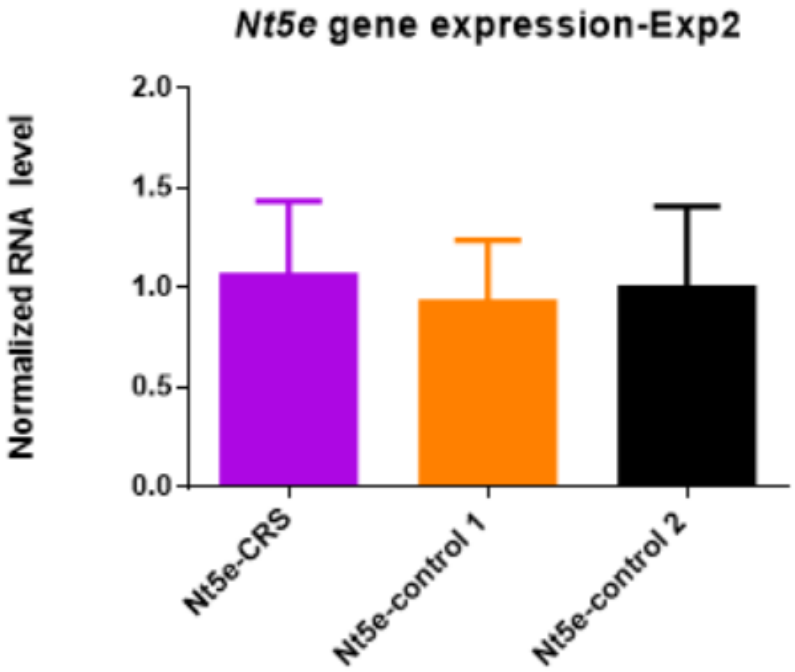


Figure 26: *Nt5e* gene expression in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by qPCR and data were analysed via ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. No significant difference was found between the three groups (*P*=ns) by one-way ANOVA.

5.3 The rat sorting nexin 14 (*Snx14*) gene

The *SNX14* gene was selected as a candidate gene as it also neighbours the exm-rs1321744 intergenic variation (Wong et al., 2014b). *Snx14*mRNA level in the rat hippocampus did not change after two weeks of CRS (Figure 27).

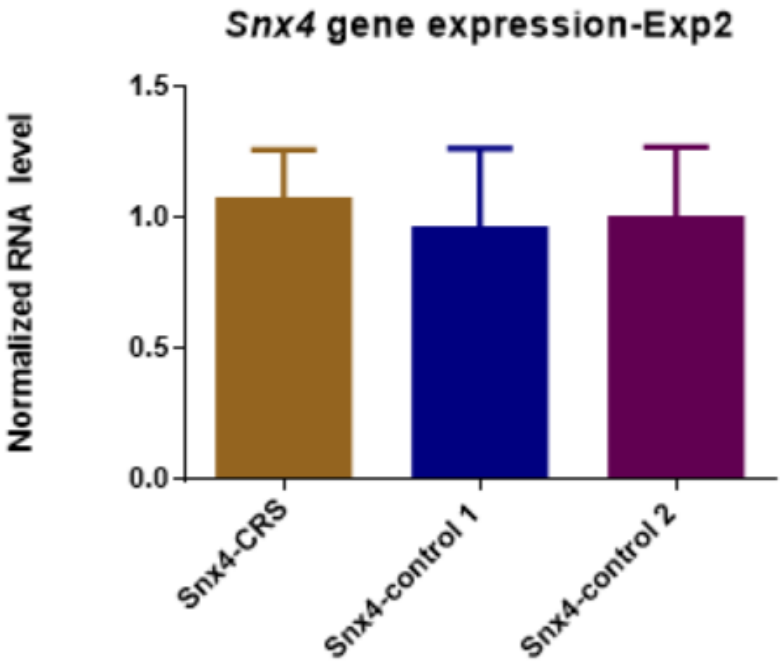


Figure 27: *Snx14* gene expression in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by qPCR and data were analysed via ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. No significant difference was found between the three groups (*P*= ns) by one-way ANOVA.

5.4 The rat Synaptotagmin binding cytoplasmic RNA interacting protein (*Syncrip*) gene

The *SYNCRIP* gene was selected as a candidate gene as it also neighbours the exm-rs1321744 intergenic variation (Wong et al., 2014b). *Syncrip* expression level was significantly decreased by social isolation, as the control 1 group (single-housed) had lower mRNA level than the control 2 group (group-housed), but no significant difference was found between the CRS and the control groups (Figure 28).

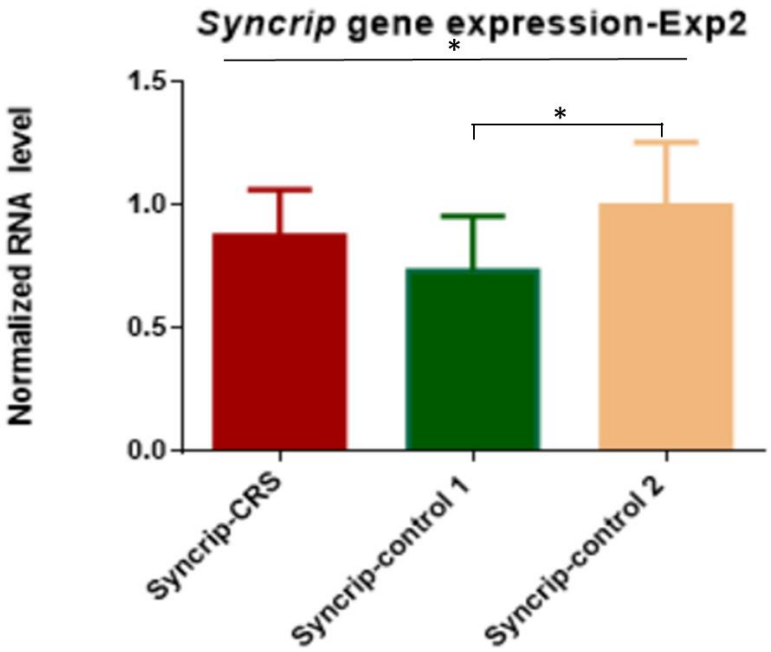


Figure 28: Expression of the *Syncrip* gene in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by real-time qPCR and data were analysed via ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. A significant difference between the three groups was found using one-way ANOVA, *P*=0.026 and the Tukey's multiple comparisons post-hoc test showed that the control 1 group had significantly lower mRNA level than the control 2 group (*P*=0.020). *=*P* ≤ 0.05.

5.5 The rat ubiquitin conjugating enzyme E2 E3 (*Ube2e3*) gene

Intergenic exm-rs16867321 was the second SNP identified by the SAHMRI Mind and Brain Lab that was likely to be associated with antidepressant remission (Wong et al., 2014b). The *UBE2E3* gene is located next to exm-rs16867321. Although exm-rs16867321 did not achieve genome-wide significance, we still studied its two adjacent genes. We tested *Ube2e3* gene expression level in the rat hippocampus; however, we found no significant changes in *Ube2e3* mRNA level between the CRS group and the 2 control groups (Figure 29).

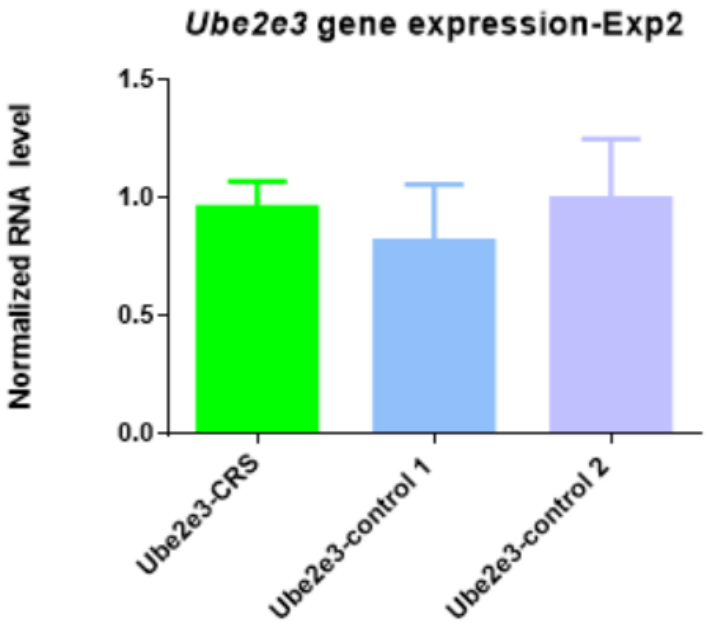


Figure 29: *Ube2e3* gene expression in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by real-time qRT-PCR as previously described. Data were analysed via ΔΔCt method using *Gapdh* and *Rps18* as reference genes. Bar graphs summarise qPCR measurements. All data are represented as mean ± SEM. No significant difference between the three groups was found by Kruskal-Wallis test (*P*=ns).

5.6 The rat *CWC22* spliceosome associated protein homolog (*Cwc22*) gene

The *CWC22* gene is also located next to exm-rs16867321, which is an SNP potentially associated with antidepressant treatment remission (Wong et al., 2014b). Therefore, *Cwc22* mRNA level was investigated by qPCR. *Cwc22* gene expression was increased by CRS when compared to the single-housed control 1 group (*P*=0.0094) and group-housed control 2 group (*P*=0.037). However, no significant difference was found between the CRS and the control 2 group (Figure 30).

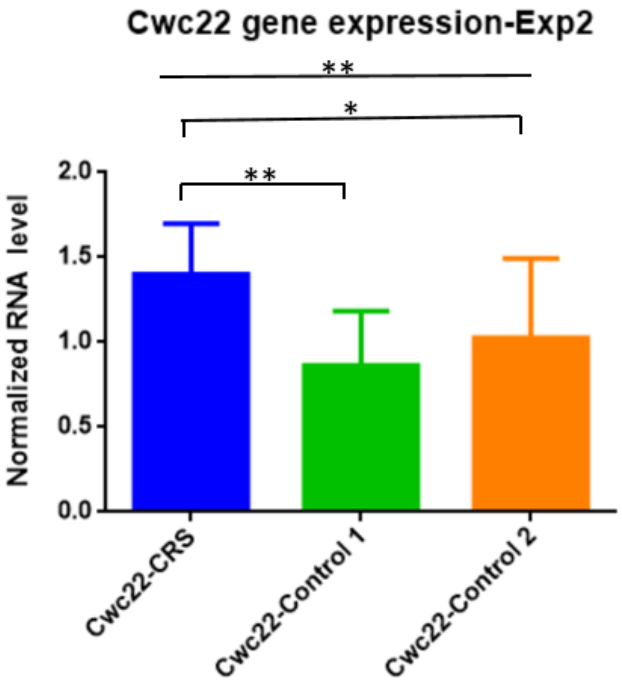


Figure 30: Expression of the *Cwc22* gene in the rat hippocampus after chronic restraint stress (CRS) in experiment 2 (Exp2).

Gene expression was assessed by real-time qRT. Data were analysed via ΔΔCt method using *Gapdh* and *Rps18* as the reference genes. Bar graphs summarise qPCR measurements and data are represented as mean ± SEM. One-way ANOVA analysis indicated that there was a significant difference between the three groups (*P*=0.0094) and the Tukey's multiple comparisons post-hoc test showed that *Cwc22* expression level was significantly increased by CRS when compared to the control 1 group (*P*=0.0094) and control 2 group (*P*=0.037). *=*P* ≤ 0.05; **=*P*≤ 0.01.

5.7 Summary of results

Previous pharmacogenetics study performed by our Mind and Brain group has identified several SNPs that associated with antidepressant treatment remission. SNP exm-rs1321744 achieved exome-wide significance for antidepressant treatment remission in Mexican-American patients with MDD (Wong et al., 2014b). Another SNP that was associated with MDD was exm-rs16867321. As those two functional

variants were intergenic SNP, their adjacent genes were investigated whether they were associated with stress response. Therefore, *TBX18*, *NT5E*, *SNX14*, *SYNCIP*, *UBE2E3* and *CWC22* were selected to understand whether they response to CRS or not. Real-time PCR was conducted to investigate above genes expression changes in response to CRS in rat hippocampus. We found that *Syncrip* expression level significantly decreased in control 1 group (individual housing group without CRS) in comparison to control 2 group (group housing without CRS), which might suggest that *Syncrip* gene was sensitive to social isolation stress, instead of CRS. Also, our data showed that Cwc22 mRNA level increased significantly in the CRS group when compared with control 1 group and control 2 group (Table 8).

Table 8: Summary of gene expression results (pharmacogenetic studies)

Gene	CRS	Control 1	Control 2	Significant
***Syncrip* (Exp 2)**	0.878 ±0.187, n=15	0.734 ± 0.222, n=10	1 ± 0.257, n=16	*P*=0.026# CRS vs. control 1: ns# CRS vs. control 2: ns# Control1 vs. control 2: *P*=0.020#
***Cwc22* (Exp 2)**	1.57 ± 0.648, n=15	0.959 ± 0.452, n=10	1 ± 0.358, n=16	*P*=0.0094# CRS vs. control 1: *P*=0.0094# CRS vs. control 2: P=0.037#

Values are presented as mean ± SEM (standard error of the mean); Exp1, chronic restraint stress experiment 1; Exp2, chronic restraint stress experiment 2; control 1, single-housed non-CRS group; control 2, group-housed non-CRS group; # = one-way ANOVA followed by the Tukey's multiple comparisons post-hoc test; significant was set at *P*<0.05.

CHAPTER 6:
PHF21B, ARHGAP8 AND PRR5 PROTEIN LEVEL CHANGES IN RESPONSE TO CRS

PHF21B has been indicated associated with the susceptibility of MDD in a Los Angeles Mexican-American cohort, and this association has been replicated in a European ancestry cohort. Therefore, PHF21B, and its neighbouring gene ARHGAP8 and PRR5, are three genes we have selected to address their relevance to the stress response. In gene expression level experiments, we have identified that both *Phf21b* and *Arhgap8* mRNA levels in the rat hippocampus were significantly changed in response to CRS. In order to further investigate and confirm the changes of our candidate MDD risk genes, we quantified their protein level changes via Western Blot analysis. The protein levels of PHF21B, ARHGAP8 and PRR5, were normalised to total protein loaded on Criterion™ TGX Stain-Free™ Precast Gels (see APPENDICES Figure 34~36) and data were analysed by the Imagine Lab V5.2.1 software.

According to our data, significant differences were found in the PHF21B protein level between the three groups (one-way ANOVA, $P<0.0001$). Tukey's multiple comparisons post-hoc test indicated that the CRS and control 1 groups had significant decreased hippocampal PHF21B protein levels in comparison to the Control 2 group (CRS vs. control 2 and control 1 vs. control 2 group, both with $P<0.0001$, Figure 31).

The relative protein expression of ARHGAP8 was significantly different between the three groups (one-way ANOVA, $P=0.0024$). Tukey's multiple comparisons post-hoc test indicated that the CRS and control 1 groups had significantly increased hippocampal ARHGAP8 protein levels in comparison to the control 2 group (CRS vs. control 2 and control 1 vs. control 2 group with $P=0.044$ and $P=0.0024$ respectively, Figure 32). However, we found no significant difference in the relative expression

level of PRR5 protein between the three groups (one-way ANOVA, *P*=0.13) (Figure 33).

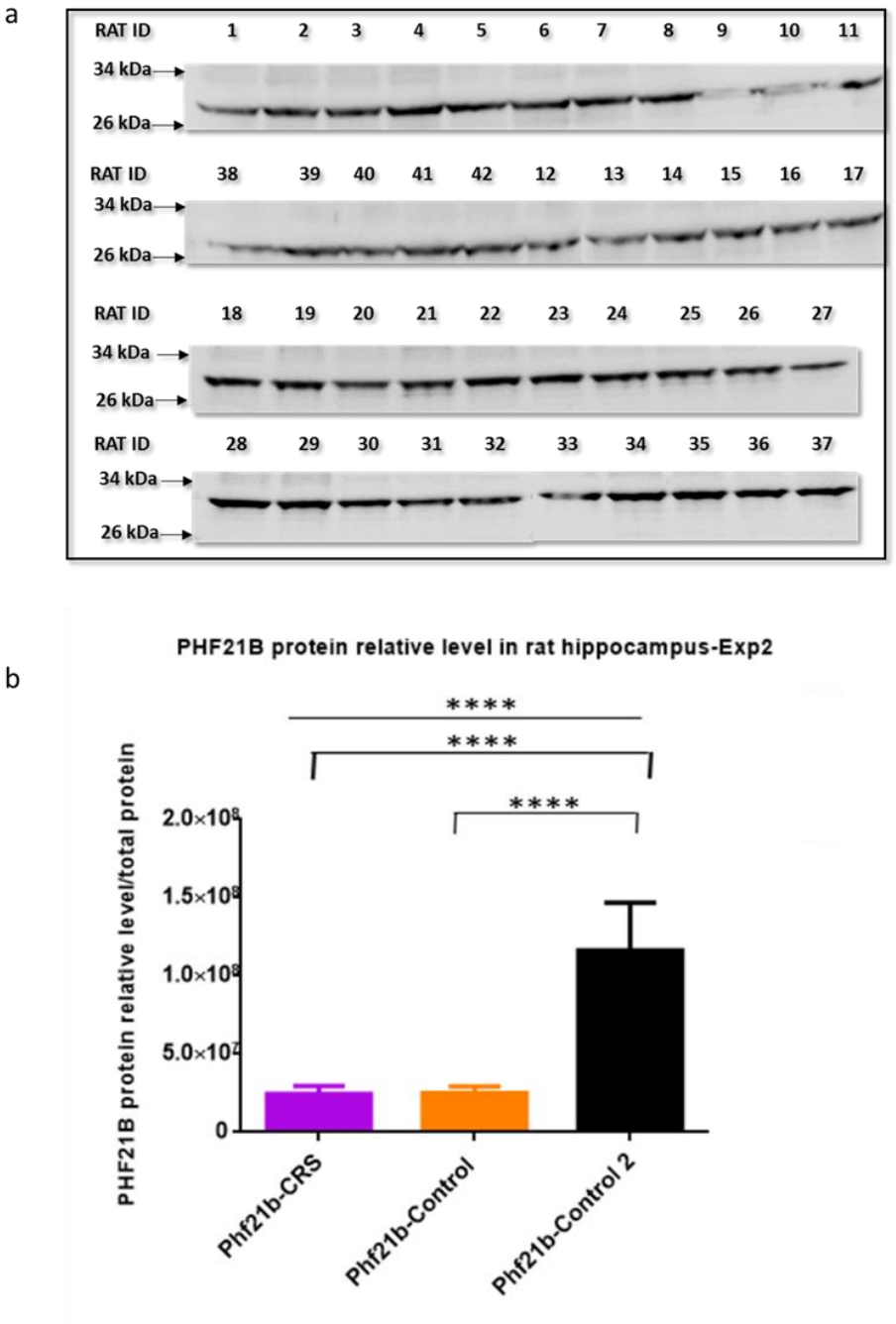


Figure 31: Western blot analyses and quantitative results of PHF21B protein levels in the rat hippocampus.

(a) Western blot analyses of PHF21B fragments in the rat hippocampus (CRS: RAT ID 1-10 and 38-42; Control1: RAT ID 11-20 ant 37; Control 2: RAT ID 21-36). (b) Quantification of PHF21B fragments. Intensities of immunoreactive bands on Western blots were quantified by densitometric analysis (Imagine Lab V5.2.1; BioRad; CA, USA). The relative protein expression level was normalised to total protein loaded. We found PHF21B protein level was significantly decreased in comparison to Control 2 group (Kruskal Wallis test, $P<0.0001$). The Dunn's multiple comparisons post-hoc test indicated that there were significant differences between CRS vs. Control 2 and Control 1 vs. Control 2 group both with $P<0.0001$. ****=$P\leq 0.0001$.

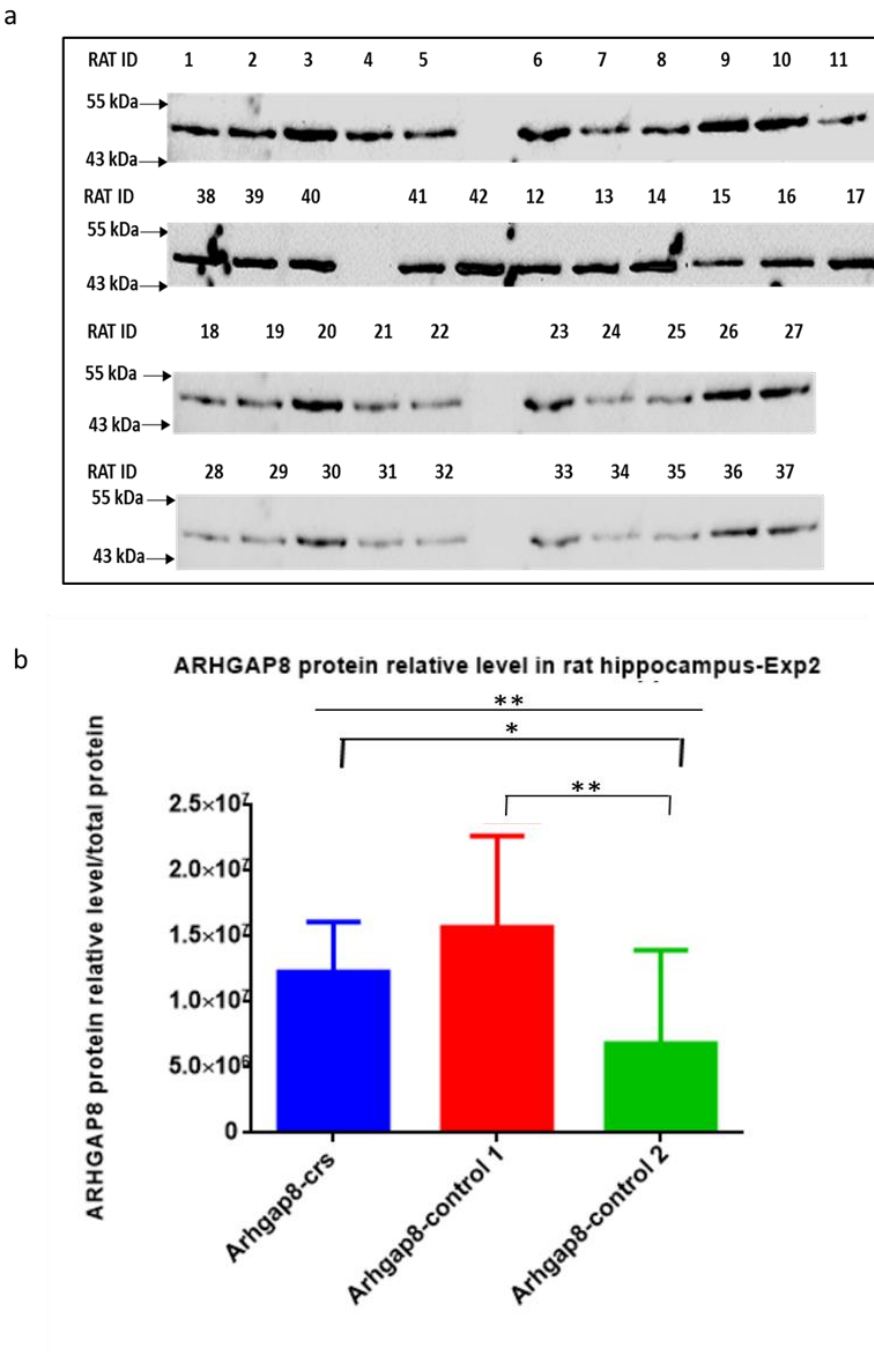


Figure 32: Western blot analyses and quantitative results of ARHGAP8 protein levels in the rat hippocampus.

(a) Western blot analyses of ARHGAP8 fragments in the rat hippocampus (CRS: RAT ID 1-10 and 38-42; Control1: RAT ID 11-20 ant 37; Control 2: RAT ID 21-36). (b) Quantification of ARHGAP8 fragments. Intensities of immunoreactive bands on Western blots were quantified by densitometric analysis (Imagine Lab V5.2.1; BioRad; CA, USA). The relative protein expression level was normalised to total protein loaded. We found that ARHGAP8 protein level was a significant increase in comparison to Control 2 group (one-way ANOVA, *P* = 0.0024). Tukey's multiple comparisons post-hoc test indicated that there were significant differences between CRS vs. Control 2 and Control 1 vs. Control 2 group with *P*=0.044 and *P*=0.0024 respectively. *=*P* ≤ 0.05 **=*P*≤ 0.01.

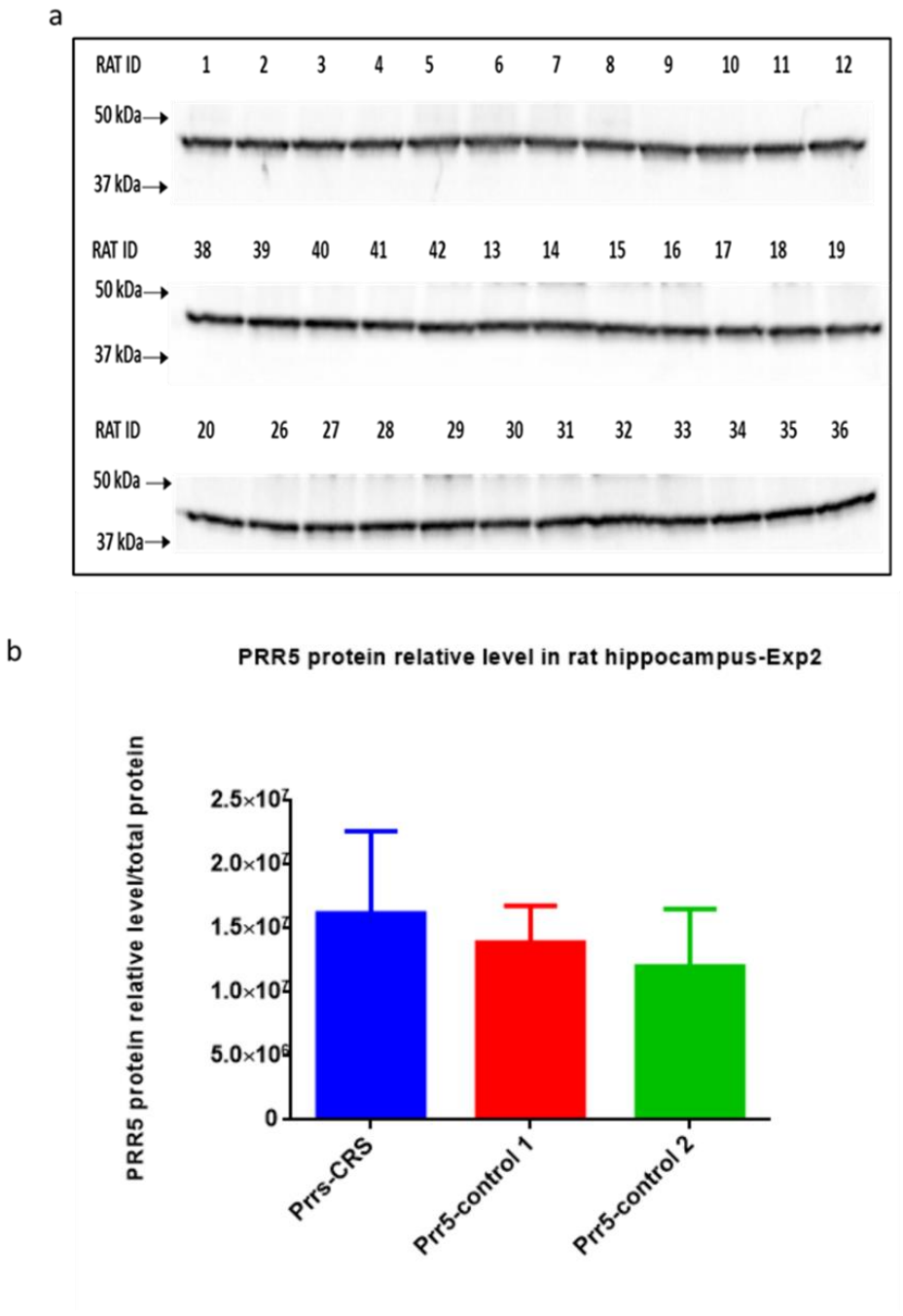


Figure 33: Western blot analyses and quantitative results of PRR5 protein levels in the rat hippocampus.

(a) Western blot analyses of PRR5 fragments in the rat hippocampus (CRS: RAT ID 1-10 and 38-42; Control1: RAT ID 11-20; Control 2: RAT ID 26-36). (b) Quantification of PRR5 fragments. Intensities of immunoreactive bands on Western blots were quantified by densitometric analysis (Imagine Lab V5.2.1; BioRad; CA, USA). The relative protein expression level was normalised to total protein loaded. We found no significant difference in the quantities of PRR5 protein relative expression level between the three groups (one-way ANOVA, *P* = ns).

CHAPTER 7:
BRAIN eQTL ANALYSIS

Our Aim 4 focused on obtaining brain quantitative trait loci (eQTL) analysis primarily in the hippocampus, as ten brain areas have been compiled in the UK Brain Expression Consortium, those areas were also included here. Data extracted from the Braineac web server (UK Brain Expression Consortium, UKBEC) revealed that *PHF21B, ARHGAP8, PRR5, TRPM2, CNTNAP1, UNC13D, ANO8, HOMER3, TBX18, NT5E, SNX14, SYNCRIPT, UBE2E3* and *CWC22* gene variants significantly change Brain Expression Quantitative trait loci (eQTL) in all ten listed brain areas (Table 9; APPENDICES: Table 23~Table 36). Seven listed variants change hippocampus eQTL of *PHF21B* (Table 10). In addition, the number of variants changed hippocampus eQTL of the *ARHGAP8, PRR5, TRPM2, UNC13D, ANO8, HOMER3, TBX18, NT5E, SNX14, SYNCRIPT,* and *CWC22* genes were twenty-two, twenty-one, fourteen, ten, seventeen, five, six, five, nineteen, six and six respectively (Table 11-21). No variants have been indicated that changed hippocampus eQTL of the *CNTNAP1, AMER2* and *UBE2E3* genes significantly.

Table 9: The number of genetic variants that affect gene expression in ten human brain regions

The number of genetic variants that affect gene expression in human brain regions											
Gene	aveLL	CRBL	FCTX	HIPP	MEDU	OCTX	PUTM	SNIG	TCTX	THAL	WHTM
PHF21B	10	29	16	7	27	4	67	15	3	32	2
ARHGAP8	13	27	27	21	10	6	11	31	32	32	32
PRR5	13	27	26	21	10	6	11	31	32	49	32
TRPM2	20	145	22	14	25	15	26	47	39	7	7
CNTNAP1	2	7	27	0	5	98	6	22	52	10	70
AMER2	0	0	0	0	0	0	0	0	0	0	0
UNC13D	36	30	25	10	35	31	20	39	28	14	33
ANO8	24	9	47	17	6	30	12	26	18	31	32
HOMER3	32	6	32	5	17	10	1	7	4	4	0
TBX18	1	11	8	6	7	26	11	12	10	10	5
NT5E	9	34	12	5	0	11	6	2	34	32	33
SNX14	47	17	18	19	14	52	19	47	21	9	37
SYNCRIP	9	23	11	6	5	4	2	3	7	21	19
UBE2E3	10	0	22	0	0	4	2	1	0	1	0
CWC22	118	12	1	6	2	8	18	8	31	20	5

Abbreviations: aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 10: Brain quantitative gene expression analyses for *PHF21B* gene variants in human hippocampus.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
3963529	rs1003851	chr22:44782265	3.90E-05	HIPP	CC=5; CT=46; TT=76	C=20.9%; T=79.1%
3963529	rs117160508	chr22:45442461	1.60E-04	HIPP	CC=1; CG=12; GG=119	C=5.2%; G=94.8%
3963529	rs118154683	chr22:45442465	1.60E-04	HIPP	TT=1; TA=12; AA=119	T=5.2%; A=94.8%
3963529	rs75806917	chr22:45442547	1.60E-04	HIPP	GG=1; GT=11; TT=119	G=4.9%; T=95.1%
3963548	rs8138025	chr22:45974757	1.90E-04	HIPP	AA=19; AG=63; GG=52	A=37.7%; G=62.3%
3963548	rs5765490	chr22:45974913	2.10E-04	HIPP	TT=19; TC=63; CC=52	T=37.7%; C=62.3%
3963550	rs62228464	chr22:45113754	6.60E-05	HIPP	CC=18; CA=51; AA=61	C=32.5%; A=67.5%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 11: Brain quantitative gene expression analyses for *ARHGAP8* gene variants in human hippocampus.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
3948261	rs2896050	chr22:44523593	1.50E-04	HIPP	AA=3;AG=25;GG=100	A=11.6%; G=88.4%
3948265	rs134834	chr22:46014135	4.00E-05	HIPP	CC=4; CG=41; GG=22	C=18.3%; G=81.7%
3948265	rs8141570	chr22:46007345	5.10E-05	HIPP	AA=35; AG=57; GG=41	A=47.4%; G=52.6%
3948265	rs6519866	chr22:46007623	5.10E-05	HIPP	TT=35; TG=57; CC=41	T=47.4%; C=52.6%
3948265	rs4823229	chr22:46007997	5.10E-05	HIPP	TT=35; TC=57; CC=41	T=47.4%; C=52.6%

3948265	rs4823309	chr22:46004023	9.80E-05	HIPP	TT=28; TC=55; CC=38	T=41.4%; C=58.6%
3948281	rs6006914	chr22:45397719	1.20E-04	HIPP	TT=2; TC=26; CC=106	T=11.2%; C=88.8%
3948281	rs1997890	chr22:45406391	2.80E-04	HIPP	AA=30; AG=64; GG=40	A=46.3%; G=53.7%
3948281	rs7293154	chr22:45412589	2.80E-04	HIPP	CC=30; CT=66; TT=38	C=47%; T=53%
3948281	rs7293173	chr22:45412630	2.90E-04	HIPP	CC=30; CT=66; TT=38	C=47%; T=53%
3948348	rs136737	chr22:45925607	7.60E-05	HIPP	AA=19; AG=61; GG=41	A=36.9%; G=63.1%
3948348	rs136732	chr22:45924094	1.70E-04	HIPP	TT=25; TC=65;CC=41	T=42.9%; C=57.1%
3948348	rs9626567	chr22:45207555	2.80E-04	HIPP	GG=26; GC=64; CC=44	G=43.3%; C=56.7%
3948348	rs470067	chr22:45934420	3.10E-04	HIPP	GG=25; GT=66; TT=41	G=43.3%; T=56.7%
3948348	rs8141472	chr22:45174346	3.70E-04	HIPP	TT=19; TC=57; CC=40	T=35.4%; C=64.6%
3948348	rs136756	chr22:45937061	3.70E-04	HIPP	AA=25; AG=68; GG=41	A=44%; G=56%
3948362	NA	chr22:44811116:C_CTT	2.20E-04	HIPP	NA	NA
3948362	rs135942	chr22:44812954	2.60E-04	HIPP	AA=12; AG=48; GG=74	A=26.9%; G=73.1%
3948364	rs132436	chr22:45149619	7.40E-05	HIPP	AA=7; AG=46; GG=70	A=22.4%; G=77.6%
3948364	rs132435	chr22:45149613	7.50E-05	HIPP	CC=7; CA=46; AA=70	C=22.4%; A=77.6%
3948364	rs4372	chr22:45149541	7.90E-05	HIPP	GG=6; GA=46; AA=70	G=21.6%; A=78.4%
3948366	rs9614187	chr22:44193626	2.00E-04	HIPP	AA=30; AC=72; CC=32	A=49.3%; C=50.7%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 12: Brain quantitative gene expression analyses for PRR5 gene variants in human hippocampus.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
3948261	rs2896050	chr22:44523593	1.50E-04	HIPP	AA=3; AG=25; GG=100	A=11.6%; G=88.4%
3948265	rs134834	chr22:46014135	4.00E-05	HIPP	CC=4; CG=41; GG=22	C=18.3%; G=81.7%
3948265	rs8141570	chr22:46007345	5.10E-05	HIPP	AA=35; AG=57; GG=41	A=47.4%; G=52.6%
3948265	rs6519866	chr22:46007623	5.10E-05	HIPP	TT=3; TC=57; CC=41	T=47.4%; C=52.6%
3948265	rs4823229	chr22:46007997	5.10E-05	HIPP	TT=35; TC=57; CC=41	T=47.4%; C=52.6%
3948265	rs4823309	chr22:46004023	9.80E-05	HIPP	TT=8; TC=55; CC=38	T=41.4%; C=58.6%
3948281	rs6006914	chr22:45397719	1.20E-04	HIPP	TT=2; TC=26; CC=106	T=11.2%; C=88.8%
3948281	rs1997890	chr22:45406391	2.80E-04	HIPP	AA=30; AG=64; GG=4	A=46.3%; G=53.7%
3948281	rs7293154	chr22:45412589	2.80E-04	HIPP	CC=30; CT=66; TT=38	C=47%; T=53%
3948281	rs7293173	chr22:45412630	2.90E-04	HIPP	CC=30; CT=66; TT=38	C=47%; T=53%
3948348	rs136737	chr22:45925607	7.60E-05	HIPP	AA=19; AG=61; GG=41	A=36.9%; G=63.1%
3948348	rs136732	chr22:45924094	1.70E-04	HIPP	TT=25; TC=65; CC=41	T=42.9%; C=57.1%
3948348	rs9626567	chr22:45207555	2.80E-04	HIPP	GG=26; GC=64; CC=44	G=43.3%; C=56.7%
3948348	rs470067	chr22:45934420	3.10E-04	HIPP	GG=25; GT=66; TT=41	G=43.3%; T=56.7%

3948348	rs8141472	chr22:45174346	3.70E-04	HIPP	TT=19; TC=57; CC=40	T=35.4%; C=64.6%
3948348	rs136756	chr22:45937061	3.70E-04	HIPP	AA=25; AG=68; GG=41	A=44%; G=56%
3948362	NA	chr22:44811116:C_CTT	2.20E-04	HIPP	NA	NA
3948362	rs135942	chr22:44812954	2.60E-04	HIPP	AA=12; AG=48; GG=74	A=26.9%; G=73.1%
3948364	rs132436	chr22:45149619	7.40E-05	HIPP	AA=7; AG=46; GG=70	A=22.4%; G=77.6%
3948364	rs132435	chr22:45149613	7.50E-05	HIPP	CC=7; CA=46; AA=70	C=22.4%; A=77.6%
3948364	rs4372	chr22:45149541	7.90E-05	HIPP	GG=6; GA=46; AA=70	G=21.6%; A=78.4%
3948366	rs9614187	chr22:44193626	2.00E-04	HIPP	AA=30; AC=72; CC=32	A=49.3%; C=50.7%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 13: Brain quantitative gene expression analyses for *TRPM2* gene variants in human hippocampus.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
3923704	rs766242	chr21:45151472	1.10E-04	HIPP	TT=4; TC=40; CC=90	T=17.9%; C=82.1%
3923704	NA	chr21:45147248:CCCTT	2.50E-04	HIPP	DD=2; DR=22; RR=102	D=9.7%; R=90.3%
3923720	NA	chr21:46803669	2.60E-05	HIPP	NA	NA
3923720	NA	chr21:46802881	2.70E-05	HIPP	NA	NA
3923720	NA	chr21:46780664	2.70E-05	HIPP	NA	NA
3923720	NA	chr21:46802819	2.80E-05	HIPP	NA	NA
3923720	NA	chr21:46802436	2.80E-05	HIPP	NA	NA
3923720	rs6518228	chr21:46772085	2.80E-05	HIPP	AA=1; AG=9; GG=97	A=14.2%; G=85.8%

3923720	NA	chr21:46798955	3.00E-05	HIPP	NA	NA
3923720	NA	chr21:46774590	3.00E-05	HIPP	NA	NA
3923720	NA	chr21:46788083	3.10E-05	HIPP	NA	NA
3923720	NA	chr21:46788995	3.10E-05	HIPP	NA	NA
3923722	rs541476	chr21:44795084	7.50E-05	HIPP	TT=9; TC=39; CC=67	T=21.3%; C=78.7%
3923722	NA	chr21:44802944:GCACC	9.90E-05	HIPP	NA	NA
3923725	rs62230080	chr21:45214365	1.70E-04	HIPP	TT=0; TC=14; CC=120	T=5.2%; C=94.8%
3923725	rs74451301	chr21:45188278	3.50E-04	HIPP	AA=1; AG=12; GG=121	A=5.2%; G=94.8%
3923738	rs149216252	chr21:45682807	1.80E-04	HIPP	TT=0; TA=22; AA=111	T=8.2%; A=91.8%
3923738	rs28681623	chr21:46105373	4.30E-04	HIPP	TT=9; TC=45; CC=77	T=23.5%; C=76.5%
3923744	rs7282380	chr21:45677248	3.10E-05	HIPP	AA=21; AG=59; GG=53	A=37.7%; G=62.3%
3923744	NA	chr21:44797174:T_TG	9.50E-05	HIPP	NA	NA
3923744	rs73223003	chr21:44797498	1.50E-04	HIPP	AA=2; AG=25; GG=103	A=10.8%; G=89.2%
3923744	rs73221000	chr21:44795804	1.50E-04	HIPP	TT=2; TC=25; CC=102	T=10.8%; C=89.2%
3923744	rs56354854	chr21:45674950	1.60E-04	HIPP	TT=19; TA=57; AA=50	T=35.4%; A=64.5%
3923752	NA	chr21:46818397	5.30E-05	HIPP	NA	NA
3923752	NA	chr21:46819149	5.30E-05	HIPP	NA	NA
3923752	NA	chr21:46818579	8.90E-05	HIPP	NA	NA
3923756	rs882549	chr21:46308441	3.10E-04	HIPP	AA=4; AC=46; CC=82	A=20.1%; C=79.9%
3923761	rs6518318	chr21:45149133	2.80E-04	HIPP	TT=22; TC=68; CC=44	T=41.8%; C=58.2%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 14: Brain quantitative gene expression analyses for *UNC13D* gene variants in human hippocampus.

Expr ID	rsID	Variant	*P-value*	tissue	Genotype_counts	Allele_frequency
3770985	rs113769601	chr17:74130237	5.70E-04	HIPP	AA=3; AG=21; GG=102	A=10.1%; G=89.9%
3770997	rs11870242	chr17:74824168	2.70E-04	HIPP	AA=11; AG=46; GG=72	A=25.4%; G=74.6%
3770997	rs12945478	chr17:74824376	2.70E-04	HIPP	CC=8; CG=46; GG=72	C=23.1%; G=76.9%
3770997	rs11870421	chr17:74824161	3.50E-04	HIPP	TT=11; TC=47; CC=72	T=25.7%; C=74.3%
3771009	rs16968673	chr17:74168831	1.60E-04	HIPP	TT=1; TA=15; AA=113	T=6.3%; A=93.7%
3771009	rs72868716	chr17:74163247	2.00E-04	HIPP	TT=1; TC=13; CC=117	T=5.6%; C=94.4%
3771009	NA	chr17:74431487:CACAC	2.80E-04	HIPP	NA	NA
3771009	rs874530	chr17:74377307	4.30E-04	HIPP	CC=19; CT=59; TT=37	C=36.2%; T=63.8%
3771012	rs112336265	chr17:74579215	3.10E-06	HIPP	GG=0; GT=12; TT=121	G=4.5%; T=95.5%
3771012	rs60276435	chr17:74580142	1.00E-05	HIPP	TT=0; TC=10; CC=122	T=3.7%; C=96.3%
3771012	rs8076344	chr17:74568303	1.10E-05	HIPP	TT=0; TC=16; CC=118	T=6%; C=94%
3771012	rs76538582	chr17:74566170	1.10E-05	HIPP	CC=0; CT=16; TT=118	C=6%; T=94%
3771012	rs78084209	chr17:74566132	1.30E-05	HIPP	TT=0; TC=16; CC=118	T=6%; C=94%
3771014	rs76114178	chr17:72933993	3.60E-05	HIPP	GG=1; GC=32; CC=88	G=12.7%; C=87.3%

3771023	rs36089184	chr17:72866377	8.10E-04	HIPP	TT=1; TC=25; CC=96	T=10.1; C=89.9%
3771027	rs72868716	chr17:74163247	5.50E-05	HIPP	TT=1; TC=13; CC=117	T=5.6%; C=94.4%
3771027	rs76114178	chr17:72933993	1.10E-04	HIPP	GG=1; GC=32; CC=88	G=12.7%; C=87.3%
3771027	rs16968673	chr17:74168831	1.40E-04	HIPP	TT=1; TA=15; AA=113	T=6.3%; A=93.7%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 15: Brain quantitative gene expression analyses for *ANO8* gene variants in human hippocampus.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
t3854376	rs4549004	chr19:17756029	2.60E-05	HIPP	AA=1; AG=21; GG=64	A=8.6%; G=91.4%
t3854376	rs4541187	chr19:17756179	3.80E-05	HIPP	CC=1; CT=23; TT=62	C=9.3%; T=90.7%
3854378	rs113502859	chr19:18019349	2.10E-04	HIPP	AA=1; AG=11; GG=119	A=4.9%; G=95.1%
3854378	rs4808102	chr19:18020685	2.70E-04	HIPP	GG=2; GA=10; AA=119	G=5.2%; A=94.8%
3854379	rs3212770	chr19:17944900	4.30E-05	HIPP	TT=2; TA=31; AA=54	T=13.1%; A=86.9%
3854379	rs2302601	chr19:17941173	1.10E-04	HIPP	GG=2; GC=35; CC=52	G=14.6%; C=85.4%
3854379	rs2302600	chr19:17941143	1.10E-04	HIPP	CC=2; CA=35; AA=52	C=14.6%; A=85.4%
3854379	rs2302603	chr19:17941294	2.40E-04	HIPP	CC=3; CT=39; TT=41	C=16.8%; T=83.2%
3854386	NA	chr19:17519240 :T_TTT	4.40E-04	HIPP	NA	NA
3854400	rs62126776	chr19:17581948	6.30E-05	HIPP	TT=1; TC=15; CC=102	T=6.3%; C=93.7%

3854400	NA	chr19:16437048	1.30E-04	HIPP	NA	NA
3854400	rs55714539	chr19:18207397	2.30E-04	HIPP	CC=12; CA=53; AA=55	C=28.7%; A=71.3%
3854400	NA	chr19:16434454	2.40E-04	HIPP	NA	NA
3854408	rs6512254	chr19:18381328	3.30E-07	HIPP	GG=5; GT=55; TT=72	G=24.3%; T=75.7%
3854408	rs2080831	chr19:18409268	1.40E-05	HIPP	TT=6; TG=51; GG=11	T=23.5%; G=76.5%
3854408	rs41446250	chr19:18390253	3.70E-05	HIPP	AA=2; AG=25; GG=107	A=10.8%; G=89.2%
3854408	rs4549004	chr19:17756029	5.10E-05	HIPP	AA=1; AG=21; GG=64	A=8.6%; G=91.4%
3854408	rs60235938	chr19:18396394	6.10E-05	HIPP	AA=2; AG=24; GG=108	A=10.4%; G=89.6%
3854408	rs113451170	chr19:18397062	6.10E-05	HIPP	CC=2; CT=24; TT=108	C=10.4%; T=89.6%
3854408	rs4541187	chr19:17756179	6.20E-05	HIPP	CC=1; CT=23; TT=62	C=9.3%; T=90.7%
3854408	rs58997823	chr19:18398720	8.60E-05	HIPP	GG=1; GA=24; AA=106	G=9.7%; A=90.3%
3854408	rs56069717	chr19:18383482	9.20E-05	HIPP	GG=2; GA=26; AA=105	G=11.2%; A=88.8%
3854408	rs16982288	chr19:18383293	1.10E-04	HIPP	CC=2; CG=27; GG=105	C=11.6%; A=88.4%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 16: Brain quantitative gene expression analyses for *HOMER3* gene variants in human hippocampus.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
3855359	rs181358521	chr19:19799184	4.10E-04	HIPP	CC=0; CT=20; TT=86	C=7.5%; T=92.5%
3855364	rs17885551	chr19:18179672	2.40E-04	HIPP	CC=3; CT=37;	C=16%; T=84%

					TT=89	
3855364	rs17886399	chr19:18179702	2.40E-04	HIPP	AA=3; AG=37; GG=89	A=16%; G=84%
3855364	NA	chr19:18179832:TTA_T	3.00E-04	HIPP	NA	NA
3855364	rs12150884	chr19:18179973	3.60E-04	HIPP	AA=4; AG=38; GG=90	A=17.2%; G=82.8%
3855364	rs2305739	chr19:18180194	3.80E-04	HIPP	AA=4; AG=40; GG=90	A=17.9%; G=82.1%
3855364	rs2305740	chr19:18180236	3.80E-04	HIPP	GG=4; GA=40; AA=90	G=17.9%; A=82.15

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 17: Brain quantitative gene expression analyses for *TBX18* gene variants in human hippocampus.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
t2963142	rs9362033	chr6:84948961	5.80E-04	HIPP	GG=1;GA=34;AA=93	G=13.4%,A=86.6%
2963145	rs6916255	chr6:85383871	2.00E-04	HIPP	CC=14;CT=61;TT=55	C=33.2%;T=66.8%
2963145	rs7768657	chr6:85383196	3.90E-04	HIPP	TT=15;TA=57;AA=57	T=32.5%;A=67.5%
2963145	rs9450002	chr6:85376381	5.00E-04	HIPP	CC=37;CT=65;TT=32	C=51.9%;T=48.1%
2963145	NA	chr6:85369726:A_AT	7.20E-04	HIPP	NA	NA
2963145	rs7743504	chr6:85379042	7.20E-04	HIPP	AA=14;AG=60;GG=60	A=32.8%;G=67.2%
2963161	rs12194396	chr6:85331136	3.60E-04	HIPP	TT=0;TC=7;CC=108	T=2.6%;C=97.4%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 18: Brain quantitative gene expression analyses for *NT5E* gene variants in human hippocampus.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
2915849	rs9444269	chr6:85683704	1.20E-04	HIPP	GG=13;GA=62;AA=59	G=32.8%;A=67.2%
2915858	rs9444291	chr6:85777885	7.90E-05	HIPP	Tt=0;TC=26;CC=105	T9.7%;C=90.3%
2915858	rs9450140	chr6:85776709	8.00E-05	HIPP	GG=0;GT=26;TT=105	G=9.7%;T=90.3%
2915858	rs9450139	chr6:85774633	8.10E-05	HIPP	AA=0;AG=27;GG=105	A=10.1%;G=89.9%
2915858	rs57664101	chr6:85773712	8.20E-05	HIPP	TT=0;TC=27;CC=105	T=10.1%;C=89.9%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 19: Brain quantitative gene expression analyses for *SNX14* gene variants in human hippocampus.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
2963323	rs191754530	chr6:87238639	6.80E-05	HIPP	TT=0;TG=12;GG=110	T=4.5%;G=95.5%
2963335	rs9353304	chr6:86080158	1.50E-04	HIPP	CC=3;CG=33;GG=97	C=14.6%;G=85.4%
2963338	rs17695108	chr6:85724717	6.20E-04	HIPP	CC=0;CT=20;TT=111	C=7.5%;T=92.5%
2963338	rs149702128	chr6:86020914	7.30E-04	HIPP	AA=0;AT=14;TT=112	A=5.2%;T=95.8%
2963338	rs75202618	chr6:86013713	7.70E-04	HIPP	GG=0;GA=14;AA=112	G=5.2%;A=94.8%
2963349	rs191754530	chr6:87238639	1.10E-04	HIPP	TT=0;TG=12;GG=110	T=4.5%;G=95.5%
2963357	rs62440692	chr6:87209701	1.70E-05	HIPP	AA=1;AG=21;GG=101	A=8.6%;G=91.4%
2963357	rs6911143	chr6:86221771	3.70E-05	HIPP	TT=21;TC=59;CC=46	T=37.7%;C=62.3%
2963357	rs2324775	chr6:86067614	1.70E-04	HIPP	GG=3;GT=34;TT=97	G=14.9%;T=85.

						1%
2963379	rs145351744	chr6:85536888	2.10E-06	HIPP	TT=1;TC=23;CC=102	T=9.3%;C=90.7 %
2963379	rs6454398	chr6:85548671	2.40E-06	HIPP	GG=1;GC=23;CC=103	G=9.3%;C=90.7 %
2963379	rs2224210	chr6:85574238	4.70E-06	HIPP	CC=1;CA=24;AA=109	C=9.7%;A=90.3 %
2963379	rs2324751	chr6:85550546	4.70E-06	HIPP	CC=1;CT=24;TT=109	C=9.7%;T=90.3 %
2963379	rs6454400	chr6:85568534	4.70E-06	HIPP	AA=1;AG=24;GG=109	A=9.7%;G=90.3 %
2963379	rs9353228	chr6:85571747	4.70E-06	HIPP	TT=1;TA=24;AA=109	T=9.7%;A=90.3 %
2963379	rs2207979	chr6:85572462	4.70E-06	HIPP	TT=1;TC=24;CC=109	T=9.7%;C=90.3 %
2963379	rs2324754	chr6:85570015	4.70E-06	HIPP	GG=1;GA=24;AA=109	G=9.7%;A=90.3 %
2963379	rs2024848	chr6:85563886	4.70E-06	HIPP	AA=1;AG=24;GG=109	A=9.7%;G=90.3 %
2963379	rs2024847	chr6:85564139	4.70E-06	HIPP	CC=1;CT=24;TT=109	C=9.7%;T=90.3 %

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 20: Brain quantitative gene expression analyses for *SYNCRIP* gene variants in human hippocampus.

Expr ID	**rsID**	**Variant**	***P*-value**	tissue	**Genotype_counts**	**Allele_frequency**
t2963407	rs139549658	chr6:85779709	4.50E-04	HIPP	TT=0;TA=13;AA=119	T=4.9%;A=95.1%
2963409	rs143405116	chr6:85537381	2.60E-04	HIPP	GG=3;GA=42;AA=26	G=17.9%;A=82.1%
2963412	rs17695108	chr6:85724717	1.50E-03	HIPP	CC=0;CT=20;TT=111	C=7.5%;T=92.5%
2963415	rs139549658	chr6:85779709	9.50E-04	HIPP	TT=0;TA=13;AA=119	T=4.9%;A=95.1%

2963415	rs193100232	chr6:87310833	1.10E-03	HIPP	AA=1;AG=7;GG=113	A=3.4%;G=96.6%
2963425	NA	chr6:85924728:G_GT	7.60E-04	HIPP	NA	NA
2963425	rs74607413	chr6:86604073	1.20E-03	HIPP	GG=3;GA=31;AA=58	G=13.8%;A=86.2%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 21: Brain quantitative gene expression analyses for *CWC22* gene variants in human hippocampus.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
2590216	NA	chr2:181492520:T_TA	4.40E-04	HIPP	NA	NA
2590216	rs16867335	chr2:181458934	4.40E-04	HIPP	TT=6;TC=44;CC=84	T=20.9%;C=79.1%
2590216	rs35579320	chr2:181463612	4.40E-04	HIPP	CC=6;CT=44;TT=84	C=20.9%;T=79.1%
2590216	rs72884242	chr2:181465486	4.40E-04	HIPP	TT=6;TA=44;AA=84	T=20.9%;A=79.1%
2590216	rs6739798	chr2:181465853	4.40E-04	HIPP	CC=6;CT=44;TT=84	C=20.9%;T=79.1%
2590216	rs34842451	chr2:181480525	4.40E-04	HIPP	CC=6;CT=44;TT=84	C=20.9%;T=79.1%
2590220	rs13424082	chr2:180227865	4.20E-04	HIPP	AA=4;AG=45;GG=84	A=19.8%;G=80.2%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; HIPP, hippocampus. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

CHAPTER 8:
DISCUSSION AND CONCLUSION

Previous studies from SAHMRI Mind and Brain Theme identified forty-four common and rare functional variants potentially associated with MDD in Mexican-Americans and several SNPs closely related with antidepressant treatment remission through pharmacogenetic studies. These genes and SNPs may also be relevant to stress response (Wong et al., 2016, Wong et al., 2014b). We used an animal model of depressive-like behaviour induced by CRS to validate candidate genes or genes nearby significant intergenic SNPs. The hippocampus is one of the most important brain regions in the stress response; therefore, our studies have determined genes expression changes in the rat hippocampus after two weeks of CRS. We used real-time qPCR to evaluate the gene expression between CRS, social isolation stress and control group-housed animals. According to our findings, we have confirmed that the gene expression for the *Phf21b*, *Arhgap8*, *Trpm2*, *Cntnap1*, *Cwc22*, *Syncrip*, and *Unc13d* are modulated by CRS or social isolation stress. Moreover, the protein level of PHF21B and ARHGAP8 were also significantly altered by CRS. These conclusions suggested that our risk genes play a critical role in the mechanism of CRS response; these genes could be novel therapeutic targets for the development of antidepressant drugs.

Major depression is a complex multifactorial disease. According to the widely used diagnostic criteria from the DSM-5 (American Psychiatric Association, 2013) and ICD-10, MDD is a broad category of mental disorder that includes a variety of symptoms and dysfunctions. It also is noticeably heterogeneous (Gold et al., 2013). Furthermore, a long treatment course with antidepressant drugs is needed for MDD. Therefore, it brings substantial economic burden to societies and families. Currently, antidepressant drugs are used to alleviate depressive symptoms. However, antidepressant therapy also has limitations as some patients have no significant

therapeutic effects from different antidepressant treatments (Henter et al., 2016). In recent years, as scholars have further examined the pathogenesis of depression, increasing evidence has shown that the occurrence of depression and the treatment effect from antidepressant drugs are associated with the patients' genetic make up (Choudary et al., 2005; Bosker et al., 2011; Wray et al., 2012; Kang et al., 2012; Levinson, 2006; Wong et al., 2006; Wong et al., 2016; Wong et al., 2014b). This conclusion has safely supported the previous studies which demonstrated that genetic variation contributes to the development of MDD, with a heritability of above 37% (Belmaker and Agam, 2008, Sullivan et al., 2000, Lesch, 2004). Therefore, it is important to identify the genes that are related to this disease for its prevention and to improve treatment approaches. The hypothesis that gene variants affect antidepressant remission in patients was initially presented based on the observations that MDD and the success of antidepressant treatment have shown a typical clustering trend (Fabbri et al., 2014). Furthermore, current research suggests that the genetic variation of neurotransmitter transporter protein, anabolism enzymes, various receptor subtypes and intracellular signal transduction systems plays a crucial role in the pathogenesis of depression. There have been a large number of genes identified that play a role in depression; however, there is still a lack of unambiguous and uniform conclusions regarding the specific role of those genes that are associated with MDD, therefore, further investigations are needed to address this issue.

8.1 The CRS-induced depression model has been successfully implemented in our lab previously

Numerous studies have shown that stressful life events have a dose-response relationship with depression (Kendler et al., 2005, Kessler, 1997, Tennant et al., 1981, Hamer et al., 2009). However, the abnormal behaviour caused by stress can

apparently be alleviated through antidepressant treatment. In this project used a depressive-like behaviour rat model induced by CRS. The CRS paradigm used consisted to restraining rats in flat-bottom clear acrylic containers for six hours each day for 14 days. During the restraint period, rats were unable to access water and food. Pham *et al.* (2003) used two different restraint paradigms (six hours of daily restraint for three weeks and six weeks) to elicit decreased hippocampal neurogenesis (Pham et al. 2003). Compared with Pham's work, this study used a modified restraint model. In our study, CRS rats were housed individually in both Exp1 and Exp2 because previous experiments in our group showed that single-housed rats displayed depressive-like behaviour more consistently. The experimental paradigm was to perform six hours of daily chronic mild stress for only two weeks. Our data indicated that this period of restraint increased the total immobility time in the FST test and decreased the percentage of 1% sucrose water intake in sucrose preference test. Additionally, this model meets the three criteria for a successful animal model of depression: good predictive validity, good face validity, and construction of validity. This study selected two different rodent behaviour tests to evaluate the successful implementation of the depressive-like behaviour model. The first behavioural test used was the FST performed to evaluate animals' behavioural despair. This study measured the total immobility time during the five-minute trial period performed twenty-four hours after a ten-minute training session. This stationary state was interpreted as the rat abandoning hope of escape and becoming depressed (Borsini et al., 1986, Ciulla et al., 2007). This behavioural despair is also similar to core symptoms of depression within humans (Dar & Khatoon 2000 and Takeda et al. 2002). In our experiment, the immobility time was increased by CRS. Additionally, in our animal depression model, two weeks of CRS-induced caused anhedonia in rats,

as ascertained by the rodent significantly reduced preference for sucrose solution compared with the none-stress control group. This change is a critical indicator for evaluating the success of animal depression models. These results are consistent with previous reports (Li et al., 2011, Chiba et al., 2012). In conclusion, the depression model of rats in this study was successful and also laid a solid foundation for the gene expression experiments.

8.2 Genes selected from our lab's published genetic study: Gene expression for 5 genes and protein expression for 2 genes were changed in the rat hippocampus in response to CRS or social isolation stress

8.2.1 *PHF21B*

The Finger Protein 21B (*PHF21B*) is a protein-coding gene located in Chr 22q13.31. Previous studies have suggested that the *PHF21B* gene may be an assumed tumour suppressor gene as the protein may play a role in chromatin-mediated transcriptional regulation (Bertonha et al., 2015). However, its primary function is still unclear. *PHF21A*, a paralog of *PHF21B*, has been reported to function as a transcriptional repressor in the process of neurodevelopment (Wong et al., 2016, Klajn et al., 2009). *PHF21A* also plays a critical role in normal brain development and cognition via regulating transcriptional regulation and remodelling chromatin (Kim et al., 2012). The SAHMRI Mind and Brain team has identified that variants of *PHF21B* and forty-three other common and rare functional variants associated with MDD by analysing the genomic sequence of a Mexican-American cohort of MDD cases and controls. Rare variant analysis replicated the PHF*21B* gene in a European-ancestry cohort. *PHF21B* is expressed in several difference regions of the brain including prefrontal cortex and hippocampus (Wong et al., 2016). Therefore, *PHF21B* variants might affect its expression status in those regions. These changes could also be

induced by external stress, which are linked to MDD. To investigate wether the variants of *PHF21B* is associated with MDD, we examined *Phf21b* gene expression changes in the hippocampus related to CRS-induced depressive-like behaviour in rats. In the Exp1 experiment, *Phf21b* mRNA levels were significantly reduced in the CRS-resilient group. *Phf21b* mRNA levels also appeared to decrease in the CRS non-resilient group, but this result was not significant (Figure 18 b). However, the animals were transported from the UK and were individually housed, which could have increased the stress levels in the control group. In Exp2 we repeated the same procedures conducted in Exp1 to examine *Phf21b* gene expression levels in the rat hippocampus and added an extra control group: a group-housed non-CRS control group. All the animals in the Exp2 were bred in the SAHMRI Bioresources vivarium, which prevented any extra, unpredictable source of stress that might confound results. In Exp2, CRS significantly decreased *Phf21b* mRNA level in the hippocampus when compared with the group-housed non-CRS control group. However, no significant effects occurred between the CRS group and the single-housed non-CRS group (Figure 18 c) or between the single-housed non-CRS group (control 1) and the group-housed non-CRS group (control 2). Altogether, it could be concluded that CRS-induced depression can down-regulate *Phf21b* mRNA level in the rat hippocampus. Brain eQTL identified 7 variants of *PHF21B* gene that affect its gene expression level in human hippocampus. These results validate the Mind and Brain's finding that rare variants within the *PHF21B* gene are associated with MDD (Wong et al., 2016).

8.2.2 *ARHGAP8* and *PRR5*

The *ARHGAP8* gene is located on chromosome 22q13.31, and encodes the Rho GTPase-activating protein 8. Downregulation of *ARHGAP8* could activated Rho

GTPases (Johnstone et al., 2004, Peck et al., 2002). The expression of *ARHGAP8* was up-regulated in the primary colorectal tumours (Johnstone et al., 2004). *ARHGAP8* has been identified as being involved in the development of breast and colorectal cancer using the candidate gene approach (Johnstone et al., 2004, Ellenbroek and Collard, 2007). Also, the *ARHGAP8* - *PRR5* transcript occurred naturally during the read-through transcription, although infrequently, encoding the fusion protein (Rithidech et al., 2015). In the GWAS analysis the *ARHGAP8-PPR5* transcript was significantly associated with MDD diagnosis in the Mexican-American cohort (Wong et al., 2016). Both the *ARHGAP8* and *PRR5* genes are located next to the *PHF21B* gene. These 3 genes are also closed located in the rat chr7q34; therefore, *Arhgap8* and *Prr5* mRNA levels in the rat hippocampus were investigated as well. In the Exp2 samples, *Arhgap8* mRNA level showed a significant increase in response to CRS in comparison with both the single- and group-housed non-CRS control groups (Figure 19). Also, it was noticed that the significance of this difference increased from the single- to the group-housed groups; however, no significantly difference was found between single- and group-housed animal mRNA levels. Regarding *Prr5*, no significant difference was found between the three groups (Figure 20). Brain eQTL analyses showed 21 variants of *ARHGAP8* and *PRR5* affect their expression in human hippocampus.

8.2.3 PHF21B, ARHGAP8 and PRR5 protein expression changes in response to CRS

PHF21B, ARHGAP8 and PRR5 are three neighbouring gene that may be associated with the susceptibility of MDD in a Los Angeles Mexican-American cohort. Our previous work replicated the association of *PHF21B* in a European ancestry cohort. Furthermore, in order to confirm our gene expression findings, we have also conducted Western blot experiments to examine the protein changes of PHF21B,

ARHGAP8 and PRR5 in response to both CRS and social isolation stress. We have found that the protein level of PHF21B declined significantly in both stressed groups in comparison to control groups (Figure 31). ARHGAP8 showed the opposite pattern: its protein level increased in both the CRS and social isolation stress groups (Figure 32). The protein expression alteration patterns for PHF21B and ARHGAP8 aligned well with results of gene expression studies. No significant change of PRR5 protein level has been found in our studies (Figure 33). However, there is a trend in our data that shows that both CRS and social isolation stress could alter the protein level of PHF21B and ARHGAP8 significantly. This suggests that rodents subjected to either CRS or social isolation stress can induce depressive-like behaviour and anxiety. It is well acknowledged that different chronic stress model induce various changes in the brain functions, neuroendocrine system and behaviour in rodents (Berton et al., 2007, Slattery et al., 2012, Ieraci et al., 2016). In addition, chronic stress-induced behavioural changes have been associated with neuroplasticity-related genes' alterations in distinct brain regions, which include immediate early genes, metabotropic glutamate receptors, and neurotrophic factors (Schmidt and Duman, 2010, Gray et al., 2013, Morley-Fletcher et al., 2011). Social isolation seldom produces long-lasting effects on the rodents' brain structure and behaviour. Limited research has been conducted to understand the behaviour consequence of social isolation, therefore, the underlying mechanism of behaviour and brain changes induced by social isolation are still poorly understood (Djordjevic et al., 2012, Koike et al., 2009, Pibiri et al., 2008, Thorsell et al., 2006). As such, it is necessary to carry out further research to identify the underlying mechanism of CRS and the protein level changes of PHF21B and ARHGAP8 during social isolation.

8.2.4 *TRPM2*

This gene, which encodes the transient receptor potential cation channel, subfamily m, member 2, was significantly associated with MDD in the Mexican-American cohort, and it was considered to be replicated because a previous publication reported its association to mood disorders in a European-ancestry sample (Wong et al., 2016a). TRPM2 is involved in insulin secretion (Togashi et al., 2006), and it also plays a role in activating the NLRP3 inflammasome. Therefore, an abnormal *TRPM2* level is associated with some metabolic and auto-inflammatory diseases (Zhong et al., 2013). *TRPM2* is highly expressed in different regions of the human brain including the cerebral cortex and the hippocampus (Nagamine et al., 1998). In the brain, *TRPM2* has been reported to regulate the toxicity of amyloid beta, which is associated with Alzheimer's disease (Fonfria et al., 2005; Yamamoto et al., 2007). Genetic variants of the *TRPM2* gene change the intracellular Ca^{2+} homoestasis that is associated with bipolar disorder (Xu et al., 2006) and type-2 diabetes mellitus (Romero et al., 2010). Through haplotype and sequential analyses, *TRPM2* was significantly associated with MDD (Wong et al., 2016). This work has also identified that *Trpm2* gene expression level increased significantly after two weeks of CRS in comparison to the group-housed non-CRS group (Figure 21). Fourteen genetic variants of *TRPM2* play a role in regulating its expression level in human hippocampus. However, no significant differences were found between the group- and single-housed non-CRS groups. These results may suggest that social isolation may increase stress levels or increase the variability of mRNA levels for this gene in the rat.

8.2.5 *CNTNAP1*

In other studies, variants within *CNTNAP1* have been associated with congenital hypomyelination neuropathy (Nizon et al., 2016, Mehta et al., 2016). The SAHMRI Mind and Brain group has applied the Kernel-based adaptive cluster (KBAC) method

to understand 47,296 exonic variants, which were identified by a genetic study using a Mexican-American cohort. SNPs in the *CNTNAP1* gene were associated with MDD in common and rare variant analyses (Wong et al., 2016). Although, the brain eQTL studies revealed that till now, no variant of *CNTNAP1* has been indicated affect its gene expression level in human hippocampus, in our animal study, according to Figure 22, it is clear that CRS significantly increased *Cntnap1* mRNA level compared to both control groups. No differences were found between the two control groups.

8.2.6 *AMER2/FAM123A*

APC membrane recruitment 2 (AMER2) has been reported as a novel regulator to maintaining the stability of microtubules through interacting with End-binding Protein 1 (Pfister et al., 2012a). Additionally, it also has been reported to be involved in brain development via negatively regulating the Wnt signalling pathway (Pfister et al., 2012b). We have quantified the mRNA level of *Amer2* in rat hippocampus between the CRS group and the two control groups to evaluate its relationship with CRS. Based on our results, no significant changes were found between the three groups (Figure 23), suggesting that *Amer2* may not be involved in the hippocampal response to chronic mild stress. However, although the gene expression level did not achieve significance in our experiment, future studies should investigate *Amer2* gene expression in other stress responsive brain areas, such as the prefrontal cortex and/or AMER2 protein expression in the brain.

8.2.7 *UNC13D, ANO8, and HOMER3*

The previous study from our lab identified that the *UNC13D, ANO8,* and *HOMER3* had variations significantly associated with MDD (Wong et al., 2016). eQTL data show that ten genetic variants affect UNC13D expression in the human

hippocampus. We found that the control 1 group had significantly decreased *Unc13d* gene expression level in the rat hippocampus when compared to the control 2 group (Figure 24 a). Since the control 1 group consisted of single-housed non-CRS rats, this might suggest that social isolation stress decreased *Unc13d* mRNA levels. The *UNC13D* gene is located on chromosome 17q25 and has a total of 32 exons. The p.Cys112Ser and p.Ala995Pro mutations in *UNC13D* results in encoded proteins that lack C2A and C2B and other binding domains, which lead to loss of a part or all of its biological function (Aricò et al., 2013). The UNC13D protein plays a significant role in the process of vesicle formation, activation, polarisation, docking, and its fusion with the cell membrane (Stepp et al., 1999). Until now, more than 100 pathogenic mutations of *UNC13D* have been found, including splice, deletion, insertion, nonsense, and missense mutations. *UNC13D* gene mutation loci are distributed in all 32 exons and introns, as well as the linking region of exons (Stepp et al., 1999). Meeths *et al.* (2011) also found related mutations that could induce hemophagocytic lymphohistiocytosis (HLH), which is an immunomodulatory disorder disease that mainly affects infants, older children and adults. It is also characterised by some clinical symptoms and signs caused by the dynamic inflammatory response, such as hypocytosis, hepatitis, and central nervous system disorder, which poses severe damage to life. HLH can be divided into primary (familial) and secondary (acquired) categories; the primary HLH is mainly considered to be associated with gene mutations. There are at least six genes, besides the *UNC13D* gene, that are associated with familial *HLH*, including Perforin 1 (*PRF1*), Syntaxin 11 (*STX11*), member RAS oncogene family (*RAB27A*), Syntaxin binding protein 2 (*STXBP2*), SH2 domain containing 1A (*SH2D1A*) and X-linked inhibitor of apoptosis (*XIAP*, also known as *BIRC4*). Among them, the *UNC13D*

gene is closely related to the expression of protein inside the perforin/granzyme cell death pathway (Zhang et al., 2011). In this pathway, cytotoxic T lymphocytes (CTL) and natural killer cells (NK cells) form offensive vesicles, which contain perforin and granzyme. The role of perforin is to break target cell membranes so that granzyme can enter the target cells to promote cell death. Coding mutations of the PRF1 gene influence the perforation, also causes HLH.

We compared *Ano8* gene expression levels in the rat hippocampus in CRS group and control groups and found no significant change of the mRNA level of *Ano8*, suggesting that *Ano8* might not be involved in stress response. However eQTL data showed that there are 17 genetic variants within *ANO8* that can affect its expression in the human hippocampus. Anoctamin 8 (*ANO8*, also known as *TMEM16H*) is an essential factor for epithelial cells decreasing their cell volume and activating the chloride channel when cell swelling occurs (Almaça et al., 2009). Also, the ANO protein family has been assumed to be involved in Ca2+-activated Cl− channels (Caputo et al., 2008, Hartzell et al., 2009). However, the exact function of *ANO8* is still unclear.

Similarly to *Ano8*, *Homer3* mRNA level was not changed by CRS (Figure 24 c). Even thought, there are seven variants located within *HOMER3* gene can significantly change its expression in the human hippocampus. Brakeman *et al.* first discovered *HOMER* in 1997. Currently, the *HOMER* family is divided into three families (*HOMER1*, *HOMER2*, and *HOMER3*). Previous studies showed that the expression of three groups of metabotropic glutamate receptors (mGluRs) inside the hindbrain cortex have changed in the rat with diffuse brain injury (DBI). Nonetheless, the mGluR1a had the most noticeable change, which is the important factor that aggravates neuronal damage. The receptors in this group had agonist-independent

activity; that is, in the absence of agonists, they could still mediate the increase of intracellular inositol trisphosphate (IP3) and the opening of the K^+ channel, which Ca^{2+} depends upon (Ango et al., 2001). This kind of activity was mediated by the intracellular signal transduction molecule HOMER.

8.3 Genes selected from our lab's published pharmacogenetic study

In the previous study, a total of 232 Mexican-American depression patients were enrolled in a randomised clinical trial with either fluoxetine or desipramine. After eight weeks of treatment, 36 patients who had remitted to antidepressant treatment and 29 who had not responded to treatment were studied. Analysis of their whole exome genotyping data identified that one functional variant achieve exome-wide significance level and nine other top functional variants were listed (Wong et al., 2014b). As most of these functional variants were intergenic SNP, their adjacent genes were investigated to understand whether they were relevant to the stress response. SNP exm-rs1321744 achieved exome-wide significance for antidepressant treatment remission in Mexican-American patients with MDD (Wong et al., 2014b). As rs13217744 is located in brain-methylated DNA immunoprecipitation sequencing sites, which suggest that it might be involved in the epigenetic regulation of neuronal gene expression (Wong et al., 2014b). Since rs1321744 is an intergenic variation, its adjacent genes, *TBX18, NT5E, SNX14*, and *SYNCIP,* were selected to understand whether they were stress responsive.

8.3.1 *TBX18*

We compared *Tbx18* gene expression levels in the rat hippocampus in CRS group and control groups and found no significant change of the mRNA level of *Tbx18*, suggesting that *Tbx18* might not be involved in stress response. However, brain eQTL data revealed that there are six genetic variants affected *TBX18* gene

expression in the human hippocampus. The T-box gene (*TBX18*) family has played a significant role in the embryonic development particularly of heart, kidney and urinary tract. Congenital heart defects could be caused by *TBX18* variations among humans. Previous studies have confirmed that the transcription factor TBX18, which a T-box gene family member, plays a vital part in the formation and differentiation phase of the sinoatrial node (Acloque et al., 2009). Thus, mice without *Tbx18* displayed a severe loss of the head part of the sinoatrial node (Christoffels et al., 2006, Wiese et al., 2009). Thus, the *Tbx18* gene played a major role in regulating the development of the heart.

8.3.2 *NT5E*

Also, *Nt5e* mRNA level was not changed by CRS, although five genetic variants of *NT5E* affect its expression level in human hippocampus in eQTL analyses. *NT5E*, namely 5'-nucleotidase, is a type of glycosylphosphatidylinositol lipid-anchored protein, and it is also known as lymphocyte differentiation antigen CD 73. Its primary function is to hydrolyse and catalyse the triphosadenine in the final step into adenosine. It seemingly serves as a "master switch" in ATP depletion and extracellular channels (Henttinen et al., 2003). Recent studies have found a high expression of *NT5E* in many human solid tumours, which was associated with the formation, invasion, and metastasis of new vessels and a short life expectancy of patients (Spychala, 2000). An in vitro experiment has found that *NT5E* can promote the migration of lymphocyte, and in vivo studies have shown that *NT5E* can promote angiogenesis, whose mechanism is closely related to its enzymatic activity (Henttinen et al., 2003). Epigenetic changes of *NT5E* CpG island can deregulate *NT5E* expression levels in melanoma (Wang et al., 2012). This conclusion has been confirmed by Nigro's team, who found that the methylation of CpG island of *NT5E*

displayed a strong association with the *NT5E* expression in breast carcinoma (Nigro et al., 2012).

8.3.3 *SNX14*

In our experiments, *Snx4* gene expression level was not changed by CRS. Sorting nexin-14 (*SNX14*, also known as *RGS-PX2*) encodes the SNX14 protein in humans (Haft et al., 1998) and belongs to the sorting nexin family. SNX14 has been indicated to be located next to lysosomes. Hence variations in *SNX14* are the leading cause of Autosomal-Recessive Cerebellar Ataxia and Intellectual Disability Syndrome (Thomas et al., 2014) and are also changes its expression status in different human brain regions including the hippocampus. Additionally, it has been reported that SNX14' PX domain can recognise phosphatidylinositol (3,5)-bisphosphate on endolysomal membrane (Akizu et al., 2015). Therefore, the defect of SNX14 shows large lysosomes and impairs effective autophagosome clearance. *Snx14* has also been identified as a neuronal-imprinted gene in mice through the microdissection of visual cortical neurones using a laser capture (Huang et al., 2014). The knockdown of the *Snx14* gene in mice induces an impairment of the inhibitory synaptic transmission (Huang et al., 2014). The phosphorylation of SNX14, which is regulated by protein kinase A, reduces the binding of the SNX14 and Gs alpha subunit (Gαs) and increases its binding with HTR6. The binding of SNX14 with HTR6 induces HTR6 degradation. This result has been confirmed by the knockdown of endogenous *SNX14*, which can reverse the HTR6 deterioration (Ha et al., 2015).

8.3.4 *SYNCRIP*

In our experiments, *Syncrip* gene expression levels significantly decreased in the control 1 group, suggesting that *Syncrip* is sensitive to social isolation stress but not to CRS (Figure 28). Brain eQTL analysis indicated that six variants of

SYNCRIP are associated with its expression changes in human brains. Synaptotagmin binding cytoplasmic RNA interacting proteins (*SYNCRIP*) is a member of the heterogeneous nuclear ribonucleoprotein (hsRNA) family localised in the cell cytoplasm. HsRNAs play a critical role in the synthesis of the mouse hepatitis virus. HsRNAs can bind to the 5′ and 3′ untranslated regions (UTRs) of the hepatitis virus RNA to regulate its expression level (Choi et al., 2004). The overexpression of *SYNCRIP* can inhibit the syncytium formation that results from a mouse hepatitis virus (MHV) infection. Therefore, downregulation of *SYNCRIP* has delayed MHV RNA synthesis (Choi et al., 2004). In addition to this, *SYNCRIP*, as a component of granule mRNA in rat hippocampus, has a role in mRNA stabilisation and protein synthesis in neuronal dendrites (Bannai et al., 2004). In flies and mammals, *SYNCRIP* has been associated with accurate translational regulation and localised transcripts (McDermott et al., 2012). *SYNCRIP* can also modulate the presynaptic vesicle release efficiency from the motoneurone and postsynaptic translation (Halstead et al., 2014).

8.3.5 *UBE2E3*

Another SNP that was associated with MDD was the exm-rs16867321. Although exm-rs16867321 did not achieve exome-wide significance in the pharmacogenetic study of antidepressant remission in depressed Mexican-American patients, MeDIP-seq raw signal indicates that this SNP is also a DNA methylation site (Wong et al., 2014b). Thus, two neighbouring genes--*UBE2E3* and *CWC22*--were selected to confirm if this SNP could be involved in stress response.

According to our findings, *Ube2e3* gene expression level was not altered by CRS. The mouse ubiquitin-conjugating enzyme E2 E3 (*Ube2e3*) gene, located in chr2q31.3, has a total length of 51,537 bp. It contains six exons, 624 bp of the coding

region for the ubiquitin-conjugated enzyme UBE2E3. Pestov *et al.* (1998) identified that the *UBE2E3* gene is a growth suppressor gene due to its ubiquitin-binding enzyme activity. If the cysteine on the protein conservation site of *UBE2E3* is mutated into serine, the cell growth will not be inhibited. The highly conserved human Musashi RNA binding protein 1 (Msi1) has been able to increase the abundance of *UBE2E3* mRNA, which affects cellular activities, such as apoptosis, protein modification, and cell proliferation, among other activities. Therefore, it was regarded as a major regulatory factor playing an important role in the formation and development of the tumour (de Sousa Abreu et al., 2009).

8.3.6 *CWC22*

The *CWC22* gene, as another neighbouring gene of exm-rs16867321, has been selected as one candidate gene that responded to antidepressant treatment. In this research, we identified that the *Cwc22* mRNA level was significantly increased in response to CRS compared with the both single-house non-CRS control and group-house non-CRS control (Figure 30). In our previous study, exm-rs16867321 was indicated to be a DNA methylation site (Wong et al., 2014b). Therefore, changes in *Cwc22* gene expression levels in the rat hippocampus in responded to CRS might be regulated by methylation. The brain eQTL study confirmed that six variants of *CWC22* alter its expression in the human hippocampus. *CWC22* has been reported as a key factor that contributes to pre-mRNA splicing in mammalian cells. Depletion of *CWC22* induced pre-mRNA splicing dysfunction (Barbosa et al., 2012, Steckelberg et al., 2012). However, the exact role of *CWC22* in the pre-mRNA splicing still not well understood (Hegele et al., 2012). Additionally, *CWC22* also play an indispensable role in assembling exon junction complex. Exon junction complex has four subunits: eukaryotic translation initiation factor 4A3 (eIF4A3, also known

asDDX48), mago homolog, exon junction complex core component (MAGOH), RNA binding motif protein 8A (RBM8A or Y14), and cancer susceptibility candidate 3 (CASC3, BTZ or MLN51) (TANGE et al., 2005). MIF4G domain within CWC22 initiates exon junction complex assembly through interacting with eIF4A3 subunit directly. And the eIF4A3 mutation can suppress the binding with CWC22 (Steckelberg et al., 2012).

8.4 Conclusion

Depression has genetic heterogeneity; therefore, patients from different regions, races, and ethnic groups have different genetic backgrounds, and the genes that trigger their diseases may also differ (Levinson, 2006, Kato, 2007, Lesch, 2004, Wong et al., 2016a). However, the exact underlying genetic mechanism is still unclear. MDD is treated primarily with antidepressants, which have been widely acknowledged as the first line of treatment in the clinic (Moller et al., 2012, Greenberg et al., 2003). However, several problems still exist with antidepressant treatment: First, several weeks of antidepressant treatment are needed to relieve the clinical syndrome of MDD. Second, some patients withdraw from antidepressant treatment due to severe side effects (PREDICTABLE, 2006, Ferguson, 2001, Khawam et al., 2006). Third, some patients become resistant to antidepressants after treatment (Shelton, 2002, Lam et al., 2002). Fourth, up to 50% of patients fail to respond to one or several types of antidepressant drugs (O'Leary et al., 2014, Trivedi et al., 2006). Therefore, new types of antidepressants need to be developed to overcome above drawbacks. During the last decade, more and more evidence supported that genetic variations contribute to the development of MDD (Wong et al., 2016a) and patients' responses to antidepressants and their side effects (Wong et al., 2014b). Therefore, investigating new genes that associated with MDD is essential for

designing novel and more effective antidepressant drugs. The SAHMRI Mind and Brain lab has identified several common and rare variants that are potentially associated with MDD and several SNPs potentially associated with antidepressant remission (Wong et al., 2016, Wong et al., 2014b). The work described in this thesis used an animal depression model induced by CRS as a tool to investigate whether the genes identified in those studies were involved in the stress response. We found that the rat hippocampus mRNA level of the *Phf21b, Arhgap8, Trpm2*, *Cntnap1*, *Syncrip*, *Unc13d* and *Cwc22* genes changed in response to CRS or social isolation stress. In addition, we also performed Western blot analyses to understand protein level changes for three genes within our replicated chromosomal locus, those studies revealed that the relative protein level of PHF21B significantly decreased by both CRS and social isolation stress and ARHGAP8 protein level showed increased significantly by CRS and social isolation. However, we found no significant alteration of PRR5 protein level. Thus, our protein data paralleled our gene expression data. We have only confirmed protein level changes for three genes in rat hippocampus, the protein levels of the other candidate genes need to be addressed in future studies. The Brain eQTL studies (Brain eQTL Almanac, http://www.braineac.org/), genetic variants of *PHF21B, ARGAP8, PRR5, TRPM2, UNC13D, ANO8, HOMER3, TBX18, NT5E, SNX14, SYNCRIPT* and *CWC22* gene affect their gene expression status in the human hippocampus. According to our studies, *Phf21b*, *Arhgap8*, *Trpm2*, *Cntnap1*, *Syncrip*, *Unc13d*, and *Cwc22* could be potentially new targets for designing and developing novel antidepressants.

8.5 Limitations and future directions

8.5.1 Research limitations

The rats used in this research came from two different sources, which caused considerable variability in the behavioural test data between batches of rats. Long-distance transportation (from the UK) might also have increased the stress levels in the transported animals. Additionally, the literature reported that maternal isolation on young animals for a few months could induce a depression state. In Exp1, animals in the non-stress control group were single-housed; thus, the control group in Exp1 was not entirely stress-free; therefore, that may have confounded the differences between the CRS and the control groups. To avoid this problem, the experiment was redesigned and repeated in Exp2. In Exp2, an extra group-housed non-CRS control group was added. Furthermore, in our research, we have investigated our candidate genes expression changes in the whole rat hippocampus. Therefore, since the hippocampus has different sub-regions subserving distinct roles, our gene expression results may have been diluted due to the lack sub-division of the rat hippocampus.

8.5.2 Future Directions

This research used an animal depression model to understand whether potential MDD risk and antidepressant remission genes could modulate the stress response, which could serve as a validation of their role in MDD/antidepressant response. However, one of the obstacles encountered was that the source for the animals obtained was not unified, which has generated significant variations among different batches of animals. Also, the long-distance transportation of rats might have increased the stress levels in some of our animals. All these factors caused data variability. The Exp2 batch of animals was bred in the SAHMRI Bioresources facility, which produced stable and entirely stress-free animals. The stress response has been shown to affect the brain. Neural circuitry, including amygdala, prefrontal

cortex and hippocampus, is key to determine the response to stress. The above research merely focused on understanding expression changes of target genes in the hippocampus. Other brain regions, such as amygdala and prefrontal cortex should be further studied. According to our previous research (Wong et al., 2014b), functional variants have been identified in the DNA methylation site, which suggests that expression changes of candidate genes could be due to epigenetic regulation. Thus, our studies were designed to understand whether methylation changes that occurred in response to CRS caused either an up-regulation or a down-regulation of candidate gene expression. This work identified genes whose mRNA level changed by two weeks of CRS. We were able to validate PHF21B and ARHGAP8 protein changes in response to CRS or social isolation stress. On the basis of Brain eQTL results, the rest genes we have studied also contain genetic variants that change their expression level in human hippocampus, which might further affect their protein levels; thus, in future experiments, the related protein levels of other potential risk genes identified by this work, in response to CRS and/or antidepressant treatment need to be addressed. In addition, according to our findings, it is also necessary to carry out further research to identify the underlying mechanism by which CRS and social isolation induced the PHF21B and ARHGAP8 protein changes.

APPENDICES

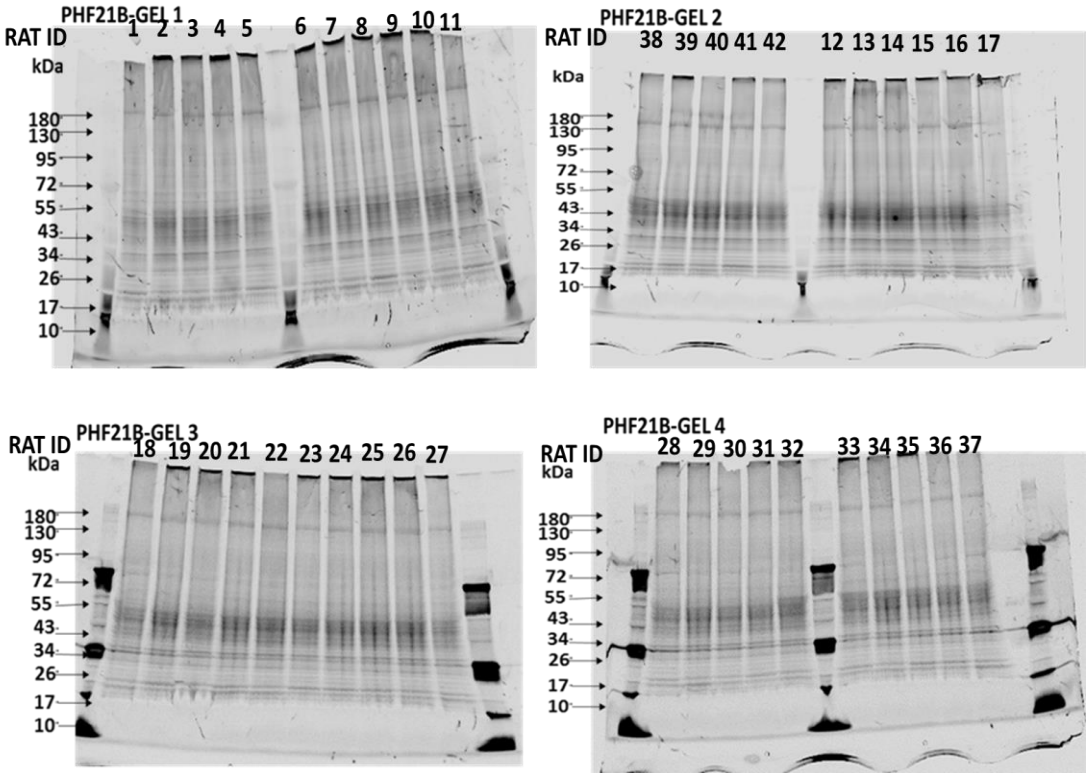


Figure 34: PHF21B Total Protein Normalization for Western Blots. Protein extracted from rat hippocampus (50 µg total protein per lane) separated by Criterion™ TGX Stain-Free™ Precast Gels and imaged with ChemiDoc MP. PHF21B-GEL 1: RAT ID: 1~11; PHF21B-GEL 2: RAT ID: 38~42 and 12~17; PHF21B-GEL 3: RAT ID: 18~27; PHF21B-GEL 4: RAT ID: 28~37.

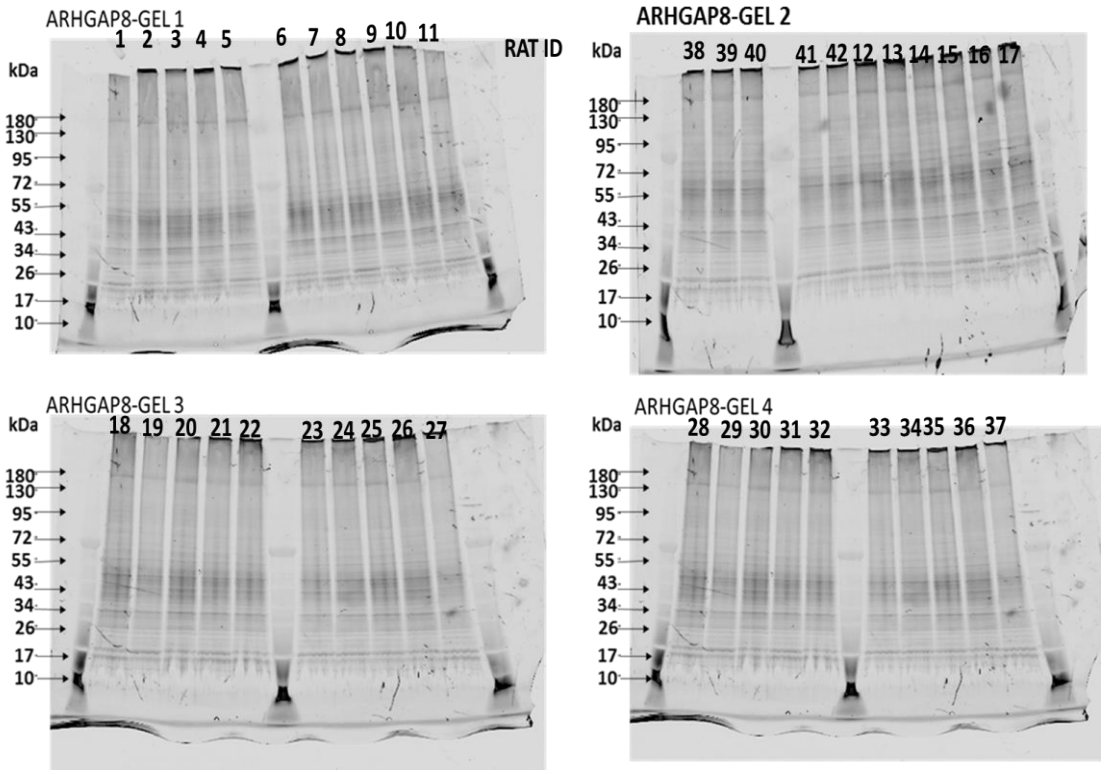


Figure 35: ARHGAP8 Total Protein Normalization for Western Blots. Protein extracted from rat hippocampus (30 µg total protein per lane) separated by Criterion™ TGX Stain-Free™ Precast Gels and imaged with ChemiDoc MP. ARHGAP8-GEL 1: RAT ID: 1~11; ARHGAP8-GEL 2: RAT ID: 38~42 and 12~17; ARHGAP8-GEL 3: RAT ID: 18~27; ARHGAP8-GEL 4: RAT ID: 28~37.

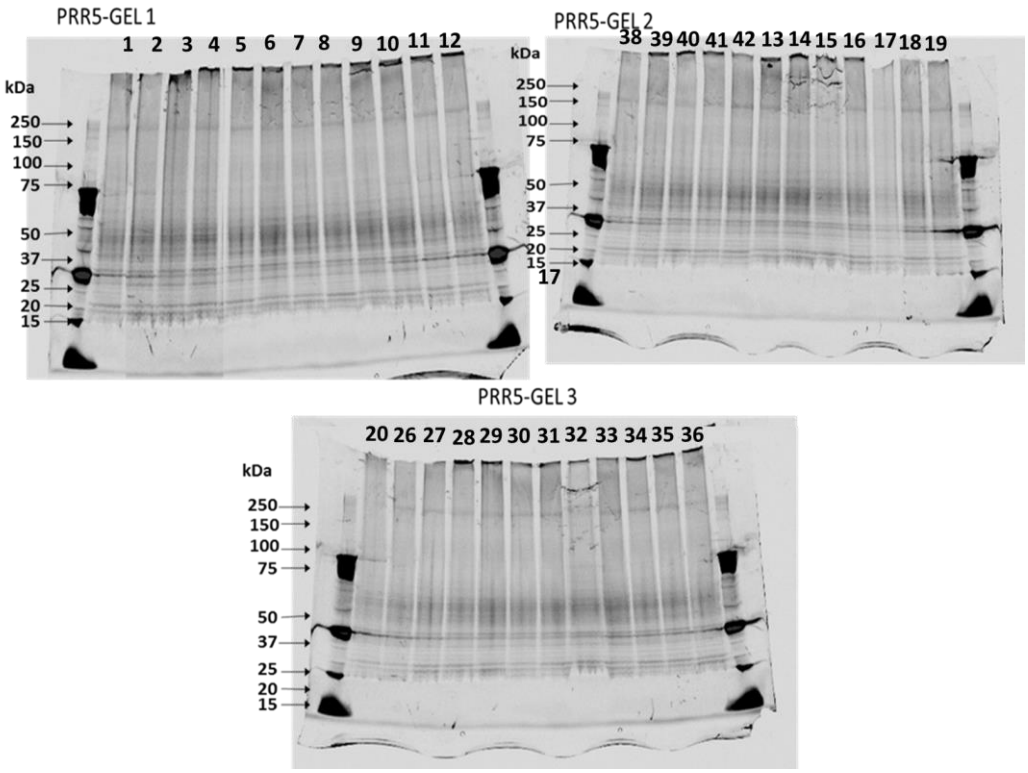


Figure 36: PRR5 Total Protein Normalization for Western Blots.

Protein extracted from rat hippocampus (30 µg total protein per lane) separated by Criterion™ TGX Stain-Free™ Precast Gels and imaged with ChemiDoc MP. PRR5-GEL 1: RAT ID: 1~12; PRR5-GEL 2: RAT ID: 38~42 and 13~19; PRR5-GEL 3: RAT ID: 20 and 26~36.

Table 22: Neighbouring gene selection (UCSC)

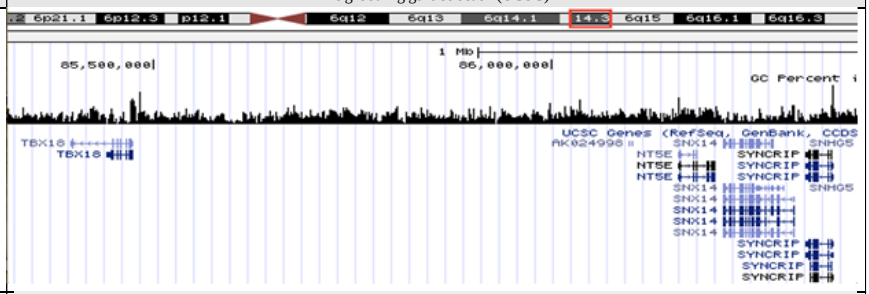
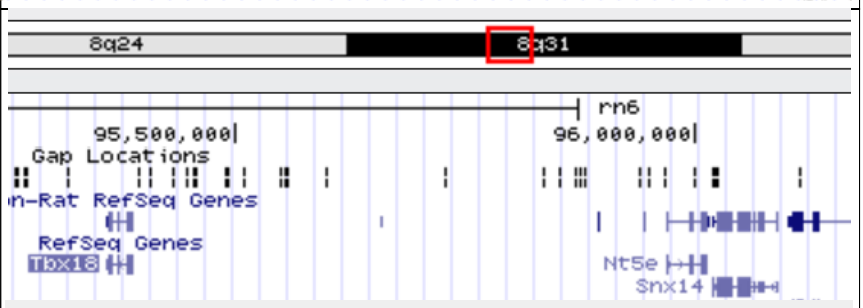
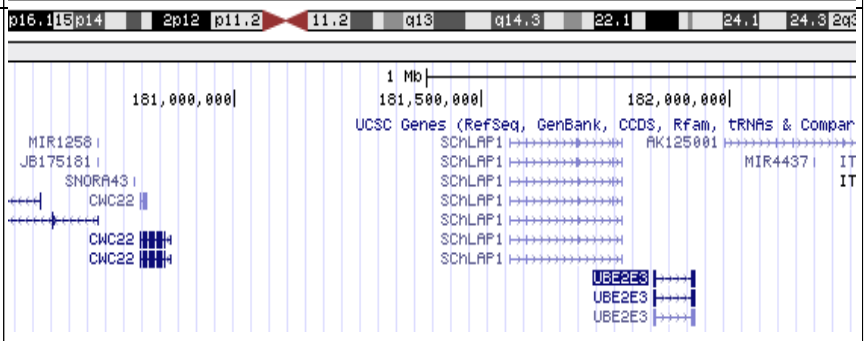
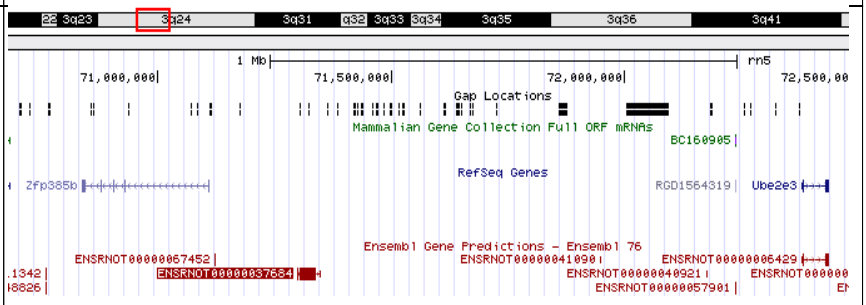
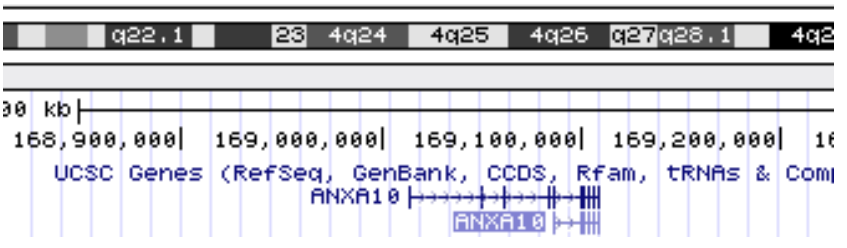
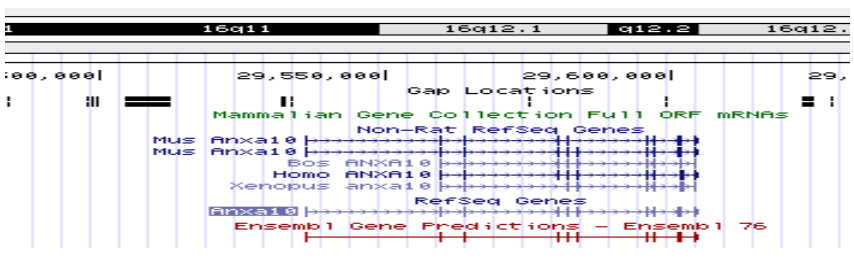
SNPS		Neighbouring gene selection (UCSC)
xm-rs1321744[a]	Human Chr 6	
	Rat Chr 8	
xm-rs16867321	Human chr2	
	Rat Chr 3	
exm433050$	Human Chr 4	
	Rat Chr 16	

Table 23: Brain quantitative gene expression analyses for *PHF21B* gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
t3963476	rs5766445	chr22:45516028	3.70E-05	aveALL	GG=21; GC=56; CC=48	G=36.6%; C=63.4%
3963477	rs5766445	chr22:45516028	1.80E-05	aveALL	GG=21; GC=56; CC=48	G=36.6%; C=63.4%
3963488	rs16993718	chr22:45623047	2.00E-04	aveALL	GG=3; GT=40; TT=91	G=17.2%; T=82.8%
3963491	rs8142612	chr22:45054904	3.70E-06	aveALL	GG=0; GA=33; AA=99	G=12.3%; A=87.7%
3963491	rs8139912	chr22:45055123	6.30E-05	aveALL	AA=0; AG=30; GG=104	A=11.2%; G=88.8%
3963491	rs9626229	chr22:45054542	6.60E-05	aveALL	AA=0; AG=30; GG=104	A=11.2%; G=88.8%
3963491	rs4823248	chr22:45053738	6.60E-05	aveALL	GG=0; GA=30; AA=104	G=11.2%; A=88.8%
3963491	rs4823359	chr22:45053586	6.60E-05	aveALL	CC=0; CT=30; TT=104	C=11.2%; T=88.8%
3963502	rs12167523	chr22:46251613	3.20E-04	aveALL	TT=1; TC=26; CC=107	T=10.4%; C=89.6%
3963504	rs3788649	chr22:45734860	2.30E-04	aveALL	CC=7; CT=53; TT=61	C=25%; T=75%
t3963476	rs5766438	chr22:45515269	1.00E-04	CRBL	TT=25; TC=70; CC=38	T=44.8%; C=55.2%
t3963476	rs78169957	chr22:45315932	1.20E-04	CRBL	TT=9; TC=52; CC=72	T=26.1%; C=73.9%
3963495	rs16993187	chr22:45342221	1.10E-04	CRBL	AA=1; AT=28; TT=104	A=11.2%; T=88.8%
3963504	rs78169957	chr22:45315932	5.30E-05	CRBL	TT=9; TC=52; CC=72	T=26.1%; C=73.9%
3963504	rs5766186	chr22:45314412	8.70E-05	CRBL	TT=6; TC=50; CC=78	T=23.1%; C=76.9%
3963504	rs5765085	chr22:45314924	9.20E-05	CRBL	TT=6; TC=50; CC=78	T=23.1%; C=76.9%

3963507	NA	chr22:44361609:A_AT	2.60E-04	CRBL	NA	NA
3963507	rs11702933	chr22:46176461	3.00E-04	CRBL	GG=3; GC=27; CC=82	G=12.3%; C=87.7%
3963529	NA	chr22:44726543:G_GT	1.40E-04	CRBL	NA	NA
3963530	rs117072966	chr22:45536211	1.80E-06	CRBL	AA=9; AG=31; GG=94	A=18.3%; G=81.7%
3963530	rs11704050	chr22:45534295	1.80E-06	CRBL	TT=9; TG=31; GG=94	T=18.3%; G=81.7%
3963530	rs138174248	chr22:45559184	1.30E-05	CRBL	AA=1; AC=8; CC=111	A=3.7%; C=96.3%
3963548	rs9697691	chr22:46309893	2.20E-04	CRBL	GG=12; GC=35; CC=64	G=22%; C=78%
3963551	rs115360564	chr22:44657034	1.40E-05	CRBL	AA=17; AT=56; TT=46	A=33.6%; T=66.4%
3963551	rs135432	chr22:44657033	1.90E-05	CRBL	AA=17; AT=56; TT=45	A=33.6%; T=66.4%
3963551	rs135426	chr22:44657735	2.60E-05	CRBL	CC=18; CT=63; TT=47	C=36.9%; T=63.1%
3963551	rs135435	chr22:44656751	4.80E-05	CRBL	CC=17; CT=59; TT=58	C=34.7%; T=65.3%
3963551	rs135436	chr22:44656693	9.00E-05	CRBL	TT=16; TC=60; CC=58	T=34.3%; C=65.7%
3963551	rs135437	chr22:44656581	9.00E-05	CRBL	CC=16; CT=60; TT=58	C=34.3%; T=65.7%
3963554	rs9614605	chr22:45505494	1.40E-05	CRBL	AA=13; AG=61; GG=57	A=32.5%; G=67.5%
3963554	rs9615030	chr22:45513062	1.40E-05	CRBL	AA=12; AG=63; GG=57	A=32.5%; G=67.5%
3963554	NA	chr22:45513061:AG_A	1.40E-05	CRBL	NA	NA
3963554	NA	chr22:45513059:A_AC	1.40E-05	CRBL	NA	NA
3963554	rs9615029	chr22:45513060	1.40E-05	CRBL	CC=12; CA=63; AA=57	C=32.5%; A=67.5%

3963554	rs5766439	chr22:45515308	1.60E-05	CRBL	CC=13; CT=63; TT=57	C=33.2%; T=66.8%
3963554	rs8138218	chr22:45514975	1.70E-05	CRBL	TT=13; TC=63; CC=57	T=33.2%; C=66.8%
3963554	rs9626283	chr22:45512358	1.80E-05	CRBL	AA=13; AC=63; CC=57	A=33.2%; C=66.8%
3963554	rs1076119	chr22:45511892	1.90E-05	CRBL	GG=13; GT=63; TT=57	G=33.2%; T=66.8%
3963554	rs9626632	chr22:45512263	1.90E-05	CRBL	TT=13; TC=63; CC=57	T=33.2%; C=66.8%
t3963476	rs1997676	chr22:44932322	1.80E-04	FCTX	TT=17; TA=47; AA=67	T=30.2%; A=69.8%
t3963476	NA	chr22:44933249:GT_G	2.00E-04	FCTX	NA	NA
t3963476	rs2076092	chr22:44933408	2.00E-04	FCTX	GG=18; GC=47; CC=68	G=31%; C=69%
3963481	rs16991522	chr22:44521036	9.30E-05	FCTX	GG=9; GT=60; TT=65	G=29.1%; T=70.9%
3963481	rs68108655	chr22:44521125	9.30E-05	FCTX	TT=9; TA=60; AA=65	T=29.1%; A=70.9%
3963481	rs1535009	chr22:44522312	9.30E-05	FCTX	CC=9; CT=60; TT=65	C=29.1%; T=70.9%
3963481	rs67317032	chr22:44521438	9.30E-05	FCTX	TT=9; TC=60; CC=65	T=29.1%; C=70.9%
3963481	NA	chr22:44521174:AAC_A	1.00E-04	FCTX	NA	NA
3963481	NA	chr22:44521176:CAA_C	1.00E-04	FCTX	NA	NA
3963481	rs3788607	chr22:44519414	1.10E-04	FCTX	TT=9; TC=60; CC=65	T=29.1%; C=70.9%
3963504	rs4823357	chr22:45050961	1.40E-04	FCTX	TT=14; TC=52; CC=44	T=29.9%; C=70.1%
3963504	rs4823358	chr22:45051196	1.40E-04	FCTX	CC=14; CG=52; GG=44	C=29.9%; G=70.1%
3963504	rs136892	chr22:45045661	1.80E-04	FCTX	GG=19; GC=51; CC=41	G=33.2%; C=66.8%

3963507	rs62228630	chr22:44770316	3.40E-04	FCTX	GG=1; GA=30; AA=103	G=11.9%; A=88.1%
3963529	rs2143931	chr22:45472084	1.10E-05	FCTX	GG=26; GA=68; AA=34	G=44.8%; A=55.2%
3963529	rs5765155	chr22:45471607	4.60E-05	FCTX	CC=38; CT=63; TT=32	C=51.9%; T=48.1%
3963529	rs1003851	chr22:44782265	3.90E-05	HIPP	CC=5; CT=46; TT=76	C=20.9%; T=79.1%
3963529	rs117160508	chr22:45442461	1.60E-04	HIPP	CC=1; CG=12; GG=119	C=5.2%; G=94.8%
3963529	rs118154683	chr22:45442465	1.60E-04	HIPP	TT=1; TA=12; AA=119	T=5.2%; A=94.8%
3963529	rs75806917	chr22:45442547	1.60E-04	HIPP	GG=1; GT=11; TT=119	G=4.9%; T=95.1%
3963548	rs8138025	chr22:45974757	1.90E-04	HIPP	AA=19; AG=63; GG=52	A=37.7%; G=62.3%
3963548	rs5765490	chr22:45974913	2.10E-04	HIPP	TT=19; TC=63; CC=52	T=37.7%; C=62.3%
3963550	rs62228464	chr22:45113754	6.60E-05	HIPP	CC=18; CA=51; AA=61	C=32.5%; A=67.5%
t3963476	NA	chr22:44833247:G_GC	1.50E-04	MEDU	NA	NA
t3963476	rs3884870	chr22:44833249	1.70E-04	MEDU	CC=9; CA=53; AA=68	C=26.5%; A=73.5%
t3963476	NA	chr22:44833250:C_CT	1.70E-04	MEDU	NA	NA
t3963476	NA	chr22:44833248:CA_C	2.00E-04	MEDU	NA	NA
3963478	rs136609	chr22:45793935	8.80E-06	MEDU	GG=16; GA=57; AA=61	G=33.2%; A=66.8%
3963478	rs2742640	chr22:45702293	1.80E-05	MEDU	CC=24; CA=67; AA=43	C=42.9%; A=57.1%
3963478	rs2742641	chr22:45702294	1.80E-05	MEDU	AA=24; AT=67; TT=43	A=42.9%; T=57.1%

3963478	NA	chr22:45702294:A_AT	1.80E-05	MEDU	NA	NA
3963478	rs226499	chr22:45703075	1.80E-05	MEDU	AA=24; AG=67; GG=43	A=42.9%; G=57.1%
3963478	rs226500	chr22:45703107	1.80E-05	MEDU	TT=24; TC=67; CC=43	T=42.9%; C=57.1%
3963478	rs226501	chr22:45703251	1.80E-05	MEDU	GG=24; GA=67; AA=43	G=42.9%; A=57.1%
3963478	rs226504	chr22:45705383	1.90E-05	MEDU	TT=23; TA=65; AA=43	T=41.4%; A=58.6%
3963478	NA	chr22:45710240:AAAAC	3.00E-05	MEDU	NA	NA
3963478	rs226507	chr22:45707737	3.20E-05	MEDU	CC=24; CG=63; GG=43	C=41.4%; G=58.6%
3963481	rs5765937	chr22:45119023	2.40E-05	MEDU	AA=1; AG=17; GG=93	A=7.1%; G=92.9%
3963481	rs5765936	chr22:45118928	2.70E-05	MEDU	TT=1; TC=17; CC=94	T=7.1%; C=92.9%
3963491	rs79697179	chr22:45829713	3.70E-05	MEDU	GG=0; GC=9; CC=120	G=3.4%; C=96.6%
3963491	rs74547861	chr22:45835335	4.10E-05	MEDU	AA=0; AG=9; GG=120	A=3.4%; G=96.6%
3963491	rs117946593	chr22:45840750	6.00E-05	MEDU	TT=0; TC=9; CC=118	T=3.4%; C=96.6%
3963502	rs36062246	chr22:44531337	1.20E-04	MEDU	TT=10; TC=61; CC=63	T=30.2%; C=69.8%
3963502	rs4823115	chr22:44538890	2.90E-04	MEDU	TT=12; TC=63; CC=59	T=32.5%; C=67.5%
3963502	rs78970178	chr22:45624153	3.20E-04	MEDU	CC=0; CT=15; TT=119	C=5.6%; T=94.4%
3963502	rs58721007	chr22:45623487	3.30E-04	MEDU	TT=0; TC=15; CC=119	T=5.6%; C=94.4%
3963529	NA	chr22:44388208	2.00E-06	MEDU	NA	NA
3963529	NA	chr22:44381223	3.20E-05	MEDU	NA	NA

3963529	NA	chr22:45071129:CA_C	1.30E-04	MEDU	NA	NA
3963530	rs136733	chr22:45924112	4.80E-05	MEDU	TT=1; TC=22; CC=109	T=9%; C=91%
3963477	rs183805343	chr22:45383937	5.90E-06	OCTX	AA=1; AG=13; GG=114	A=5.6%; G=94.4%
3963507	rs116827256	chr22:44405981	3.90E-05	OCTX	TT=0; TC=18; CC=107	T=6.7%; C=93.3%
3963507	NA	chr22:44960163:A_AT	3.20E-04	OCTX	NA	NA
3963507	rs4823340	chr22:44961161	3.50E-04	OCTX	CC=0; CA=31; AA=103	C=11.6%; A=88.4%
3963477	rs5766445	chr22:45516028	1.30E-05	PUTM	GG=21; GC=56; CC=48	G=36.6%; C= 63.4%
3963477	rs2350232	chr22:45414515	1.40E-05	PUTM	AA=2; AG=34; GG=94	A=14.2%; G=85.8%
3963477	rs132005	chr22:45415832	1.80E-05	PUTM	TT=1; TC=24; CC=101	T=9.7%; C=90.3%
3963477	rs132003	chr22:45413404	4.10E-05	PUTM	AA=2; AG=41; GG=91	A=16.8%; G=83.2%
3963477	rs131997	chr22:45410347	4.20E-05	PUTM	GG=2; GC=41; CC=91	G=16.8%; C=83.2%
3963477	rs132000	chr22:45412407	4.20E-05	PUTM	AA=2; AG=41; GG=91	A=16.8%; G=83.2%
3963477	rs132001	chr22:45412866	4.20E-05	PUTM	TT=2; TC=41; CC=91	T=16.8%; C=83.2%
3963477	rs132002	chr22:45413112	4.20E-05	PUTM	AA=2; AG=41; GG=91	A=16.8%; G=83.2%
3963479	rs7288032	chr22:45147925	1.00E-05	PUTM	GG=7; GA=51; AA=36	G=24.3%; A=75.7%
3963479	rs132430	chr22:45147278	1.20E-05	PUTM	AA=7; AG=51; GG=45	A=24.3%; G=75.7%
3963479	rs132429	chr22:45147065	1.20E-05	PUTM	AA=7; AG=52; GG=45	A=24.6%; G=75.4%
3963479	rs132428	chr22:45146574	1.20E-05	PUTM	TT=7; TA=54; AA=46	T=25.4%; A=74.6%

3963479	rs739171	chr22:45147760	1.40E-05	PUTM	AA=7; AG=50; GG=43	A=23.9%; G=76.1%
3963479	rs5765951	chr22:45146425	1.50E-05	PUTM	CC=7; CT=55; TT=45	C=25.7%; T=74.3%
3963479	rs4823366	chr22:45145310	1.60E-05	PUTM	CC=7; CT=55; TT=45	C=25.7%; T=74.3%
3963479	rs5765949	chr22:45144978	1.70E-05	PUTM	GG=7; GT=55; TT=45	G=25.7%; T=74.3%
3963479	rs5764983	chr22:45146224	2.90E-05	PUTM	AA=7; AC=55; CC=44	A=25.7%; C=74.3%
3963479	rs9614899	chr22:45144106	3.10E-05	PUTM	GG=7; GT=55; TT=45	G=25.7%; T=74.3%
3963481	rs187099634	chr22:45197111	1.30E-05	PUTM	TT=0; TC=12; CC=107	T=4.5%; C=95.5%
3963483	rs138174	chr22:46140473	3.20E-05	PUTM	AA=2; AG=31; GG=100	A=13.1%; G=86.9%
3963483	rs11703006	chr22:46171505	1.40E-04	PUTM	AA=2; AG=28; GG=98	A=11.9%; G=88.1%
3963483	rs17574591	chr22:46175914	1.50E-04	PUTM	AA=2; AG=28; GG=98	A=11.9%; G=88.1%
3963483	rs78476361	chr22:46168644	1.60E-04	PUTM	AA=2; AG=29; GG=98	A=12.3%; G=87.7%
3963486	NA	chr22:44398201	3.50E-05	PUTM	NA	NA
3963488	rs2187734	chr22:44928840	1.70E-04	PUTM	TT=21; TC=56; CC=57	T=36.6%; C=63.4%
3963488	rs11703429	chr22:44928897	1.80E-04	PUTM	TT=21; TC=56; CC=57	T=36.6%; C=63.4%
3963488	rs11704006	chr22:44928906	1.80E-04	PUTM	AA=21; AG=56; GG=57	A=36.6%; G=63.4%
3963488	rs8138953	chr22:44929432	2.00E-04	PUTM	TT=21; TC=56; CC=57	A=36.6%; G=63.4%
3963488	rs5764891	chr22:44927952	2.20E-04	PUTM	AA=34; AG=64; GG=36	A=49.3%; G=50.7%

3963488	rs5765760	chr22:44927981	2.50E-04	PUTM	TT=34; TG=63; GG=36	T=48.9%; G=51.1%
3963488	rs1001008	chr22:44928369	3.30E-04	PUTM	GG=30; GA=65; AA=37	G=46.6%; A=53.4%
3963491	rs2283670	chr22:46248170	5.80E-05	PUTM	CC=15; CT=55; TT=63	C=31.7%; T=68.3%
3963491	rs916286	chr22:46256334	7.40E-05	PUTM	CC=15; CG=53; GG=65	C=31%; G=69%
3963502	rs136029	chr22:46236425	1.40E-04	PUTM	AA=20; AG=66; GG=44	A=39.6%; G=60.4%
3963502	rs8141212	chr22:46238069	2.00E-04	PUTM	CC=21; CT=71; TT=42	C=42.2%; T=57.8%
3963502	rs7293204	chr22:46231145	2.10E-04	PUTM	TT=20; TG=66; GG=45	T=39.6%; G=60.4%
3963502	rs2071872	chr22:46068144	2.80E-04	PUTM	AA=4; AG=41; GG=64	A=18.3%; G=81.7%
3963504	rs12484773	chr22:45455599	1.60E-04	PUTM	GG=2; GA=12; AA=120	G=6%; A=94%
3963504	rs111226774	chr22:45454918	1.60E-04	PUTM	AA=2; AG=12; GG=120	A=6%; G=94%
3963504	NA	chr22:45188708:GGT_G	1.70E-04	PUTM	NA	NA
3963527	rs2267611	chr22:44513658	2.50E-05	PUTM	CC=10; CT=63; TT=61	C=31%; T=69%
3963527	rs62227723	chr22:44514257	2.50E-05	PUTM	TT=10; TC=63; CC=61	T=31%; C=69%
3963527	rs11703393	chr22:44512124	2.50E-05	PUTM	GG=10; GA=63; AA=61	G=31%; A=69%
3963527	rs11705133	chr22:44512099	2.50E-05	PUTM	GG=10; GC=63; CC=61	G=31%; C=69%
3963527	rs67355122	chr22:44511930	2.50E-05	PUTM	CC=10; CT=63; TT=61	C=31%; T=69%
3963527	rs72619560	chr22:44511893	2.50E-05	PUTM	CC=10; CT=63; TT=61	C=31%; T=69%

3963527	rs62227671	chr22:44507872	5.10E-05	PUTM	AA=8; AG=57; GG=63	A=27.2%; G=72.8%
3963527	rs76393758	chr22:44508200	5.10E-05	PUTM	TT=8; TG=57; GG=63	T=27.2%; G=72.8%
3963527	rs3788607	chr22:44519414	7.10E-05	PUTM	TT=9; TC=60; CC=65	T=29.1%; C=70.9%
3963527	rs16991522	chr22:44521036	8.10E-05	PUTM	GG=9; GT=60; TT=65	G=29.1%; T=70.9%
3963530	rs4823418	chr22:45315232	1.60E-05	PUTM	TT=30; TG=65; GG=39	T=46.6%; G=53.4%
3963530	rs4823419	chr22:45315441	1.60E-05	PUTM	AA=30; AG=65; GG=39	A=46.6%; G=53.4%
3963530	rs5766188	chr22:45315672	1.60E-05	PUTM	GG=30; GA=65; AA=39	G=46.6%; A=53.4%
3963530	rs5766195	chr22:45317309	3.10E-05	PUTM	TT=31; TC=64; CC=39	T=47%; C=53%
3963530	rs6006909	chr22:45317650	3.50E-05	PUTM	TT=31; TC=64; CC=38	T=47%; C=53%
3963548	rs715557	chr22:45866488	8.90E-05	PUTM	TT=6; TA=48; AA=80	T=22.4%; A=77.6%
3963549	rs12485059	chr22:44766791	4.20E-05	PUTM	AA=5; AC=45; CC=81	A=20.5%; C=79.5%
3963550	rs2071872	chr22:46068144	8.60E-06	PUTM	AA=4; AG=41; GG=64	A=18.3%; G=81.7%
3963550	rs2238827	chr22:46118313	2.20E-05	PUTM	TT=5; TC=47; CC=82	T=21.3%; C=78.7%
3963550	rs2071851	chr22:46114147	4.70E-05	PUTM	TT=5; TC=44; CC=85	T=20.1%; C=79.9%
3963550	rs138157	chr22:46116272	7.50E-05	PUTM	TT=5; TA=46; AA=83	T=20.9%; A=79.1%
3963550	rs4823231	chr22:46088119	7.70E-05	PUTM	TT=3; TA=42; AA=88	T=17.9%; A=82.1%
3963550	rs727699	chr22:46087110	7.70E-05	PUTM	CC=3; CA=42; AA=88	C=17.9%; A=82.1%

3963550	rs2351089	chr22:46093963	7.70E-05	PUTM	TT=3; TG=42; GG=88	T=17.9%; G=82.1%
3963550	rs9626191	chr22:46091526	7.70E-05	PUTM	GG=3; GA=42; AA=88	G=17.9%; A=82.1%
3963551	NA	chr22:44338134	3.20E-05	PUTM	NA	NA
3963551	NA	chr22:44341986	3.90E-05	PUTM	NA	NA
3963486	rs75977328	chr22:44613848	5.10E-05	SNIG	AA=2; AG=10; GG=122	A=5.2%; G=94.8%
3963486	rs28578752	chr22:46321190	5.90E-05	SNIG	CC=8; CT=33; TT=64	C=18.3%; T=81.7%
3963486	rs10453445	chr22:46321566	6.10E-05	SNIG	CC=8; CT=33; TT=64	C=18.3%; T=81.7%
3963486	rs28541591	chr22:46300220	7.80E-05	SNIG	CC=12; CA=52; AA=11	C=28.4%; A=71.6%
3963486	rs9330799	chr22:46301368	8.40E-05	SNIG	GG=12; GA=53; AA=11	G=28.7%; A=71.3%
3963486	rs9330798	chr22:46301348	8.50E-05	SNIG	GG=12; GT=53; TT=11	G=28.7%; T=71.3%
3963507	rs5766038	chr22:45197177	5.70E-05	SNIG	AA=0; AT=17; TT=71	A=6.3%; T=93.7%
3963507	rs132812	chr22:45527343	1.20E-04	SNIG	CC=30; CT=63; TT=31	C=45.9%; T=54.1%
3963507	NA	chr22:44300473	1.50E-04	SNIG	NA	NA
3963548	rs13054899	chr22:45253473	4.60E-05	SNIG	AA=0; AG=23; GG=107	A=8.6%; G=91.4%
3963548	rs4823396	chr22:45253079	6.00E-05	SNIG	GG=0; GC=24; CC=107	G=9%; C=91%
3963548	rs11913791	chr22:45254340	6.70E-05	SNIG	CC=0; CT=24; TT=107	C=9%; T=91%
3963548	rs11704168	chr22:45255769	7.10E-05	SNIG	TT=0; TC=25; CC=107	T=9.3%; C=90.7%
3963550	rs135961	chr22:44818518	4.20E-05	SNIG	TT=8; TC=42; CC=80	T=21.6%; C=78.4%

3963551	rs738364	chr22:45018181	2.20E-05	SNIG	AA=1; AG=10; GG=122	A=4.5%; G=95.5%
3963483	rs76498283	chr22:44758421	5.00E-05	TCTX	AA=0; AG=10; GG=119	A=3.7%; G=96.3%
3963530	rs136674	chr22:45237239	6.10E-05	TCTX	TT=26; TC=60; CC=40	T=41.8%; C=58.2%
3963551	rs62230310	chr22:44709875	3.00E-05	TCTX	AA=9; AG=38; GG=42	A=20.9%; G=79.1%
3963483	rs1473811	chr22:45339473	5.40E-05	THAL	GG=18; GA=60; AA=54	G=35.8%; A=64.2%
3963483	rs961501	chr22:45339063	6.00E-05	THAL	CC=21; CA=60; AA=53	C=38.1%; A=61.9%
3963483	rs6007397	chr22:45339200	6.00E-05	THAL	CC=21; CT=60; TT=53	C=38.1%; T=61.9%
3963483	rs80020166	chr22:45339209	6.00E-05	THAL	GG=21; GA=60; AA=53	G=38.1%; A=61.9%
3963483	rs4823266	chr22:45344328	1.30E-04	THAL	GG=18; GA=60; AA=55	G=35.8%; A=64.2%
3963486	rs8138834	chr22:45257870	3.50E-05	THAL	GG=1; GC=39; CC=93	G=15.3%; C=84.7%
3963486	rs8135269	chr22:45258789	3.60E-05	THAL	TT=1; TC=40; CC=92	T=15.7%; C=84.3%
3963486	rs8139116	chr22:45258012	6.30E-05	THAL	TT=1; TC=40; CC=90	T=15.7%; C=84.3%
3963495	NA	chr22:46249975:ATG_A	5.90E-06	THAL	NA	NA
3963495	rs2283669	chr22:46218668	2.10E-05	THAL	CC=7; CT=48; TT=69	C=23.1%; T=76.9%
3963495	rs5765645	chr22:46223912	4.80E-05	THAL	CC=10; CA=53; AA=65	C=27.2%; A=72.8%
3963495	rs5765670	chr22:46248789	9.50E-05	THAL	AA=8; AC=51; CC=73	A=25%; C=75%
3963495	rs2238828	chr22:46246529	9.60E-05	THAL	GG=8; GA=50; AA=73	G=24.6%; A=75.4%

3963495	rs5765622	chr22:46182756	9.70E-05	THAL	AA=7; AG=48; GG=79	A=23.1%; G=76.9%
3963495	rs5765620	chr22:46179537	1.00E-04	THAL	TT=8; TC=48; CC=78	T=23.9%; C=76.1%
3963495	rs5765619	chr22:46178379	1.10E-04	THAL	AA=8; AG=48; GG=76	A=23.9%; G=76.1%
3963495	rs5764861	chr22:46249977	1.20E-04	THAL	AA=8; AG=52; GG=74	A=25.4%; G=74.6%
3963502	rs13058561	chr22:46090251	3.40E-04	THAL	TT=1; TG=6; GG=115	T=3%; G=97%
3963507	rs62227685	chr22:44511293	3.40E-04	THAL	CC=0; CT=22; TT=61	C=8.2%; T=91.8%
3963548	rs877666	chr22:45188601	1.30E-04	THAL	CC=14; CT=53; TT=65	C=30.2%; T=69.8%
3963548	rs877667	chr22:45188624	1.50E-04	THAL	TT=12; TC=52; CC=70	T=28.4%; C=71.6%
3963549	rs5764805	chr22:45991798	2.10E-05	THAL	AA=12; AG=44; GG=53	A=25.4%; G=74.6%
3963549	rs5765721	chr22:44919749	4.30E-05	THAL	CC=1; CT=14; TT=116	C=6%; T=94%
3963549	rs5764887	chr22:44925725	4.80E-05	THAL	AA=1; AG=14; GG=118	A=6%; G=94%
3963549	rs5765728	chr22:44922408	5.60E-05	THAL	AA=1; AG=14; GG=119	A=6%; G=94%
3963549	rs5765730	chr22:44922455	5.60E-05	THAL	AA=1; AG=14; GG=119	A=6%; G=94%
3963549	rs5765740	chr22:44924195	5.60E-05	THAL	AA=1; AG=14; GG=119	A=6%; G=94%
3963549	rs5765742	chr22:44924370	5.60E-05	THAL	CC=1; CT=14; TT=119	C=6%; T=94%
3963549	rs5765743	chr22:44924441	5.60E-05	THAL	AA=1; AG=14; GG=119	A=6%; G=94%
3963549	rs5765744	chr22:44924633	5.60E-05	THAL	CC=1; CT=14; TT=119	C=6%; T=94%

3963488	rs73434537	chr22:44731595	2.40E-04	WHMT	AA=2; AG=27; GG=104	A=11.6%; G=88.4%
3963488	rs6007026	chr22:45810049	3.50E-04	WHMT	TT=16; TC=64; CC=51	T=35.8%; C=64.2%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 24: Brain quantitative gene expression analyses for *ARHGAP8* gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
3948293	rs4823163	chr22:44301924	1.20E-04	aveALL	GG=12; GA=56; AA=61	G=29.9%; A=70.1%
3948265	rs76110348	chr22:45417158	7.40E-05	aveALL	AA=0; AG=19; GG=111	A=7.1%; G=92.9%
3948274	rs116774661	chr22:45964637	3.00E-04	aveALL	AA=1; AG=24; GG=67	A=9.7%; G=90.3%
3948290	rs62228462	chr22:45107296	1.60E-04	aveALL	AA=0; AG=12; GG=120	A=4.5%; G=95.5%
3948292	rs135416	chr22:44666892	3.90E-06	aveALL	AA=20; AG=68; GG=40	A=40.3%; G=59.7%
3948292	rs135412	chr22:44668792	5.80E-05	aveALL	GG=24; GA=70; AA=38	G=44%; A=56%
3948292	rs28584938	chr22:44667314	6.20E-05	aveALL	GG=24; GA=70; AA=38	G=44%; A=56%
3948292	rs135415	chr22:44667156	6.30E-05	aveALL	CC=24; CA=70; AA=38	C=44%; A=56%
3948292	rs1807715	chr22:44666676	6.40E-05	aveALL	GG=24; GA=70; AA=38	G=44%; A=56%
3948338	NA	chr22:45263188:A_AC	2.00E-04	aveALL	NA	NA
3948338	rs55744143	chr22:45254799	2.20E-04	aveALL	TT=1; TC=24; CC=100	T=9.7%; C=90.3%

3948338	NA	chr22:45255532:CCT_C	2.20E-04	aveALL	NA	NA
3948338	rs4490294	chr22:45255527	2.20E-04	aveALL	CC=6; CA=40; AA=80	C=19.4%; A=80.6%
3948261	rs734561	chr22:44324104	1.90E-04	CRBL	TT=2; TC=44;CC=88	T=17.9%; C=82.1%
3948262	rs12628484	chr22:44881837	1.40E-04	CRBL	TT=5; TG=42; GG=87	T=19.4%; G=80.6%
3948262	rs5765602	chr22:44881127	1.40E-04	CRBL	AA=5; AG=42; GG=87	A=19.4%; G=80.6%
3948262	rs35737845	chr22:44882231	1.50E-04	CRBL	AA=5; AC=41; CC=87	A=19%; C=81%
3948262	rs2349252	chr22:44877911	1.80E-04	CRBL	CC=5; CT=41; TT=86	C=19%; T=81%
3948262	rs2239770	chr22:44875652	2.10E-04	CRBL	CC=4; CT=37; TT=86	C=16.8%; T=83.2%
3948262	rs5764965	chr22:45097815	2.10E-04	CRBL	TT=6; TC=52; CC=76	T=23.9%; C=76.1%
3948262	rs4365563	chr22:44865642	2.30E-04	CRBL	TT=4; TG=37; GG=86	T=16.8%; G=83.2%
3948262	rs8140396	chr22:44866786	2.30E-04	CRBL	GG=4; GA=37; AA=86	G=16.8%; A=83.2%
3948262	rs5764819	chr22:44871273	2.50E-04	CRBL	AA=4; AT=37; TT=86	A=16.8%; T=83.2%
3948262	rs5764754	chr22:44855856	2.60E-04	CRBL	AA=5; AG=40; GG=89	A=18.7%; G=81.3%
3948287	rs6007041	chr22:45837410	1.30E-05	CRBL	GG=11; GA=56; AA=66	G=29.1%; A=70.9
3948287	rs5765366	chr22:45837032	1.40E-05	CRBL	AA=11; AT=56; TT=66	A=29.1%; T=70.9%
3948287	rs5765367	chr22:45837033	1.40E-05	CRBL	AA=11; AT=56; TT=66	A=29.1%; T=70.9%
3948287	rs4823297	chr22:45840721	1.50E-05	CRBL	GG=11; GT=57; TT=66	G=29.5%; T=70.5%

3948287	rs5764733	chr22:45841045	1.70E-05	CRBL	GG=11; GT=57; TT=66	G=29.5%; T=70.5%
3948287	rs5765370	chr22:45838156	2.10E-05	CRBL	AA=11; AG=57; GG=66	A=29.5%; G=70.5%
3948287	rs4823296	chr22:45839551	3.00E-05	CRBL	CC=10; CT=54; TT=66	C=27.6%; G=72.4
3948287	rs5764743	chr22:45864559	3.20E-05	CRBL	AA=27; AT=62; TT=45	A=43.3%; T=56.7%
3948287	rs5764742	chr22:45864459	3.20E-05	CRBL	TT=27; TC=62; CC=45	T=43.3%; C=56.7%
3948287	rs2350953	chr22:45863515	3.20E-05	CRBL	TT=27; TC=62; CC=45	T=43.3%; C=56.7%
3948288	rs2746582	chr22:44818895	4.60E-05	CRBL	GG=15; GA=56; AA=24	G=32.1%; A=67.9%
3948293	rs2267610	chr22:44499643	2.70E-07	CRBL	CC=0; CT=20; TT=106	C=7.5%; T=92.5%
3948364	rs3329	chr22:45133238	9.20E-05	CRBL	GG=1; GA=34; AA=99	G=13.4%; A=86.6%
3948374	rs138136	chr22:44292371	6.30E-05	CRBL	CC=17; CT=58; TT=44	C=34.3%; T=65.7%
3948376	rs112696678	chr22:45456089	2.60E-04	CRBL	TT=1; TC=8; CC=107	T=3.7%; C=96.3%
3948376	rs10854828	chr22:45456646	3.40E-04	CRBL	TT=3; TC=43; CC=39	T=18.3%; C=81.7%
t3948259	s9614274	chr22:44196183	5.50E-05	FCTX	TT=0; TC=13; TC=110	T=4.9%; C=95.1%
t3948259	rs151013726	chr22:45246711	7.00E-04	FCTX	AA=0;AG-8;GG=116	A=3%; G=97%
3948274	rs5764455	chr22:44398524	2.00E-04	FCTX	AA=17; AG=70; GG=47	A=38.8%; G=61.2%
3948290	rs11090724	chr22:45451191	1.80E-04	FCTX	CC=1; CT=11; TT=122	C=4.9%; T=95.1%
3948290	rs2057111	chr22:45452872	2.00E-04	FCTX	TT=1; TG=11; GG=122	C=4.9%; T=95.1%

3948290	rs2057112	chr22:45453200	2.00E-04	FCTX	AA=1; AG=11; GG=122	A=4.9%; G=95.1%
3948290	rs7288379	chr22:44753219	2.20E-04	FCTX	AA=6; AG=49; GG=79	A=22.8%; G=77.2%
3948290	rs6006920	chr22:45453867	2.80E-04	FCTX	AA=1; AG=11; GG=122	A=4.9%; G=95.1%
3948292	rs135416	chr22:44666892	5.30E-05	FCTX	AA=20; AG=68; GG=40	A=40.3%; G=59.7%
3948292	rs135406	chr22:44672019	6.10E-05	FCTX	AA=22; AC=65; CC=47	A=40.7%; C=59.3%
3948292	rs135408	chr22:44670881	6.20E-05	FCTX	CC=22; CT=65; TT=47	C=40.7%; T=59.3%
3948292	rs135409	chr22:44670216	6.50E-05	FCTX	AA=21; AG=64; GG=47	A=39.6%; G=60.4%
3948292	rs135413	chr22:44667857	6.60E-05	FCTX	AA=21; AG=64; GG=47	A=39.6%; G=60.4%
3948293	rs9614187	chr22:44193626	8.70E-05	FCTX	AA=30; AC=72; CC=32	A=49.3%; C=50.7%
3948293	rs9614277	chr22:44199299	8.90E-05	FCTX	GG=30; GC=72; CC=32	G=49.3%; C=50.7%
3948293	rs6006549	chr22:44201534	9.10E-05	FCTX	TT=30; TC=72; CC=32	T=49.3%; C=50.7%
3948293	rs9626029	chr22:44204149	9.60E-05	FCTX	TT=30; TC=72; CC=32	T=49.3%; C=50.7%
3948338	NA	chr22:45262790:ACT_A	1.40E-04	FCTX	NA	NA
3948338	rs111669848	chr22:45262300	1.50E-04	FCTX	GG=24; GC=53; CC=51	G=37.7%; C=62.3%
3948343	rs111779845	chr22:44984945	2.30E-04	FCTX	GG=1; GC=13; CC=119	G=5.6%; C=94.4%
3948343	rs6006913	chr22:45390276	2.40E-04	FCTX	GG=27; GA=66; AA=40	G=44.8%; A=55.2%
3948343	rs6007404	chr22:45388501	2.80E-04	FCTX	CC=27; CA=64; AA=40	C=44%; A=56%

3948346	rs9306482	chr22:44996472	4.20E-05	FCTX	AA=29; AG=71; GG=34	A=48.1%; G=51.9%
3948346	rs9306481	chr22:44996215	9.40E-05	FCTX	GG=29; GC=68; CC=28	G=47%; C=53%
3948348	rs5766446	chr22:45516763	2.80E-04	FCTX	GG=19; GA=47; AA=45	G=31.7%; A=68.3%
3948376	NA	chr22:44420858:TA_T	1.20E-04	FCTX	NA	NA
3948376	rs9614882	chr22:45095527	1.40E-04	FCTX	TT=0; TC=16; CC=118	T=6%; C=94%
3948261	rs2896050	chr22:44523593	1.50E-04	HIPP	AA=3;AG=25;GG=100	A=11.6%; G=88.4%
3948265	rs134834	chr22:46014135	4.00E-05	HIPP	CC=4; CG=41; GG=22	C=18.3%; G=81.7%
3948265	rs8141570	chr22:46007345	5.10E-05	HIPP	AA=35; AG=57; GG=41	A=47.4%; G=52.6%
3948265	rs6519866	chr22:46007623	5.10E-05	HIPP	TT=35; TG=57; CC=41	T=47.4%; C=52.6%
3948265	rs4823229	chr22:46007997	5.10E-05	HIPP	TT=35; TC=57; CC=41	T=47.4%; C=52.6%
3948265	rs4823309	chr22:46004023	9.80E-05	HIPP	TT=28; TC=55; CC=38	T=41.4%; C=58.6%
3948281	rs6006914	chr22:45397719	1.20E-04	HIPP	TT=2; TC=26; CC=106	T=11.2%; C=88.8%
3948281	rs1997890	chr22:45406391	2.80E-04	HIPP	AA=30; AG=64; GG=40	A=46.3%; G=53.7%
3948281	rs7293154	chr22:45412589	2.80E-04	HIPP	CC=30; CT=66; TT=38	C=47%; T=53%
3948281	rs7293173	chr22:45412630	2.90E-04	HIPP	CC=30; CT=66; TT=38	C=47%; T=53%
3948348	rs136737	chr22:45925607	7.60E-05	HIPP	AA=19; AG=61; GG=41	A=36.9%; G=63.1%
3948348	rs136732	chr22:45924094	1.70E-04	HIPP	TT=25; TC=65;CC=41	T=42.9%; C=57.1%

3948348	rs9626567	chr22:45207555	2.80E-04	HIPP	GG=26; GC=64; CC=44	G=43.3%; C=56.7%
3948348	rs470067	chr22:45934420	3.10E-04	HIPP	GG=25; GT=66; TT=41	G=43.3%; T=56.7%
3948348	rs8141472	chr22:45174346	3.70E-04	HIPP	TT=19; TC=57; CC=40	T=35.4%; C=64.6%
3948348	rs136756	chr22:45937061	3.70E-04	HIPP	AA=25; AG=68; GG=41	A=44%; G=56%
3948362	NA	chr22:44811116:C_CTT	2.20E-04	HIPP	NA	NA
3948362	rs135942	chr22:44812954	2.60E-04	HIPP	AA=12; AG=48; GG=74	A=26.9%; G=73.1%
3948364	rs132436	chr22:45149619	7.40E-05	HIPP	AA=7; AG=46; GG=70	A=22.4%; G=77.6%
3948364	rs132435	chr22:45149613	7.50E-05	HIPP	CC=7; CA=46; AA=70	C=22.4%; A=77.6%
3948364	rs4372	chr22:45149541	7.90E-05	HIPP	GG=6; GA=46; AA=70	G=21.6%; A=78.4%
3948366	rs9614187	chr22:44193626	2.00E-04	HIPP	AA=30; AC=72; CC=32	A=49.3%; C=50.7%
t3948259	NA	chr22:45212045:C_CAT	4.40E-04	MEDU	NA	NA
3948265	rs2882259	chr22:45149281	8.20E-05	MEDU	AA=5; AG=49; GG=60	A=22%; G=78%
3948265	NA	chr22:45446914:AG_A	1.00E-04	MEDU	NA	NA
3948274	rs12484755	chr22:45017526	3.30E-04	MEDU	GG=6; GA=57; AA=69	G=25.7%; A=74.3%
3948281	rs3810620	chr22:44112400	2.70E-04	MEDU	AA=1; AT=31; TT=102	A=12.3%; T=87.7%
3948288	rs9614906	chr22:45157852	1.30E-04	MEDU	AA=0; AC=31; CC=65	A=11.6%; G=88.4%
3948288	rs7284294	chr22:45155288	1.90E-04	MEDU	TT=5; TC=62; CC=63	T=26.9%; C=73.1%

3948290	rs11090720	chr22:44740527	1.70E-04	MEDU	GG=8; GA=56; AA=70	G=26.9%; A=73.1%
3948293	rs9614199	chr22:44494047	8.90E-05	MEDU	TT=21; TC=59; CC=52	T=37.7%; C=62.3%
3948342	rs5765762	chr22:44928102	6.00E-05	MEDU	TT=1; TC=13; CC=59	T=5.6%; C=94.4%
3948266	rs8138173	chr22:44760039	8.80E-05	OCTX	AA=3; AG=43; GG=88	A=18.3; G=81.7
3948266	rs5765777	chr22:44760501	8.80E-05	OCTX	TT=3; TG=43; CC=88	T=18.3%; C=81.7%
3948274	NA	chr22:44682951:TG_T	3.70E-04	OCTX	NA	NA
3948288	rs77069626	chr22:45116170	2.70E-04	OCTX	AA=2; AG=26; GG=104	A=11.2%; G=88.8%
3948290	rs2267624	chr22:44562445	3.60E-04	OCTX	AA=0; AG=18; GG=115	A=6.7%; G=93.3%
3948293	rs6007249	chr22:45094043	6.60E-05	OCTX	GG=9; GA=53; AA=70	G=26.5%; A=73.5%
3948265	rs5766170	chr22:45286486	7.20E-05	PUTM	AA=2; AG=11; GG=115	A=5.6%; G=94.4%
3948266	NA	chr22:46045139:TC_T	1.10E-04	PUTM	NA	NA
3948281	rs13054771	chr22:44880343	1.50E-04	PUTM	TT=1; TG=10; GG=114	T=4.5%; G=95.5%
3948288	rs9614902	chr22:45148348	4.10E-05	PUTM	GG=35; GT=71; TT=23	G=52.6%; T=47.4%
3948290	rs713741	chr22:45909153	2.60E-04	PUTM	CC=25; CT=72; TT=36	C=45.5%; T=54.5%
3948338	rs58756368	chr22:45304742	2.30E-04	PUTM	GG=1; GA=24; AA=109	G=9.7%; A=90.3%
3948338	rs4823413	chr22:45305325	2.30E-04	PUTM	TT=1; TC=24; CC=109	T=9.7%; C=90.3%
3948342	rs2076213	chr22:44322922	4.00E-05	PUTM	GG=0; GT=23; TT=111	G=8.6%; T=91.4%

3948342	rs2076212	chr22:44322970	6.50E-05	PUTM	TT=1; TG=36; GG=96	T=14.2%; G=85.8%
3948343	NA	chr22:45614310:CT_C	6.50E-04	PUTM	NA	NA
3948343	rs41467347	chr22:45611226	7.20E-04	PUTM	CC=2; CA=16; AA=115	C=7.5%; A=92.5%
3948261	rs9626231	chr22:45072227	2.70E-04	SNIG	AA=0; AC=22; CC=112	A=8.2%; C=91.8%
3948274	rs7289955	chr22:45812562	3.90E-04	SNIG	GG=16; GT=64; TT=52	G=35.8%; T=64.2%
3948274	rs6006746	chr22:45812198	4.10E-04	SNIG	TT=16; TA=64; AA=52	T=35.8%; A=64.2%
3948274	rs6006745	chr22:45811176	4.10E-04	SNIG	TT=16; TC=64; CC=52	T=35.8%; C=64F.2%
3948274	rs8139085	chr22:45811050	4.10E-04	SNIG	GG=16; GC=64; CC=52	G=35.8%; C=64.2%
3948281	rs6006540	chr22:44154254	9.00E-05	SNIG	GG=9; GT=64; TT=61	G=30.6%; T=69.4%
3948288	rs8136048	chr22:44594821	8.90E-05	SNIG	CC=2; CT=35; TT=27	C=14.6%; T=85.4%
3948293	NA	chr22:46258113	7.20E-05	SNIG	NA	NA
3948343	rs75977328	chr22:44613848	2.80E-04	SNIG	AA=2; AG=10; GG=122	A=5.2%; G=94.8%
3948343	rs148703652	chr22:45192078	7.10E-04	SNIG	TT=0; TC=9; CC=107	T=3.4%; C=96.6%
3948365	rs5764359	chr22:44264217	2.20E-05	SNIG	TT=34; TG=74; GG=26	T=53%; G=47%
3948365	rs5764372	chr22:44278752	3.90E-05	SNIG	AA=12; AG=63; GG=59	A=32.5%; G=67.5%
3948365	rs55989331	chr22:44275459	3.90E-05	SNIG	AA=12; AG=63; GG=59	A=32.5%; G=67.5%
3948365	rs6006568	chr22:44278398	3.90E-05	SNIG	AA=12; AC=63; CC=59	A=32.5%; C=67.5%

3948365	rs4823151	chr22:44265323	3.90E-05	SNIG	GG=12; GA=63; AA=59	G=32.5%; A=67.5%
3948365	rs5764009	chr22:44270592	3.90E-05	SNIG	GG=12; GC=63; CC=59	G=32.5%; C=67.5%
3948365	rs5764362	chr22:44268576	3.90E-05	SNIG	CC=12; CT=63; TT=59	C=32.5%; T=67.5%
3948365	rs5764007	chr22:44267665	4.00E-05	SNIG	GG=12; GA=63; AA=59	G=32.5%; A=67.5%
3948365	rs5764367	chr22:44272450	4.00E-05	SNIG	TT=12; TC=63; CC=59	T=32.5%; C=67.5%
3948365	rs28569955	chr22:44275189	4.00E-05	SNIG	AA=12; AC=63; CC=59	A=32.5%; G=67.5%
3948366	rs3788634	chr22:45559741	1.40E-05	SNIG	TT=5; TG=38; GG=78	T=17.9%; C=82.1%
3948366	rs13054435	chr22:45553459	1.90E-05	SNIG	AA=5; AG=39; GG=80	A=18.3%; G=81.7%
3948366	rs11090732	chr22:45608360	6.00E-05	SNIG	CC=18; CG=58; GG=57	C=32.5%; G=67.5%
3948366	rs12628758	chr22:45612315	7.00E-05	SNIG	TT=15; TC=56; CC=53	T=32.1%; C=67.9%
3948366	rs12628275	chr22:45612317	7.00E-05	SNIG	CC=15; CT=56; TT=53	C=32.5%; T=67.5%
3948366	rs12485064	chr22:45608347	9.40E-05	SNIG	AA=18; AG=58; GG=58	A=35.1%; G=64.9%
3948366	rs28753815	chr22:45609617	9.70E-05	SNIG	AA=18; AG=58; GG=58	A=35.1%; G=64.9%
3948366	rs713695	chr22:44753508	1.30E-04	SNIG	TT=13; TC=65; CC=56	T=34%; C=66%
3948366	rs742018	chr22:45604885	1.50E-04	SNIG	AA=17; AG=58; GG=59	A=34.3%; G=65.7%
3948375	rs8139097	chr22:44747334	3.10E-05	SNIG	TT=8; TC=58; CC=63	T=27.6%; C=72.4%
3948375	rs739161	chr22:44745251	1.80E-04	SNIG	CC=8; CT=65; TT=55	C=30.2%; T=69.8%

t3948259	rs13055414	chr22:44522350	6.80E-04	TCTX	CC=11;CG=52;GG=45	C=27.6%; G=72.4
t3948259	rs133906	chr22:44521886	7.00E-04	TCTX	GG=28; GC=58;CC=44	G=42.5%; C=57.5%
t3948259	rs5764541	chr22:44514809	7.40E-04	TCTX	CC=28; CT=59; TT=47	C=42.9%; T=57.1%
t3948259	NA	chr22:44513713:T_TG	7.40E-04	TCTX	NA	NA
3948266	rs7286242	chr22:44704939	9.70E-06	TCTX	CC=1; CT=18; TT=115	C=7.5%; T=92.5%
3948266	rs13055374	chr22:44702472	1.70E-05	TCTX	AA=2; AG=20; GG=111	A=9%; G=91%
3948266	rs9614438	chr22:44705361	2.20E-05	TCTX	TT=7; TG=29; GG=98	T=16%; G=84%
3948266	rs9614437	chr22:44705269	2.20E-05	TCTX	CC=1; CT=17; TT=114	C=7.1%; T=92.9%
3948266	rs12163406	chr22:44699502	8.40E-05	TCTX	CC=0; CG=17; GG=117	C=6.3%; G=93.7%
3948266	rs9614433	chr22:44700197	9.00E-05	TCTX	TT=0; TC=19; CC=114	T=7.1%; C=92.9%
3948266	rs12162686	chr22:44702427	1.00E-04	TCTX	AA=0; AG=19; GG=114	A=7.1%; G=92.9%
3948288	rs140563	chr22:45431847	3.40E-04	TCTX	GG=15; GA=68; AA=51	G=36.6%; A=63.4%
3948290	rs5766361	chr22:45447241	3.10E-04	TCTX	AA=10; AG=35; GG=32	A=20.5%; G=79.5%
3948338	rs6006540	chr22:44154254	3.80E-05	TCTX	GG=9; GT=64; TT=61	G=30.6%; T=69.4%
3948338	rs715512	chr22:44832617	2.10E-04	TCTX	CC=0; CT=17; TT=116	C=6.3%; T=93.7%
3948362	rs6007414	chr22:45431796	2.90E-05	TCTX	GG=0; GA=16; AA=118	G=6%; A=94%
3948362	rs5766346	chr22:45436629	5.90E-05	TCTX	CC=0; CG=15; GG=119	C=5.6%; G=94.4%

3948362	rs6006915	chr22:45432447	5.90E-05	TCTX	GG=0; GC=15; GG=119	G=5.6%; C=94.4%
3948362	rs6007417	chr22:45432574	5.90E-05	TCTX	CC=0; CG=15; GG=119	C=5.6%; G=94.4%
3948362	rs6007418	chr22:45432928	5.90E-05	TCTX	TT=0; TG=15; GG=119	T=5.6%; G=94.4%
3948362	rs35752156	chr22:45433868	5.90E-05	TCTX	TT=0; TC=15; CC=119	T=5.6%; C=94.4%
3948364	rs12628758	chr22:45612315	3.50E-05	TCTX	TT=15; TC=56; CC=53	T=32.1%; C=67.9%
3948364	rs12628275	chr22:45612317	3.50E-05	TCTX	CC=15; CT=56; TT=53	C=32.1%; T=67.9%
3948364	rs5764956	chr22:45065761	5.40E-05	TCTX	GG=8; GC=51; CC=75	G=25%; C=75%
3948364	rs5765890	chr22:45065544	5.40E-05	TCTX	CC=8; CT=51; TT=51	C=25%; T=75%
3948364	rs11090732	chr22:45608360	7.00E-05	TCTX	CC=18; CG=58; GG=57	C=35.1%; G=64.9%
3948364	NA	chr22:45064428:GC_G	8.10E-05	TCTX	NA	NA
3948374	rs9306488	chr22:45327223	3.80E-05	TCTX	AA=8; AG=53; GG=70	A=25.7%; G=74.3%
3948374	rs5764152	chr22:44657401	1.00E-04	TCTX	AA=0; AG=7; GG=118	A=2.6%; G=97.4%
3948375	rs4823376	chr22:45171729	2.70E-04	TCTX	GG=8; GA=51; AA=75	G=25%; A=75%
3948375	rs5765972	chr22:45170602	2.70E-04	TCTX	GG=8; GA=51; AA=75	G=25%; A=75%
3948375	rs132471	chr22:45169772	3.20E-04	TCTX	CC=2; CA=35; AA=94	C=14.6%; A=85.4%
t3948259	rs56396134	chr22:44952160	4.20E-04	THAL	AA=10;AT=50;TT=58	A=26.1%; T=73.9%
t3948259	rs28411066	chr22:44319440	6.60E-04	THAL	CC=0;CT=7;TT=116	C=2.6%; T=97.4%

t3948259	NA	chr22:46240090	6.70E-04	THAL	NA	NA
3948261	rs1807589	chr22:44354398	2.60E-04	THAL	AA=19; AG=70; GG=23	A=40.3%; G=59.7%
3948261	NA	chr22:46143103	3.30E-04	THAL	NA	NA
3948265	rs74758439	chr22:45141835	8.50E-05	THAL	CC=0; CG=13; GG=120	C=4.9%; G=95.1%
3948274	rs71330783	chr22:45526633	5.10E-05	THAL	TT=3; TC=35; CC=83	T=215.3%; C=84.7%
3948281	rs2097358	chr22:44434674	1.80E-04	THAL	CC=5; CA=40; AA=83	C=18.7%; A=81.3%
3948288	rs13054616	chr22:44603299	2.30E-04	THAL	TT=14; TC=59; CC=56	T=32.5%; C=67.5%
3948322	NA	chr22:46091096	4.40E-05	THAL	NA	NA
3948322	NA	chr22:46106674	5.30E-05	THAL	NA	NA
3948322	NA	chr22:46080380	5.80E-05	THAL	NA	NA
3948322	NA	chr22:46160991	7.10E-05	THAL	NA	NA
3948322	NA	chr22:46153898	7.60E-05	THAL	NA	NA
3948322	NA	chr22:46154366	7.60E-05	THAL	NA	NA
3948322	NA	chr22:46145176	1.10E-04	THAL	NA	NA
3948322	NA	chr22:46149455	1.40E-04	THAL	NA	NA
3948322	NA	chr22:46151121	1.40E-04	THAL	NA	NA
3948322	NA	chr22:46166458:TG_T	1.60E-04	THAL	NA	NA

3948342	rs6006890	chr22:45238329	6.00E-06	THAL	AA=0; AT=15; TT=119	A=5.6%; G=94.4%
3948342	rs7286363	chr22:45238395	6.00E-06	THAL	TT=0; TC=15; CC=119	T=5.6%; C=94.4%
3948342	rs9614579	chr22:45238185	6.00E-06	THAL	CC=0; CA=15; AA=119	C=5.6%; A=94.4%
3948342	rs6007316	chr22:45238877	6.00E-06	THAL	AA=0; AG=15; GG=119	A=5.6%; G=94.4%
3948342	rs9614578	chr22:45238181	6.00E-06	THAL	AA=0; AG=15; GG=119	A=5.6%; G=94.4%
3948342	rs73176172	chr22:45242022	1.50E-04	THAL	GG=1; GA=32; AA=98	G=12.7%; A=87.3%
3948342	rs8139116	chr22:45258012	1.90E-04	THAL	TT=1; TV=40; CC=90	T=15.7%; C=84.3%
3948345	rs9615096	chr22:45665159	1.10E-07	THAL	AA=1; AG=14; GG=75	A=6%; G=94%
3948345	rs9615095	chr22:45661864	4.30E-06	THAL	CC=1; CA=10; AA=82	C=4.5%; A=95.5%
3948345	rs28437962	chr22:45659082	5.00E-06	THAL	GG=1; GT=10; TT=80	G=4.5%; T=95.5%
3948345	rs226496	chr22:45671001	9.20E-06	THAL	CC=6; CT=35; TT=86	C=17.5%; T=82.5%
3948345	rs226495	chr22:45669729	9.60E-06	THAL	TT=8; TC=43; CC=83	T=22%; C=78%
3948345	rs74541407	chr22:45664258	1.10E-05	THAL	TT=8; TA=42; AA=82	T=21.6%; A=78.4%
3948345	rs2458933	chr22:45663408	1.20E-05	THAL	CC=8; CG=42; GG=81	C=21.6%; G=78.4%
3948345	rs172865	chr22:45670674	1.40E-05	THAL	TT=8; TC=41; CC=82	T=21.3%; C=78.7%
3948345	NA	chr22:45663041:CAT_C	1.50E-05	THAL	NA	NA
3948345	rs7364185	chr22:45660503	3.20E-05	THAL	CC=6; CT=38; TT=81	C=18.7%; T=81.3%

3948348	rs9614856	chr22:45030752	2.10E-04	THAL	TT=0; TC=8; CC=114	T=3%; C=97%
3948348	rs4823351	chr22:45024417	2.70E-04	THAL	TT=0; TA=7; AA=113	T=2.6%; A=97.4%
3948362	rs5765972	chr22:45170602	5.20E-05	THAL	GG=8; GA=51; AA=75	G=25%; A=75%
3948362	rs4823376	chr22:45171729	5.70E-05	THAL	GG=8; GA=51; AA=75	G=25%; A=75%
3948375	rs9614566	chr22:45143668	2.40E-04	THAL	AA=11; AT=52; TT=44	A=27.6%; T=72.4%
3948375	rs9614898	chr22:45143453	2.40E-04	THAL	AA=11; AG=52; GG=44	A=27.6%; G=72.4%
3948375	rs2299847	chr22:44473752	2.70E-04	THAL	AA=9; AG=40; GG=61	A=21.6%; G=78.4%
3948376	rs13055282	chr22:44612099	1.60E-04	THAL	CC=0; CT=15; TT=118	C=5.6%; T=94.4%
3948376	rs35474321	chr22:44613662	1.60E-04	THAL	GG=0; GT=15; TT=118	G=5.6%; T=94.4%
3948376	rs34367101	chr22:44614443	1.70E-04	THAL	AA=0; AC=15; CC=118	A=5.6%; C=94.4%
3948376	rs138575	chr22:44951267	3.20E-04	THAL	AA=14; AC=56; CC=55	A=31.3%; C=68.7%
3948376	rs12172404	chr22:44948411	3.20E-04	THAL	GG=18; GA=57; AA=55	G=34.7%; A=65.3%
3948376	rs742200	chr22:44947361	3.30E-04	THAL	CC=19; CG=59; GG=55	C=36.3%; G=63.8%
3948261	rs71330751	chr22:44805506	3.50E-04	WHM	TT=3; TC=36; CC=93	T=15.7%; C=84.3%
3948261	rs7290106	chr22:45219187	1.20E-04	WHMT	AA=20;AG=57;GG-=45	A=36.3%; G=63.8%
3948261	rs2071760	chr22:45221062	2.10E-04	WHMT	TT=23; TG=57; GG=45	T=38.4%; G=61.6%
3948261	rs136677	chr22:45238437	3.10E-04	WHMT	TT=25; TC=58;CC=49	T=40.3%; C=50.7%

3948261	rs136678	chr22:45240256	3.10E-04	WHMT	GG=25; GT=60; TT=49	G=41%; T=59%
3948274	rs2896024	chr22:44458618	1.30E-04	WHMT	TT=23; TC=63; CC=43	T=40.7%; C=59.3%
3948281	NA	chr22:45426774:T_TG	1.50E-04	WHMT	NA	NA
3948281	NA	chr22:45426773:T_TTG	1.70E-04	WHMT	NA	NA
3948288	rs5015416	chr22:45179079	2.70E-04	WHMT	CC=2; CG=19; GG=111	C=8.6%; G=91.4%
3948288	rs6006884	chr22:45178783	3.20E-04	WHMT	CC=2; CG=19; GG=111	C=8.6%; G=91.4%
3948293	rs5765371	chr22:45838887	1.20E-04	WHMT	TT=29; TC=74; CC=31	T=49.3%; C=50.7%
3948343	rs226519	chr22:45587269	2.90E-04	WHMT	CC=3; CG=20; GG=111	C=9.7%; G=90.3%
3948343	rs226520	chr22:45587746	3.50E-04	WHMT	TT=2; TC=20; C=111	T=9%; C=91%
3948343	rs77109785	chr22:45584396	4.00E-04	WHMT	AA=3; AG=20; GG=110	A=9.7%; G=90.3%
3948346	rs9626286	chr22:45529502	7.30E-05	WHMT	TT=25; TG=67; GG=39	T=43.7%; G=56.3%
3948346	rs12166859	chr22:45537097	8.40E-05	WHMT	AA=26; AG=67; GG=39	A=44.4%; G=55.6%
3948346	rs8139733	chr22:45537518	8.40E-05	WHMT	CC=26; CG=67; GG=39	C=44.4%; G=55.6%
3948346	rs9626288	chr22:45534688	8.50E-05	WHMT	AA=26; AG=68; GG=40	A=44.8%; G=55.2%
3948346	rs7289818	chr22:45539002	8.80E-05	WHMT	AA=27; AG=68; GG=39	A=45.5%; G=54.5%
3948346	rs9985182	chr22:45539841	9.00E-05	WHMT	TT=27; TG=68; GG=39	T=45.5%; G=54.4%
3948346	NA	chr22:45540063:AAGAC	9.50E-05	WHMT	NA	NA

3948346	rs132887	chr22:45570105	1.10E-04	WHMT	GG=20; GC=56; CC=57	G=35.8%; C=64.2%
3948348	rs4508710	chr22:45693443	1.00E-04	WHMT	AA=2; AG=10; GG=122	A=5.2%; G=94.8%
3948374	rs965027	chr22:45005361	2.40E-05	WHMT	AA=19; AG=63; GG=52	A=37.7%; G=62.3%
3948374	rs2103594	chr22:45006830	2.70E-05	WHMT	TT=29; TC=60; CC=45	T=44%; C=56%
3948374	rs4611748	chr22:45006759	2.90E-05	WHMT	TT=14; TA=49; AA=29	T=28.7%; A=71.3%
3948374	rs2142854	chr22:45009295	4.50E-05	WHMT	AA=23; AG=61; GG=50	A=39.9%; G=0.1%
3948374	NA	chr22:45009072:A_AT	4.90E-05	WHMT	NA	NA
3948374	rs6007205	chr22:45004972	6.60E-05	WHMT	AA=17; AG=62; GG=49	A=35.8%; G=64.2%
3948374	rs738361	chr22:45003878	1.30E-04	WHMT	TT=21; TC=61; CC=52	T=38.4%; C=61.6%
3948375	rs148703652	chr22:45192078	2.10E-05	WHMT	TT=0; TC=9; CC=107	T=3.4%; C=96.6%
3948375	rs17650186	chr22:46008858	3.30E-04	WHMT	TT=40; TC=56; CC=38	T=50.7%; C=49.3%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 25: Brain quantitative gene expression analyses for PRR5 gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
3948265	rs76110348	chr22:45417158	7.40E-05	aveALL	AA=0; AG=19; GG=111	A=7.1%; G=92.9%
3948274	rs116774661	chr22:45964637	3.00E-04	aveALL	AA=1; AG=24; GG=67	A=9.7%; G=90.3%

3948290	rs62228462	chr22:45107296	1.60E-04	aveALL	AA=0; AG=12; GG=120	A=4.5%; G=95.5%
3948292	rs135416	chr22:44666892	3.90E-06	aveALL	AA=20; AG=68; GG=40	A=40.3%; G=59.7%
3948292	rs135412	chr22:44668792	5.80E-05	aveALL	GG=24; GA=70; AA=38	G=44%; A=56%
3948292	rs28584938	chr22:44667314	6.20E-05	aveALL	GG=24; GA=70; AA=38	G=44%; A=56%
3948292	rs135415	chr22:44667156	6.30E-05	aveALL	CC=24; CA=70; AA=38	C=44%; A=56%
3948292	rs1807715	chr22:44666676	6.40E-05	aveALL	GG=24; GA=70; AA=38	C=44%; A=56%
3948293	rs4823163	chr22:44301924	1.20E-04	aveALL	GG=12; GA=56; AA=61	G=29.9%; A=70.1%
3948338	NA	chr22:45263188:A_AC	2.00E-04	aveALL	NA	NA
3948338	rs55744143	chr22:45254799	2.20E-04	aveALL	TT=1; TC=24; CC=100	T=9.7%; C=90.3%
3948338	NA	chr22:45255532:CCT_C	2.20E-04	aveALL	NA	NA
3948338	rs4490294	chr22:45255527	2.20E-04	aveALL	CC=6; CA=40; AA=88	C=19.4%; A=80.6%
3948261	rs734561	chr22:44324104	1.90E-04	CRBL	TT=2; TC=44; CC=88	T=17.9%; C=82.1%
3948262	rs12628484	chr22:44881837	1.40E-04	CRBL	TT=5; TG=42; GG=87	T=19.4%; G=80.6%
3948262	rs5765602	chr22:44881127	1.40E-04	CRBL	AA=5; AG=42; GG=87	A=19.4%; G=80.6%
3948262	rs35737845	chr22:44882231	1.50E-04	CRBL	AA=5; AC=41; CC=87	A=19%; C=81%
3948262	rs2349252	chr22:44877911	1.80E-04	CRBL	CC=5; CT=41; TT=86	C=19%; T=81%
3948262	rs2239770	chr22:44875652	2.10E-04	CRBL	CC=4; CT=37; TT=86	C=16.8%; T=83.2%
3948262	rs5764965	chr22:45097815	2.10E-04	CRBL	TT=6; TC=52; CC=76	T=23.9%; C=76.1%

3948262	rs4365563	chr22:44865642	2.30E-04	CRBL	TT=4; TG=37; GG=86	T=16.8%; G=83.2%
3948262	rs8140396	chr22:44866786	2.30E-04	CRBL	GG=4; GA=37; AA=86	G=16.8%; A=83.2%
3948262	rs5764819	chr22:44871273	2.50E-04	CRBL	AA=4; AT=37; TT=86	A=16.8%; T=83.2%
3948262	rs5764754	chr22:44855856	2.60E-04	CRBL	AA=5; AG=40; GG=89	A=18.7%; G=81.3%
3948287	rs6007041	chr22:45837410	1.30E-05	CRBL	GG=11; GA=56; AA=66	G=29.1%; A=70.9%
3948287	rs5765366	chr22:45837032	1.40E-05	CRBL	AA=11; AT=56; TT=66	A=29.1%; T=70.9%
3948287	rs5765367	chr22:45837033	1.40E-05	CRBL	AA=11; AC=56; CC=66	A=29.1%; C=70.9%
3948287	rs4823297	chr22:45840721	1.50E-05	CRBL	GG=11; GT=57; TT=66	G=29.5%; T=70.5%
3948287	rs5764733	chr22:45841045	1.70E-05	CRBL	GG=11. GC=57; CC=66	G=29.5%; C=70.5%
3948287	rs5765370	chr22:45838156	2.10E-05	CRBL	AA=11; AG=57; GG=66	A=29.5%; G=70.5%
3948287	rs4823296	chr22:45839551	3.00E-05	CRBL	CC=10; CT=54; TT=66	C=27.6%; T=72.4%
3948287	rs5764743	chr22:45864559	3.20E-05	CRBL	AA=27; AT=62; TT=45	A=43.3%; T=56.7%
3948287	rs5764742	chr22:45864459	3.20E-05	CRBL	AA=27; AG=62; GG=45	A=43.3%; G=56.7%
3948287	rs2350953	chr22:45863515	3.20E-05	CRBL	TT=27; TC=62; CC=45	T=43.3.%; C=56.7%
3948288	rs2746582	chr22:44818895	4.60E-05	CRBL	GG=15; GA=56; AA=24	G=32.1%; A=67.9%
3948293	rs2267610	chr22:44499643	2.70E-07	CRBL	CC=0; CT=20; TT=106	C=7.5%; T=92.5%
3948364	rs3329	chr22:45133238	9.20E-05	CRBL	GG=1; GA=34; AA=99	G=13.4%; A=86.6%

3948374	rs138136	chr22:44292371	6.30E-05	CRBL	CC=17; CT=58; TT=44	C=34.3%; T=65.7%
3948376	rs112696678	chr22:45456089	2.60E-04	CRBL	TT=1; TC=8; CC=107	T=3.7%; C=96.3%
3948376	rs10854828	chr22:45456646	3.40E-04	CRBL	TT=3; TC=43; CC=39	T=18.3%; C=81.7%
t3948259	rs9614274	chr22:44196183	5.50E-05	FCTX	TT=0; TC=13; CC=110	T=4.9%; C=95.1%
t3948259	rs151013726	chr22:45246711	7.00E-04	FCTX	AA=0; AG=8; GG=116	A=3%; G=97%
3948274	rs5764455	chr22:44398524	2.00E-04	FCTX	AA=17; AG=70; GG=47	A=38.8%; G=61.2%
3948290	rs11090724	chr22:45451191	1.80E-04	FCTX	CC=1; CT=1; TT=122	C=4.9%; T=95.1%
3948290	rs2057111	chr22:45452872	2.00E-04	FCTX	TT=1; TG=11; GG=122	T=4.9%; G=95.1%
3948290	rs2057112	chr22:45453200	2.00E-04	FCTX	AA=1; AG=11; GG=122	A=4.9%; G=95.1%
3948290	rs7288379	chr22:44753219	2.20E-04	FCTX	AA=6; AG=49; GG=79	A=22.8%; G=77.2%
3948290	rs6006920	chr22:45453867	2.80E-04	FCTX	AA=1; AG=11; GG=122	A=4.9%; G=95.1%
3948292	rs135416	chr22:44666892	5.30E-05	FCTX	AA=20; AG=68; GG=40	A=40.3%; G=59.7%
3948292	rs135406	chr22:44672019	6.10E-05	FCTX	AA=22; AC=65; CC=47	A=40.7%; C=59.3%
3948292	rs135408	chr22:44670881	6.20E-05	FCTX	CC=22; CT=65; TT=47	C=40.7%; T=59.3%
3948292	rs135409	chr22:44670216	6.50E-05	FCTX	AA=21; AG=64; GG=46	A=39.6%; G=60.4%
3948292	rs135413	chr22:44667857	6.60E-05	FCTX	AA=21; AG=64; GG=46	A=39.6%; G=60.4%
3948293	rs9614187	chr22:44193626	8.70E-05	FCTX	AA=30; AC=72; CC=32	A=49.3%; C=50.7%

3948293	rs9614277	chr22:44199299	8.90E-05	FCTX	GG=30; GC=72; CC=32	G=49.3%; C=50.7%
3948293	rs6006549	chr22:44201534	9.10E-05	FCTX	TT=30; TC=72; CC=32	T=49.3%; C=50.7%
3948293	rs9626029	chr22:44204149	9.60E-05	FCTX	TT=30; TC=72; CC=32	T=49.3%; C=50.7%
3948338	NA	chr22:45262790:ACT_A	1.40E-04	FCTX	NA	NA
3948338	rs111669848	chr22:45262300	1.50E-04	FCTX	GG=24; GC=53; CC=51	G=37.7%; C=62.3%
3948343	rs111779845	chr22:44984945	2.30E-04	FCTX	GG=1; GC=13; CC=119	G=5.6%; C=94.4%
3948343	rs6006913	chr22:45390276	2.40E-04	FCTX	GG=27; GA=66; AA=40	G=44.8%; A=55.2%
3948343	rs6007404	chr22:45388501	2.80E-04	FCTX	CC=27; CA=64; AA=40	C=44%; A=56%
3948346	rs9306482	chr22:44996472	4.20E-05	FCTX	AA=29; AG=71; GG=34	A=48.1%; G=51.9%
3948346	rs9306481	chr22:44996215	9.40E-05	FCTX	GG=29; GC=68; CC=28	G=47%; C=53%
3948348	rs5766446	chr22:45516763	2.80E-04	FCTX	GG=19; GA=47; AA=45	G=31.7%; A=68.3%
3948376	NA	chr22:44420858:TA_T	1.20E-04	FCTX	NA	NA
3948376	rs9614882	chr22:45095527	1.40E-04	FCTX	TT=0;TC=16; CC=118	T=6%; C=94%
3948261	rs2896050	chr22:44523593	1.50E-04	HIPP	AA=3; AG=25; GG=100	A=11.6%; G=88.4%
3948265	rs134834	chr22:46014135	4.00E-05	HIPP	CC=4; CG=41; GG=22	C=18.3%; G=81.7%
3948265	rs8141570	chr22:46007345	5.10E-05	HIPP	AA=35; AG=57; GG=41	A=47.4%; G=52.6%
3948265	rs6519866	chr22:46007623	5.10E-05	HIPP	TT=3; TC=57; CC=41	T=47.4%; C=52.6%
3948265	rs4823229	chr22:46007997	5.10E-05	HIPP	TT=35; TC=57; CC=41	T=47.4%; C=52.6%

3948265	rs4823309	chr22:46004023	9.80E-05	HIPP	TT=8; TC=55; CC=38	T=41.4%; C=58.6%
3948281	rs6006914	chr22:45397719	1.20E-04	HIPP	TT=2; TC=26; CC=106	T=11.2%; C=88.8%
3948281	rs1997890	chr22:45406391	2.80E-04	HIPP	AA=30; AG=64; GG=4	A=46.3%; G=53.7%
3948281	rs7293154	chr22:45412589	2.80E-04	HIPP	CC=30; CT=66; TT=38	C=47%; T=53%
3948281	rs7293173	chr22:45412630	2.90E-04	HIPP	CC=30; CT=66; TT=38	C=47%; T=53%
3948348	rs136737	chr22:45925607	7.60E-05	HIPP	AA=19; AG=61; GG=41	A=36.9%; G=63.1%
3948348	rs136732	chr22:45924094	1.70E-04	HIPP	TT=25; TC=65; CC=41	T=42.9%; C=57.1%
3948348	rs9626567	chr22:45207555	2.80E-04	HIPP	GG=26; GC=64; CC=44	G=43.3%; C=56.7%
3948348	rs470067	chr22:45934420	3.10E-04	HIPP	GG=25; GT=66; TT=41	G=43.3%; T=56.7%
3948348	rs8141472	chr22:45174346	3.70E-04	HIPP	TT=19; TC=57; CC=40	T=35.4%; C=64.6%
3948348	rs136756	chr22:45937061	3.70E-04	HIPP	AA=25; AG=68; GG=41	A=44%; G=56%
3948362	NA	chr22:44811116:C_CTT	2.20E-04	HIPP	NA	NA
3948362	rs135942	chr22:44812954	2.60E-04	HIPP	AA=12; AG=48; GG=74	A=26.9%; G=73.1%
3948364	rs132436	chr22:45149619	7.40E-05	HIPP	AA=7; AG=46; GG=70	A=22.4%; G=77.6%
3948364	rs132435	chr22:45149613	7.50E-05	HIPP	CC=7; CA=46; AA=70	C=22.4%; A=77.6%
3948364	rs4372	chr22:45149541	7.90E-05	HIPP	GG=6; GA=46; AA=70	G=21.6%; A=78.4%
3948366	rs9614187	chr22:44193626	2.00E-04	HIPP	AA=30; AC=72; CC=32	A=49.3%; C=50.7%
t3948259	NA	chr22:45212045:C_CAT	4.40E-04	MEDU	NA	NA

3948265	rs2882259	chr22:45149281	8.20E-05	MEDU	AA=5; AG=49; GG=60	A=22%; G=78%
3948265	NA	chr22:45446914:AG_A	1.00E-04	MEDU	NA	NA
3948274	rs12484755	chr22:45017526	3.30E-04	MEDU	GG=6; GA=57; AA=69	G=25.7%; A=74.3%
3948281	rs3810620	chr22:44112400	2.70E-04	MEDU	AA=1; AT=31; TT=102	A=12.3%; T=87.7%
3948288	rs9614906	chr22:45157852	1.30E-04	MEDU	AA=0; AC=31; CC=56	A=11.6%; C=88.4%
3948288	rs7284294	chr22:45155288	1.90E-04	MEDU	TT=5;TC=62; CC=63	T=26.9%; C=73.1%
3948290	rs11090720	chr22:44740527	1.70E-04	MEDU	GG=8; GA=56; AA=70	G=26.9%; A=73.1%
3948293	rs9614199	chr22:44494047	8.90E-05	MEDU	TT=21; TC=59; CC=52	T=37.7%; C=62.3%
3948342	rs5765762	chr22:44928102	6.00E-05	MEDU	TT=1; TC=13; CC=59	T=5.6%; C=94.4%
3948266	rs8138173	chr22:44760039	8.80E-05	OCTX	AA=3; AG=43; GG=88	A=18.3%; G=81.7%
3948266	rs5765777	chr22:44760501	8.80E-05	OCTX	TT=3; TC=43; CC=88	AT=18.3%; C=81.7%
3948274	NA	chr22:44682951:TG_T	3.70E-04	OCTX	NA	NA
3948288	rs77069626	chr22:45116170	2.70E-04	OCTX	AA=2; AG=26; GG=104	A=11.2%; G=88.8%
3948290	rs2267624	chr22:44562445	3.60E-04	OCTX	AA=0; AG=18; GG=115	A=6.7%; G=93.3%
3948293	rs6007249	chr22:45094043	6.60E-05	OCTX	GG=9; GA=53; AA=70	G=26.5%; A=73.5%
3948265	rs5766170	chr22:45286486	7.20E-05	PUTM	AA=2; AG=11; GG=115	A=5.6%; G=94.4%
3948266	NA	chr22:46045139:TC_T	1.10E-04	PUTM	NA	NA
3948281	rs13054771	chr22:44880343	1.50E-04	PUTM	TT=1; TG=10; GG=114	T=4.5%; G=95.5%

3948288	rs9614902	chr22:45148348	4.10E-05	PUTM	GG=35; GT=71; TT=23	G=52.6%; T=47.4%
3948290	rs713741	chr22:45909153	2.60E-04	PUTM	CC=25, CT=72; TT=36	C=45.5%; T=54.4%
3948338	rs58756368	chr22:45304742	2.30E-04	PUTM	GG=1; GA=24; AA=109	G=9.7%; A=90.3%
3948338	rs4823413	chr22:45305325	2.30E-04	PUTM	TT=1; TC=24; CC=100	T=9.7%; C=90.3%
3948342	rs2076213	chr22:44322922	4.00E-05	PUTM	GG=0; GT=23; TT=111	G=8.6%; T=91.4%
3948342	rs2076212	chr22:44322970	6.50E-05	PUTM	TT=1; TG=36; GG=96	T=14.2%; G=85.8%
3948343	NA	chr22:45614310:CT_C	6.50E-04	PUTM	NA	NA
3948343	rs41467347	chr22:45611226	7.20E-04	PUTM	CC=2; CA=16; AA=115	C=7.5%; A=92.5%
3948261	rs9626231	chr22:45072227	2.70E-04	SNIG	AA=0; AC=22; CC=112	A=8.2%; C=91.8%
3948274	rs7289955	chr22:45812562	3.90E-04	SNIG	GG=16; GT=64; TT=52	G=35.8%; T=64.2%
3948274	rs6006746	chr22:45812198	4.10E-04	SNIG	TT=16; TA=64; AA=52	T=35.8%; A=64.2%
3948274	rs6006745	chr22:45811176	4.10E-04	SNIG	T=16; TC=64; CC=52	T=35.8%; C=64.2%
3948274	rs8139085	chr22:45811050	4.10E-04	SNIG	GG=16; GC=64; CC=52	G=35.8%; C=64.2%
3948281	rs6006540	chr22:44154254	9.00E-05	SNIG	GG=9; GT=64; TT=61	G=30.6%; T=69.4%
3948288	rs8136048	chr22:44594821	8.90E-05	SNIG	CC=2; CT=35; TT=27	C=14.6%; T=85.4%
3948293	NA	chr22:46258113	7.20E-05	SNIG	NA	NA
3948343	rs75977328	chr22:44613848	2.80E-04	SNIG	AA=2; AG=10; GG=122	A=5.2%; G=94.8%
3948343	rs148703652	chr22:45192078	7.10E-04	SNIG	TT=0; TC=9; CC=107	T=3.4%; C=96.6%

3948365	rs5764359	chr22:44264217	2.20E-05	SNIG	TT=34; TG=74; GG=26	T=53%; G=47%
3948365	rs5764372	chr22:44278752	3.90E-05	SNIG	AA=12; AG=63; GG=59	A=32.5%; G=67.5%
3948365	rs55989331	chr22:44275459	3.90E-05	SNIG	AA=12; AG=63; GG=59	A=32.5%; G=67.5%
3948365	rs6006568	chr22:44278398	3.90E-05	SNIG	AA=12; AC=64; CC=59	A=32.5%; C=67.5%
3948365	rs4823151	chr22:44265323	3.90E-05	SNIG	GG=12; GA=63; AA=59	G=32.5%; A=67.5%
3948365	rs5764009	chr22:44270592	3.90E-05	SNIG	GG=12; GC=63; CC=59	G=32.5%; C=67.5%
3948365	rs5764362	chr22:44268576	3.90E-05	SNIG	CC=12; CT=63; TT=59	C=32.5%; T=67.5%
3948365	rs5764007	chr22:44267665	4.00E-05	SNIG	GG=12; GA=63; AA=59	G=32.5%; A=67.5%
3948365	rs5764367	chr22:44272450	4.00E-05	SNIG	TT=12; TC=63; CC=59	T=32.5%; C=67.5%
3948365	rs28569955	chr22:44275189	4.00E-05	SNIG	AA=12; AC=63; CC=59	A=32.5%; C=67.5%
3948366	rs3788634	chr22:45559741	1.40E-05	SNIG	TT=5; TG=38; GG=78	T=17.9%; G=82.1%
3948366	rs13054435	chr22:45553459	1.90E-05	SNIG	AA=5; AG=39; GG=80	A=18.3%; G=81.7%
3948366	rs11090732	chr22:45608360	6.00E-05	SNIG	CC=18; CG=58; GG=57	C=35.1%; G=64.9%
3948366	rs12628758	chr22:45612315	7.00E-05	SNIG	TT=15; TC=56; CC=53	T=32.1%; C=67.9%
3948366	rs12628275	chr22:45612317	7.00E-05	SNIG	CC=15; CT=56; TT=53	C=32.1%; T=67.9%
3948366	rs12485064	chr22:45608347	9.40E-05	SNIG	AA=18; AG=58; GG=58	A=35.1%; G=64.9%
3948366	rs28753815	chr22:45609617	9.70E-05	SNIG	AA=18; AG=58; GG=58	A=35.1%; G=64.9%

3948366	rs713695	chr22:44753508	1.30E-04	SNIG	TT=13; TC=65; CC=56	T=34%; C=66%
3948366	rs742018	chr22:45604885	1.50E-04	SNIG	AA=17; AG=58; GG=59	A=34.3%; G=65.7%
3948375	rs8139097	chr22:44747334	3.10E-05	SNIG	TT=8; TC=58; CC=63	T=27.6%; C=72.4%
3948375	rs739161	chr22:44745251	1.80E-04	SNIG	CC=8; CT=65; TT=55	C=30.2%; T=69.8%
t3948259	rs13055414	chr22:44522350	6.80E-04	TCTX	AA=20, AG=57; GG=45	A=36.2%; G=63.8%
t3948259	rs133906	chr22:44521886	7.00E-04	TCTX	GG=28; GC=58; CC=44	G=42.5%; C=57.5%
t3948259	rs5764541	chr22:44514809	7.40E-04	TCTX	CC=28; CT=59; TT=47	C=42.9%; T=57.1%
t3948259	NA	chr22:44513713:T_TG	7.40E-04	TCTX	NA	NA
3948266	rs7286242	chr22:44704939	9.70E-06	TCTX	CC=1; CT=18; TT=115	C=7.5%; T=92.5%
3948266	rs13055374	chr22:44702472	1.70E-05	TCTX	AA=2; AG=2; GG=111	A=9%; G=91%
3948266	rs9614438	chr22:44705361	2.20E-05	TCTX	TT=7; TG=29; GG=98	T=16%; G=84%
3948266	rs9614437	chr22:44705269	2.20E-05	TCTX	CC=1; CT=17; TT=114	C=7.1%; T=92.9%
3948266	rs12163406	chr22:44699502	8.40E-05	TCTX	CC=0; CG=17; GG=117	C=6.3%; G=93.7%
3948266	rs9614433	chr22:44700197	9.00E-05	TCTX	TT=0; TC=19; CC=114	T=7.1%; C=92.9%
3948266	rs12162686	chr22:44702427	1.00E-04	TCTX	AA=0; AG=19; GG=114	A=7.1%; G=92.9%
3948288	rs140563	chr22:45431847	3.40E-04	TCTX	GG=15; GA=68; AA=51	G=36.6%; A=63.4%
3948290	rs5766361	chr22:45447241	3.10E-04	TCTX	AA=10; AG=35; GG=32	A=20.5%; G=79.5%
3948338	rs6006540	chr22:44154254	3.80E-05	TCTX	GG=9; GT=64; TT=61	G=30.6%; T=69.4%

3948338	rs715512	chr22:44832617	2.10E-04	TCTX	CC=0; CT=17; TT=116	C=6.3%; T=93.7%
3948362	rs6007414	chr22:45431796	2.90E-05	TCTX	GG=0; GA=16; AA=118	G=6%; A=94%
3948362	rs5766346	chr22:45436629	5.90E-05	TCTX	CC=0; CG=15; GG=119	C=5.6%; G=94.4%
3948362	rs6006915	chr22:45432447	5.90E-05	TCTX	GG=0; GC=15; CC=119	G=5.6%; C=94.4%
3948362	rs6007417	chr22:45432574	5.90E-05	TCTX	CC=0; CG=15; GG=119	C=5.6%; G=94.4%
3948362	rs6007418	chr22:45432928	5.90E-05	TCTX	TT=0; TG=15; GG=119	T=5.6%; G=94.4%
3948362	rs35752156	chr22:45433868	5.90E-05	TCTX	TT=0; TC=15; CC=119	T=5.6%; C=94.4%
3948364	rs12628758	chr22:45612315	3.50E-05	TCTX	TT=15; TC=56; CC=53	T=32.1%; C=67.9%
3948364	rs12628275	chr22:45612317	3.50E-05	TCTX	CC=15; CT=56; TT=53	C=32.1%; T=67.9%
3948364	rs5764956	chr22:45065761	5.40E-05	TCTX	GG=8; GC=51; CC=75	G=25%; C=75%
3948364	rs5765890	chr22:45065544	5.40E-05	TCTX	CC=8; CT=51; TT=75	C=25%; T=75%
3948364	rs11090732	chr22:45608360	7.00E-05	TCTX	CC=18; CG=58; GG=57	C=35.1%; G=64.9%
3948364	NA	chr22:45064428:GC_G	8.10E-05	TCTX	NA	NA
3948374	rs9306488	chr22:45327223	3.80E-05	TCTX	AA=8; AG=53; GG=70	A=25.7%; G=74.3%
3948374	rs5764152	chr22:44657401	1.00E-04	TCTX	AA=0; AG=7; GG=118	A=2.6%; G=97.4%
3948375	rs4823376	chr22:45171729	2.70E-04	TCTX	GG=8; GA=51; AA=75	G=25%; A=75%
3948375	rs5765972	chr22:45170602	2.70E-04	TCTX	GG=8; GA=51; AA=75	G=25%; A=75%
3948375	rs132471	chr22:45169772	3.20E-04	TCTX	CC=2; CA=35; AA=94	C=14.6%; A=85.4%

t3948259	rs56396134	chr22:44952160	4.20E-04	THAL	AA=10; AT=50; TT=58	A=26.1%; T=73.9%
t3948259	rs28411066	chr22:44319440	6.60E-04	THAL	CC=0; CT=7; TT=116	C=2.6%; T=97.4%
t3948259	NA	chr22:46240090	6.70E-04	THAL	NA	NA
3948261	rs1807589	chr22:44354398	2.60E-04	THAL	AA=19; AG=70; GG=23	A=40.3%; G=59.7%
3948261	NA	chr22:46143103	3.30E-04	THAL	NA	NA
3948265	rs74758439	chr22:45141835	8.50E-05	THAL	CC=0; CT=13; GG=120	C=4.9%; G=95.1%
3948274	rs71330783	chr22:45526633	5.10E-05	THAL	TT=3; TC=35; CC=83	T=15.3%; C=84.7%
3948281	rs2097358	chr22:44434674	1.80E-04	THAL	CC=5; CA=40; AA=83	C=18.7%; A=81.3%
3948288	rs13054616	chr22:44603299	2.30E-04	THAL	TT=14; TC=59; CC=56	T=32.5%; C=67.5%
3948322	NA	chr22:46091096	4.40E-05	THAL	NA	NA
3948322	NA	chr22:46106674	5.30E-05	THAL	NA	NA
3948322	NA	chr22:46080380	5.80E-05	THAL	NA	NA
3948322	NA	chr22:46160991	7.10E-05	THAL	NA	NA
3948322	NA	chr22:46153898	7.60E-05	THAL	NA	NA
3948322	NA	chr22:46154366	7.60E-05	THAL	NA	NA
3948322	NA	chr22:46145176	1.10E-04	THAL	NA	NA
3948322	NA	chr22:46149455	1.40E-04	THAL	NA	NA
3948322	NA	chr22:46151121	1.40E-04	THAL	NA	NA
3948322	NA	chr22:46166458:TG_T	1.60E-04	THAL	NA	NA
3948342	rs6006890	chr22:45238329	6.00E-06	THAL	AA=0; AT=15; TT=119	A=5.6%; T=94.4%
3948342	rs7286363	chr22:45238395	6.00E-06	THAL	TT=0; TC=15; CC=119	T=5.6%; C=94.4%

3948342	rs9614579	chr22:45238185	6.00E-06	THAL	CC=0; CA=15; AA=119	C=5.6%; A=94.4%
3948342	rs6007316	chr22:45238877	6.00E-06	THAL	AA=0; AT=15; TT=119	A=5.6%; T=94.4%
3948342	rs9614578	chr22:45238181	6.00E-06	THAL	AA=0; AT=15; TT=119	A=5.6%; T=94.4%
3948342	rs73176172	chr22:45242022	1.50E-04	THAL	GG=1; GA=32; AA=98	G=12.7%; A=87.3%
3948342	rs8139116	chr22:45258012	1.90E-04	THAL	TT=1; TC=40; CC=90	T=15.7%; C=84.3%
3948345	rs9615096	chr22:45665159	1.10E-07	THAL	AA=1; AG=14; GG=75	A=6%; G=94%
3948345	rs9615095	chr22:45661864	4.30E-06	THAL	CC=1; CA=10; AA=82	C=4.5%; A=95.5%
3948345	rs28437962	chr22:45659082	5.00E-06	THAL	GG=1; GT=10; TT=80	G=4.5%; T=95.5.%
3948345	rs226496	chr22:45671001	9.20E-06	THAL	CC=6; CT=35; TT=86	C=17.5%; T=82.5%
3948345	rs226495	chr22:45669729	9.60E-06	THAL	TT=8; TC=43; CC=83	T=22%; C=78%
3948345	rs74541407	chr22:45664258	1.10E-05	THAL	TT=8; TA=42; AA=82	T=21.6%; A=78.4%
3948345	rs2458933	chr22:45663408	1.20E-05	THAL	CC=8; CG=42; GG=81	C=21.6%; G=78.4%
3948345	rs172865	chr22:45670674	1.40E-05	THAL	TT=8; TC=41; CC=82	T=21.3%; C=78.7%
3948345	NA	chr22:45663041:CAT_C	1.50E-05	THAL	NA	NA
3948345	rs7364185	chr22:45660503	3.20E-05	THAL	CC=6; CT=38; TT=81	C=18.7%; T=81.3%
3948348	rs9614856	chr22:45030752	2.10E-04	THAL	TT=0; TC=8; CC=114	T=3%; C=97%
3948348	rs4823351	chr22:45024417	2.70E-04	THAL	TT=0; TA=7; AA=113	T=2.6%; A=97.4%
3948362	rs5765972	chr22:45170602	5.20E-05	THAL	GG=8; GA=51; AA=75	G=25%; A=75%

3948362	rs4823376	chr22:45171729	5.70E-05	THAL	GG=8; GA=51; AA=75	G=25%; A=75%
3948375	rs9614566	chr22:45143668	2.40E-04	THAL	AA=11; AT=52; TT=44	A=27.6%; T=72.4%
3948375	rs9614898	chr22:45143453	2.40E-04	THAL	AA=11; AG=52; GG=44	A=27.6%; G=72.4%
3948375	rs2299847	chr22:44473752	2.70E-04	THAL	AA=9; AG=40-; GG=61	A=21.6%; G=78.4%
3948376	rs13055282	chr22:44612099	1.60E-04	THAL	CC=0; CT=15; TT=118	C=5.6%; T=94.4%
3948376	rs35474321	chr22:44613662	1.60E-04	THAL	GG=0; GT=15; TT=118	G=5.6%; T=94.4%
3948376	rs34367101	chr22:44614443	1.70E-04	THAL	AA=0; AC=15; CC=118	A=5.6%; C=94.4%
3948376	rs138575	chr22:44951267	3.20E-04	THAL	AA=14; AC=56; CC=55	A=31.3%; C=68.7%
3948376	rs12172404	chr22:44948411	3.20E-04	THAL	GG=18; GA=57; AA=55	G=34.7%; A=65.3%
3948376	rs742200	chr22:44947361	3.30E-04	THAL	CC=19; GG=59; GG=55	C=36.2%; G=63.8%
3948261	rs7290106	chr22:45219187	1.20E-04	WHMT	AA=20; AG=57; GG=45	A=36.2%; G=63.8%
3948261	rs2071760	chr22:45221062	2.10E-04	WHMT	TT=23; TG=57; GG=45	t=38.4%; G=61.6%
3948261	rs136677	chr22:45238437	3.10E-04	WHMT	TT=25; TC=58; CC=49	T=40.3%; C=59.7%
3948261	rs136678	chr22:45240256	3.10E-04	WHMT	GG=25; GT=60; TT=49	G=41%; T=59%
3948261	rs71330751	chr22:44805506	3.50E-04	WHMT	TT=3; TC=36; CC=93	T=15.7%; C=84.3%
3948274	rs2896024	chr22:44458618	1.30E-04	WHMT	TT=23; TC=63; CC=43	T=40.7%; C=59.3%
3948281	NA	chr22:45426774:T_TG	1.50E-04	WHMT	NA	NA
3948281	NA	chr22:45426773:T_TTG	1.70E-04	WHMT	NA	NA

3948288	rs5015416	chr22:45179079	2.70E-04	WHMT	CC=2; CG=19; GG=112	C=8.6%; G=91.4%
3948288	rs6006884	chr22:45178783	3.20E-04	WHMT	CC=2; CG=19;GG=111	C=8.6%; G=91.4%
3948293	rs5765371	chr22:45838887	1.20E-04	WHMT	TT=29; TC=74; CC=31	T=49.3%; C=50.7%
3948343	rs226519	chr22:45587269	2.90E-04	WHMT	CC=3; CG=20; GG=111	C=9.7%; G=90.3%
3948343	rs226520	chr22:45587746	3.50E-04	WHMT	TT=2; TC=20; CC=111	T=9%; C=91%
3948343	rs77109785	chr22:45584396	4.00E-04	WHMT	AA=3; AG=20; GG=110	A=9.7%; G=90.3%
3948346	rs9626286	chr22:45529502	7.30E-05	WHMT	TT=25; TG=67; GG=39	T=43.7%; G=56.3%
3948346	rs12166859	chr22:45537097	8.40E-05	WHMT	AA=26; AG=67; GG=39	A=44.4%; G=55.6%
3948346	rs8139733	chr22:45537518	8.40E-05	WHMT	CC=26; CG=67; GG=39	C=44.4%; G=55.6%
3948346	rs9626288	chr22:45534688	8.50E-05	WHMT	AA=26; AG=68; GG=40	A=44.8%; G=55.2%
3948346	rs7289818	chr22:45539002	8.80E-05	WHMT	AA=27; AG=68; GG=39	A=45.5%; G=54.5%
3948346	rs9985182	chr22:45539841	9.00E-05	WHMT	TT=27; TG=68; GG=39	T=45.5%; G=54.5%
3948346	NA	chr22:45540063:AAGAC	9.50E-05	WHMT	NA	NA
3948346	rs132887	chr22:45570105	1.10E-04	WHMT	GG=20; GC=56; CC=57	G=35.8%; C=64.2%
3948348	rs4508710	chr22:45693443	1.00E-04	WHMT	AA=2; AG=10; GG=122	A=5.2%; G=94.8%
3948374	rs965027	chr22:45005361	2.40E-05	WHMT	AA=19; AG=63; GG=52	A=37.7%; G=62.3%
3948374	rs2103594	chr22:45006830	2.70E-05	WHMT	TT=29; TC=60; CC=45	T=44%; C=56%

3948374	rs4611748	chr22:45006759	2.90E-05	WHMT	TT=14; TA=49; AA=29	T=28.7%; A=71.3%
3948374	rs2142854	chr22:45009295	4.50E-05	WHMT	AA=23; AG=61; GG=50	A=39.9%; G=60.1%
3948374	NA	chr22:45009072:A_AT	4.90E-05	WHMT	NA	NA
3948374	rs6007205	chr22:45004972	6.60E-05	WHMT	AA=17; AG=62; GG=49	A=35.8%; G=64.2%
3948374	rs738361	chr22:45003878	1.30E-04	WHMT	TT=21; TC=61; CC=52	T=38.4%; C=61.6%
3948375	rs148703652	chr22:45192078	2.10E-05	WHMT	TT=0; TC=9; CC=107	T=3.4%; C=96.6%
3948375	rs17650186	chr22:46008858	3.30E-04	WHMT	TT=40; TC=56; CC=38	T=50.7%; C=49.3%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 26: Brain quantitative gene expression analyses for *TRPM2* gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
3923703	NA	chr21:44886421:CCCT_	1.80E-04	aveALL	NA	NA
3923725	rs75185599	chr21:46759899	3.60E-05	aveALL	CC=0; CT=11; TT=119	C=4.1%; T=95.9%
3923725	rs76633993	chr21:46748714	4.80E-05	aveALL	GG=1; GC=14; CC=119	G=6%; C=94%
3923725	rs2838875	chr21:46756700	5.00E-05	aveALL	TT=1; TC=14; CC=119	T=6%; C=94%
3923725	rs56116019	chr21:46753396	5.20E-05	aveALL	TT=1; TC=14; CC=119	T=6%; C=94%
3923725	NA	chr21:46752046:CAGGC	6.00E-05	aveALL	NA	NA
3923725	rs115132998	chr21:46755452	2.00E-04	aveALL	AA=1; AG=14; GG=114	A=6%; G=94%

3923733	rs235258	chr21:46259884	2.00E-04	aveALL	CC=1; CT=32; TT=99	C=12.7%; T=87.3%
3923738	rs76040172	chr21:46488959	1.30E-04	aveALL	AA=0; AG=19; GG=114	A=7.1%; T=92.9%
3923738	rs7281332	chr21:46485548	1.30E-04	aveALL	TT=3; TG=43; GG=88	T=18.3%; C=81.7%
3923738	rs79585412	chr21:46487730	1.40E-04	aveALL	CC=0; CT=19, TT=114	C=7.1%; T=92.9%
3923738	rs72613652	chr21:46484612	1.80E-04	aveALL	CC=3; CT=42; TT=87	C=17.9%; T=82.1%
3923745	rs78270802	chr21:45340041	1.60E-05	aveALL	AA=8; AC=40; CC=64	A=20.9%; C=79.1%
3923747	rs12483608	chr21:44800001	5.10E-05	aveALL	TT=0; TC=11; CC=113	T=4.1%; C=95.9%
3923750	rs76040172	chr21:46488959	2.70E-04	aveALL	AA=0; AG=19; GG=114	A=7.1%; G=92.9%
3923750	rs79585412	chr21:46487730	2.80E-04	aveALL	CC=0; CT=19, TT=114	C=7.1%; T=92.9%
3923758	rs233231	chr21:45966733	2.60E-04	aveALL	GG=6; CT=54; TT=73	G=24.6%; T=75.4%
3923758	rs233323	chr21:45964669	2.60E-04	aveALL	AA=6; AT=52; TT=74	A=23.9%; T=76.1%
3923758	rs233233	chr21:45968373	4.10E-04	aveALL	CC=6; CT=64; TT=64	C=28.4%; T=71.6%
3923758	rs233232	chr21:45968354	4.30E-04	aveALL	CC=6; CT=64; TT=64	C=28.4%; T=71.6%
t3923702	rs59394517	chr21:45770725	1.20E-07	CRBL	TT=7; TG=47; GG=38	T=22.8%; G=77.2%
t3923702	rs6518184	chr21:45770790	7.00E-07	CRBL	GG=5; GC=45; CC=71	G=20.5%; C=79.5%
t3923702	rs62220412	chr21:45759486	9.80E-07	CRBL	AA=3; AG=34; GG=97	A=14.9%; G=85.1%
t3923702	rs2838552	chr21:45764434	9.80E-07	CRBL	GG=4; GA=35; AA=95	G=16%; A=84%

t3923702	rs4818908	chr21:45763642	9.90E-07	CRBL	GG=4; GA=35; AA=95	G=16%; A=84%
t3923702	rs55926438	chr21:45764222	9.90E-07	CRBL	TT=4; TC=35; CC=95	G=16%; A=84%
t3923702	rs62218764	chr21:45791063	1.50E-06	CRBL	TT=2; TC=33; CC=90	T=13.8%; C=86.2%
t3923702	rs12627182	chr21:45794867	1.50E-06	CRBL	CC=2; CG=33; GG=91	C=13.8%; G=86.2%
t3923702	NA	chr21:45783372:CA_C	2.10E-06	CRBL	NA	NA
t3923702	rs2838556	chr21:45799164	2.60E-06	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923705	NA	chr21:45813170:C_CA	4.20E-06	CRBL	NA	NA
3923705	rs2838557	chr21:45812703	5.90E-06	CRBL	AA=3; AG=85; GG=85	A=18.3%; G=81.7%
3923705	rs1556314	chr21:45811343	6.70E-06	CRBL	GG=3; GT=45; TT=86	G=19%; T=81%
3923705	rs56195574	chr21:45806160	6.70E-06	CRBL	AA=3; AG=45; GG=86	A=19%; G=81%
3923705	rs2226686	chr21:45805392	6.70E-06	CRBL	TT=3; TC=45; CC=86	T=19%; C=81%
3923705	rs28752243	chr21:45807821	6.70E-06	CRBL	CC=3; CT=45; TT=86	C=19%; T=81%
3923705	rs62218767	chr21:45804596	6.70E-06	CRBL	TT=3; TC=45; CC=86	T=19%; C=81%
3923705	rs62218769	chr21:45807376	6.80E-06	CRBL	AA=3; AG=45; GG=86	A=19%; G=81%
3923705	rs11911332	chr21:45803612	6.80E-06	CRBL	CC=3; CA=45; TT=86	C=19%; A=81%
3923705	rs11911248	chr21:45803097	6.80E-06	CRBL	GG=3; GT=45; TT=86	C=19%; T=81%
3923708	rs12627182	chr21:45794867	2.20E-09	CRBL	CC=2; CG=33; GG=91	C=13.8%; G=86.2%
3923708	rs4818908	chr21:45763642	2.60E-09	CRBL	GG=4; GA=35; AA=95	G=16%; A=84%

3923708	rs2838552	chr21:45764434	2.60E-09	CRBL	GG=4; GA=35; AA=95	G=16%; A=84%
3923708	rs55926438	chr21:45764222	2.70E-09	CRBL	TT=4; TC=35; CC=95	T=16%; C=84%
3923708	rs62218764	chr21:45791063	2.80E-09	CRBL	TT=2; TC=33; CC=90	T=13.8%; C=86.2%
3923708	rs4818917	chr21:45799280	6.90E-09	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923708	rs2838556	chr21:45799164	7.00E-09	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923708	NA	chr21:45813170:C_CA	7.30E-09	CRBL	NA	NA
3923708	rs62220412	chr21:45759486	7.70E-09	CRBL	AA=3; AG=34; GG=97	A=14.9%; G=85.1%
3923708	rs62218767	chr21:45804596	7.90E-09	CRBL	TT=3; TC=45; CC=86	T=19%; C=81%
3923709	rs62220412	chr21:45759486	8.30E-06	CRBL	AA=3; AG=34; GG=97	A=14.9%; G=85.1%
3923709	rs4818908	chr21:45763642	1.40E-05	CRBL	GG=4; GA=35; AA=95	G=16%; A=84%
3923709	rs55926438	chr21:45764222	1.50E-05	CRBL	TT=4; TC=35; CC=95	T=16%; C=84%
3923709	rs2838552	chr21:45764434	1.50E-05	CRBL	GG=4; GA=35; AA=95	G=16%; A=84%
3923709	rs62220413	chr21:45759510	1.60E-05	CRBL	GG=3; GA=29; AA=97	G=13.1%; A=86.9%
3923709	NA	chr21:45813170:C_CA	4.00E-05	CRBL	NA	NA
3923709	rs12627182	chr21:45794867	4.80E-05	CRBL	CC=2; GG=33; GG=91	C=13.8%; G=86.2%
3923709	rs2838557	chr21:45812703	5.40E-05	CRBL	AA=3; AG=43; GG=85	A=18.3%; G=81.7%
3923709	rs9975366	chr21:45773265	5.60E-05	CRBL	GG=3; GC=40; CC=91	G=17.2%; C=82.8%
3923710	rs62218764	chr21:45791063	3.10E-05	CRBL	TT=2; TC=33; CC=90	T=13.8%; C=86.2%

3923710	rs12627182	chr21:45794867	3.50E-05	CRBL	CC=2; CG=33; GG=91	C=13.8%; G=86.2%
3923710	rs4818917	chr21:45799280	8.70E-05	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923710	rs2838556	chr21:45799164	8.70E-05	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923710	rs7278527	chr21:45793962	1.00E-04	CRBL	CC=2; CT=40; TT=86	C=16.4%; T=83.6%
3923710	rs62218765	chr21:45793331	1.00E-04	CRBL	TT=2; TC=40; AA=86	T=16.4% A=83.6%
3923710	rs45590835	chr21:45795148	1.00E-04	CRBL	TT=2; TC=40; AA=86	T=16.4% A=83.6%
3923710	rs11088949	chr21:45794731	1.00E-04	CRBL	CC=2; CG=40; GG=86	C=16.4%; G=83.6%
3923710	rs7277517	chr21:45792279	1.00E-04	CRBL	GG=2; GA=39; AA=86	G=16%; A=84%
3923710	rs45621438	chr21:45790238	1.00E-04	CRBL	TT=2; TC=39; CC=86	T=16%; C=84%
3923711	rs7277517	chr21:45792279	9.00E-07	CRBL	GG=2; GA=39; AA=86	G=16%; A=84%
3923711	rs45621438	chr21:45790238	9.30E-07	CRBL	TT=2; TC=39; CC=86	T=16%; C=84%
3923711	rs4818917	chr21:45799280	1.70E-06	CRBL	CC=2; CT=40;TT=85	C=16.4%; T=83.6%
3923711	rs2838556	chr21:45799164	1.70E-06	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923711	rs62218765	chr21:45793331	1.70E-06	CRBL	TT=2; TA=40; AA=86	T=16.4% A=83.6%
3923711	rs7278527	chr21:45793962	1.80E-06	CRBL	CC=2; CT=40; TT=86	C=16.4%; T=83.6%
3923711	rs11088949	chr21:45794731	1.80E-06	CRBL	CC=2; CG=40; GG=86	C=16.4%; G=83.6%
3923711	rs45590835	chr21:45795148	1.90E-06	CRBL	TT=2; TC=40; CC=86	T=16.4%; C=83.6%

3923711	rs11911248	chr21:45803097	4.10E-06	CRBL	CC=3; CT=45; TT=86	C=19%; T=81%
3923711	rs11908814	chr21:45784900	4.10E-06	CRBL	CC=1; CT=31; TT=91	C=12.3%; T=87.7%
3923714	rs7277517	chr21:45792279	1.20E-06	CRBL	GG=2; GA=39; AA=86	G=16%; A=84%
3923714	rs45621438	chr21:45790238	1.20E-06	CRBL	TT=2; TC=39; CC=86	T=16%; C=84%
3923714	rs62218764	chr21:45791063	1.30E-06	CRBL	TT=2; TC=39; CC=90	T=13.8%; C=86.2%
3923714	rs62218765	chr21:45793331	1.40E-06	CRBL	TT=2; TA=40; AA=86	T=16.4% A=83.6%
3923714	rs7278527	chr21:45793962	1.40E-06	CRBL	CC=2; CT=40; TT=86	C=16.4%; T=83.6%
3923714	rs11088949	chr21:45794731	1.40E-06	CRBL	CC=2; CT=40; CG=86	C=16.4%; G=83.6%
3923714	rs45590835	chr21:45795148	1.40E-06	CRBL	TT=2; TC=40; CC=86	T=16.4%; C=83.6%
3923714	rs4818917	chr21:45799280	1.50E-06	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923714	rs2838556	chr21:45799164	1.50E-06	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923714	rs12627182	chr21:45794867	1.70E-06	CRBL	CC=2; CG=33; GG=91	C=13.8%; G=86.2%
3923716	rs12627182	chr21:45794867	1.10E-05	CRBL	CC=2; CG=33; GG=91	C=13.8%; G=86.2%
3923716	rs62218764	chr21:45791063	1.10E-05	CRBL	TT=2; TC=33; CC=90	T=13.8%; C=86.2%
3923716	rs6518184	chr21:45770790	1.20E-05	CRBL	GG=5; GC=45; CC=71	G=20.5%; C=79.5%
3923716	rs2096860	chr21:45768598	1.40E-05	CRBL	TT=3; TG=38; GG=91	T=16.4%; G=83.6%
3923716	rs56306722	chr21:45770681	1.40E-05	CRBL	TT=3; TC=40; CC=91	T=17.2%; C=82.8%

3923716	rs9975366	chr21:45773265	1.50E-05	CRBL	GG=3; GC=40; CC=91	G=17.2%; C=82.8%
3923716	NA	chr21:45783372:CA_C	1.60E-05	CRBL	NA	NA
3923716	rs9982831	chr21:45788034	1.80E-05	CRBL	GG=4; GA=40; AA=89	G=17.9%; A=82.1%
3923716	rs762426	chr21:45787250	1.80E-05	CRBL	GG=4; GA=40; AA=89	G=17.9%; A=82.1%
3923716	rs4818917	chr21:45799280	1.90E-05	CRBL	CC=2; CT=40;TT=85	C=16.4%; T=83.6%
3923717	rs9982136	chr21:45767226	1.70E-07	CRBL	TT=5; TC=39; CC=90	T=18.3%; C=81.7%
3923717	rs734336	chr21:45768350	1.90E-07	CRBL	CC=6; CT=42; TT=86	C=20.1%; T=79.9%
3923717	rs62220416	chr21:45766262	1.90E-07	CRBL	TT=5; TC=39; CC=90	T=18.3%; C=81.7%
3923717	rs2838552	chr21:45764434	2.20E-07	CRBL	GG=4; GA=35; AA=95	G=16%; A=84%
3923717	rs55926438	chr21:45764222	2.30E-07	CRBL	TT=4; TC=35; CC=95	T=16%; C=84%
3923717	rs4818908	chr21:45763642	2.30E-07	CRBL	GG=4; GA=35; AA=95	G=16%; A=84%
3923717	rs9982466	chr21:45767247	3.70E-07	CRBL	GG=18; GA=66; AA=49	G=38.1%; A=61.9%
3923717	rs11701842	chr21:45765331	3.80E-07	CRBL	CC=18; CT=66; TT=49	C=38.1%; T=61.9%
3923717	rs6518184	chr21:45770790	6.60E-07	CRBL	GG=5; GC=45; CC=71	G=20.5%; C=79.5%
3923717	rs62220412	chr21:45759486	6.70E-07	CRBL	AA=3; AG=34; GG=97	A=14.9%; G=85.1%
3923718	rs62220413	chr21:45759510	1.10E-06	CRBL	GG=3; GA=29; AA=97	G=13.1%; A=86.9%
3923718	rs62220412	chr21:45759486	1.50E-06	CRBL	AA=3; AG=34; GG=97	A=14.9%; G=85.1%

3923718	rs4818908	chr21:45763642	1.70E-06	CRBL	GG=4; GA=35; AA=95	G=16%; A=84%
3923718	rs55926438	chr21:45764222	1.70E-06	CRBL	TT=4; TC=35; CC=95	T=16%; C=84%
3923718	rs2838552	chr21:45764434	1.70E-06	CRBL	GG=4; GA=35; AA=95	G=16%; A=84%
3923718	rs1556314	chr21:45811343	2.20E-06	CRBL	GG=3; GT=45; TT=86	G=19%; T=81%
3923718	rs28752243	chr21:45807821	2.30E-06	CRBL	CC=3; CT=45; TT=86	C=19%; T=81%
3923718	rs62218769	chr21:45807376	2.30E-06	CRBL	AA=3; AG=45; GG=86	A=19%; G=81%
3923718	rs56195574	chr21:45806160	2.30E-06	CRBL	AA=3; AG=45; GG=86	A=19%; G=81%
3923718	rs2226686	chr21:45805392	2.30E-06	CRBL	TT=3; TC=45; CC=86	T=19%; C=81%
3923721	rs11909011	chr21:45255650	4.40E-05	CRBL	AA=4; AG=34; GG=95	A=15.7%; G=84.3%
3923721	rs2838422	chr21:45255151	4.50E-05	CRBL	TT=4; TC=34; CC=95	T=15.7%; C=84.3%
3923721	rs6518328	chr21:45254480	4.60E-05	CRBL	CC=4; CT=34; TT=95	C=15.7%; T=84.3%
3923725	rs62220412	chr21:45759486	2.80E-04	CRBL	AA=3; AG=34; GG=97	A=14.9%; G=85.1%
3923726	rs6518184	chr21:45770790	3.10E-05	CRBL	GG=5; GC=45; CC=71	G=20.5%; C=79.5%
3923726	rs59394517	chr21:45770725	9.40E-05	CRBL	TT=7; TG=47; GG=38	T=22.8%; G=77.2%
3923726	rs9975366	chr21:45773265	1.00E-04	CRBL	GG=3; GC=40; CC=91	G=17.2%; C=82.8%
3923726	rs56306722	chr21:45770681	1.00E-04	CRBL	TT=3; TC=40; CC=91	T=17.2%; C=82.8%
3923727	rs13052278	chr21:46566043	1.70E-05	CRBL	GG=1; GT=8; TT=104	G=3.7%; T=96.3%

3923727	rs59394517	chr21:45770725	1.10E-04	CRBL	TT=7; TG=47; GG=38	T=22.8%; G=77.2%
3923727	rs1296487	chr21:46114597	2.90E-04	CRBL	GG=2; GT=12; TT=120	G=6%; C=94%
3923728	NA	chr21:45778959:G_GA	9.00E-05	CRBL	NA	NA
3923728	rs12626318	chr21:45778960	9.50E-05	CRBL	AA=3; AC=38; CC=89	A=16.4%; C=83.6%
3923728	rs12627182	chr21:45794867	1.00E-04	CRBL	CC=2; CG=33; GG=91	C=13.8%; G=86.2%
3923728	rs62218764	chr21:45791063	1.10E-04	CRBL	TT=2; TC=33; CC=90	T=13.8%; C=86.2%
3923728	rs62220412	chr21:45759486	1.30E-04	CRBL	AA=3; AG=34; GG=97	A=14.9%; G=85.1%
3923728	rs762426	chr21:45787250	1.30E-04	CRBL	GG=4; GA=40; AA=89	G=17.9%; A=82.1%
3923728	rs9982831	chr21:45788034	1.30E-04	CRBL	GG=4; GA=40; AA=89	G=17.9%; A=82.1%
3923728	NA	chr21:45783372:CA_C	1.40E-04	CRBL	NA	NA
3923728	rs2838555	chr21:45785478	1.50E-04	CRBL	CC=4; CT=39; TT=89	C=17.5%; T=82.5%
3923729	rs59394517	chr21:45770725	5.80E-05	CRBL	TT=7; TG=47; GG=38	T=22.8%; G=77.2%
3923729	rs2838556	chr21:45799164	6.60E-05	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923729	rs4818917	chr21:45799280	6.60E-05	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923729	rs62218764	chr21:45791063	7.00E-05	CRBL	TT=2; TC=33; CC=90	T=13.8%; C=86.2%
3923729	rs9982831	chr21:45788034	7.60E-05	CRBL	GG=4; GA=40; AA=89	G=17.9%; A=82.1%
3923729	rs762426	chr21:45787250	7.70E-05	CRBL	GG=4; GA=40; AA=89	G=17.9%; A=82.1%
3923729	rs45621438	chr21:45790238	7.70E-05	CRBL	TT=2; TC=39; CC=86	T=16%; C=84%

3923729	rs7277517	chr21:45792279	7.70E-05	CRBL	GG=2; GA=39; AA=86	G=16%; A=84%
3923729	rs12627182	chr21:45794867	7.90E-05	CRBL	CC=2; GG=33; GG=91	C=13.8%; G=86.2%
3923729	rs7278527	chr21:45793962	8.00E-05	CRBL	CC=2; CT=40; TT=86	C=16.4%; T=83.6%
3923733	NA	chr21:45684198:T_TA	3.60E-04	CRBL	NA	NA
3923738	rs28620173	chr21:46127194	4.60E-04	CRBL	AA=2; AG=40; GG=92	A=16.4%; C=83.6%
3923738	rs857553	chr21:44825519	5.30E-04	CRBL	CC=14; CA=53; AA=27	C=30.2%; A=69.8%
3923752	rs73228973	chr21:45607209	2.00E-04	CRBL	AA=1; AC=19; CC=89	A=7.8%; C=92.2%
3923754	rs62218764	chr21:45791063	2.90E-05	CRBL	TT=2; TC=33; CC=90	T=13.8%; C=86.2%
3923754	rs2838556	chr21:45799164	4.30E-05	CRBL	CC=2, CT=40; TT=85	C=16.4%; T=83.6%
3923754	rs4818917	chr21:45799280	4.30E-05	CRBL	CC=2; CT=40; TT=85	C=16.4%; T=83.6%
3923754	rs12627182	chr21:45794867	4.40E-05	CRBL	CC=2; GG=33; GG=91	C=13.8%; G=86.2%
3923754	rs7277517	chr21:45792279	4.60E-05	CRBL	GG=2; GA=39; AA=86	G=16%; A=84%
3923754	rs45621438	chr21:45790238	4.60E-05	CRBL	TT=2; TC=39; CC=86	T=16%; C=84%
3923754	rs62218765	chr21:45793331	6.10E-05	CRBL	TT=2; TA=40; AA=86	T=16.4%; A=83.6%
3923754	rs11088949	chr21:45794731	6.20E-05	CRBL	CC=2; GG=40; GG=86	C=16.4%; G=83.6%
3923754	rs7278527	chr21:45793962	6.20E-05	CRBL	CC=2; GG=40; GG=86	C=16.4%; T=83.6%
3923754	rs45590835	chr21:45795148	6.30E-05	CRBL	CC=2; GG=40; GG=86	T=16.4%; C=83.6%

3923756	rs13847	chr21:45402820	4.80E-05	CRBL	AA=4; AG=27; GG=101	A=13.1%; G=86.9%
3923756	rs7282631	chr21:45408911	8.80E-05	CRBL	TT=15; TC=46; CC=63	T=28.4%; C=71.6%
3923703	rs8134268	chr21:45243194	1.30E-04	FCTX	GG=0; GC=11; CC=96	G=4.1%; C=95.9%
3923703	rs73234886	chr21:46130548	2.80E-04	FCTX	AA=0; AG=30; GG=101	A=11.2%; G=88.8%
3923704	rs2282527	chr21:45081426	2.50E-04	FCTX	AA=13; AC=64; CC=52	A=33.6%; CC=66.4%
3923721	rs79268608	chr21:45128449	7.30E-05	FCTX	GG=2; GA=44; AA=87	G=17.9%; A=82.1%
3923721	rs77753871	chr21:45177719	2.60E-04	FCTX	AA=5; AG=41; GG=85	A=19%; G=81%
3923721	rs17004612	chr21:45246268	3.50E-04	FCTX	AA=5; AG=29,GG=97	A=14.6%; G=85.4%
3923722	rs73365812	chr21:44887082	6.90E-06	FCTX	AA=0; AG=8; GG=120	A=3%; G=97%
3923722	rs2838311	chr21:44891160	5.60E-05	FCTX	AA=1; AG=24; GG=101	A=9.7%; G=90.3%
3923722	rs77520217	chr21:44946378	8.10E-05	FCTX	AA=1; AG=25; GG=99	A=10.1%; GG=89.9%
3923723	rs74592050	chr21:45243217	2.00E-04	FCTX	TT=0; TC=6; CC=111	T=2.2%; C=97.8%
3923730	NA	chr21:45754400:A_AC	1.60E-04	FCTX	NA	NA
3923733	rs496799	chr21:44832525	1.80E-05	FCTX	CC=2; CT=38; TT=85	C=15.7%; T=84.3%
3923733	rs529770	chr21:44833854	1.50E-04	FCTX	TT=0; TC=38; CC=96	T=14.2%; C=85.8%
3923733	rs495827	chr21:44832427	2.80E-04	FCTX	TT=0; TG=35; GG=95	T=13.1%; G=86.9%
3923733	rs548250	chr21:44830707	3.10E-04	FCTX	GG=0; GC=35; CC=94	G=13.1%; A=86.9%

3923745	rs235259	chr21:46261211	1.80E-04	FCTX	GG=13; GA=61; AA=60	G=32.5%; A=67.5%
3923759	rs77753871	chr21:45177719	3.30E-06	FCTX	AA=5; AG=41; GG=86	A=19%; G=81%
3923759	NA	chr21:45177868:T_TA	7.70E-06	FCTX	NA	NA
3923759	rs3211245	chr21:45180206	7.90E-06	FCTX	AA=6; AC=44; CC=83	A=20.9%; C=79.1%
3923759	rs2299811	chr21:45174992	8.00E-06	FCTX	AA=6; AG=45; GG=82	A=21.3%; G=78.7%
3923759	rs3194230	chr21:45181189	8.00E-06	FCTX	GG=6; GC=45; CC=83	G=21.3%; C=78.7%
3923759	rs2006288	chr21:45172860	1.40E-05	FCTX	TT=6; TG=47; GG=81	T=22%; G=78%
3923704	rs766242	chr21:45151472	1.10E-04	HIPP	TT=4; TC=40; CC=90	T=17.9%; C=82.1%
3923704	NA	chr21:45147248:CCCTT	2.50E-04	HIPP	DD=2; DR=22; RR=102	D=9.7%; R=90.3%
3923720	NA	chr21:46803669	2.60E-05	HIPP	NA	NA
3923720	NA	chr21:46802881	2.70E-05	HIPP	NA	NA
3923720	NA	chr21:46780664	2.70E-05	HIPP	NA	NA
3923720	NA	chr21:46802819	2.80E-05	HIPP	NA	NA
3923720	NA	chr21:46802436	2.80E-05	HIPP	NA	NA
3923720	rs6518228	chr21:46772085	2.80E-05	HIPP	AA=1; AG=9; GG=97	A=14.2%; G=85.8%
3923720	NA	chr21:46798955	3.00E-05	HIPP	NA	NA
3923720	NA	chr21:46774590	3.00E-05	HIPP	NA	NA
3923720	NA	chr21:46788083	3.10E-05	HIPP	NA	NA
3923720	NA	chr21:46788995	3.10E-05	HIPP	NA	NA
3923722	rs541476	chr21:44795084	7.50E-05	HIPP	TT=9; TC=39; CC=67	T=21.3%; C=78.7%
3923722	NA	chr21:44802944:GCACC	9.90E-05	HIPP	NA	NA

3923725	rs62230080	chr21:45214365	1.70E-04	HIPP	TT=0; TC=14; CC=120	T=5.2%; C=94.8%
3923725	rs74451301	chr21:45188278	3.50E-04	HIPP	AA=1; AG=12; GG=121	A=5.2%; G=94.8%
3923738	rs149216252	chr21:45682807	1.80E-04	HIPP	TT=0; TA=22; AA=111	T=8.2%; A=91.8%
3923738	rs28681623	chr21:46105373	4.30E-04	HIPP	TT=9; TC=45; CC=77	T=23.5%; C=76.5%
3923744	rs7282380	chr21:45677248	3.10E-05	HIPP	AA=21; AG=59; GG=53	A=37.7%; G=62.3%
3923744	NA	chr21:44797174:T_TG	9.50E-05	HIPP	NA	NA
3923744	rs73223003	chr21:44797498	1.50E-04	HIPP	AA=2; AG=25; GG=103	A=10.8%; G=89.2%
3923744	rs73221000	chr21:44795804	1.50E-04	HIPP	TT=2; TC=25; CC=102	T=10.8%; C=89.2%
3923744	rs56354854	chr21:45674950	1.60E-04	HIPP	TT=19; TA=57; AA=50	T=35.4%; A=64.5%
3923752	NA	chr21:46818397	5.30E-05	HIPP	NA	NA
3923752	NA	chr21:46819149	5.30E-05	HIPP	NA	NA
3923752	NA	chr21:46818579	8.90E-05	HIPP	NA	NA
3923756	rs882549	chr21:46308441	3.10E-04	HIPP	AA=4; AC=46; CC=82	A=20.1%; C=79.9%
3923761	rs6518318	chr21:45149133	2.80E-04	HIPP	TT=22; TC=68; CC=44	T=41.8%; C=58.2%
3923738	rs9975471	chr21:46764597	2.60E-04	MEDU	TT=30; TC=66; CC=38	T=47%; C=53%
3923744	rs77659106	chr21:46123866	1.30E-04	MEDU	GG=3; GA=19; AA=111	G=9.3%; A=90.7%
3923744	rs117434156	chr21:46094452	1.40E-04	MEDU	AA=3; AG=13; GG=112	A=7.1%; T=92.9%
3923747	rs1160263	chr21:46306138	1.10E-04	MEDU	TT=3; TG=38; GG=93	T=16.4%; G=83.6%

3923747	rs113221535	chr21:46305400	1.10E-04	MEDU	CC=3; CT=38; TT=93	C=16.4%; T=83.6%
3923747	rs2248034	chr21:46292384	1.70E-04	MEDU	CC=8; CT=49; TT=77	C=24.3%; T=75.7%
3923747	rs2282115	chr21:46289951	1.80E-04	MEDU	CC=8; CG=49; GG=77	C=24.3%; T=75.7%
3923747	rs2282113	chr21:46288339	1.90E-04	MEDU	TT=8; TC=49; CC=77	T=24.3%; C=75.7%
3923747	rs62221472	chr21:46293070	1.90E-04	MEDU	CC=8, CT=49; TT=77	C=24.3%; T=75.7%
3923747	rs62221471	chr21:46286908	2.10E-04	MEDU	AA=8; AG=76, GG=76	A=24.3%; G=75.7%
3923747	rs2277810	chr21:46285722	2.20E-04	MEDU	AA=8; AG=49, GG=75	A=24.3%; G=75.7%
3923748	rs74619412	chr21:46599557	1.30E-04	MEDU	AA=0; AC=13; CC=117	A=4.9%; C=95.1%
3923748	rs79858539	chr21:46745384	3.50E-04	MEDU	AA=0; AG=8; GG=118	A=3%; G=97%
3923748	rs117376569	chr21:46747372	3.70E-04	MEDU	CC=0; CG=13; GG=119	C=4.9%; G=95.1%
3923748	rs117554468	chr21:46745221	3.80E-04	MEDU	CC=0; CT=8; TT=118	C=3%; T=97%
3923750	rs56328754	chr21:45716548	6.20E-04	MEDU	AA=1; AG=34; GG=85	A=13.4%; G=86.6%
3923755	rs1071792	chr21:46190410	2.00E-05	MEDU	AA=20; AG=61; GG=51	A=37.7%; G=62.3%
3923755	rs11088964	chr21:46244410	2.80E-05	MEDU	AA=10; AC=45; CC=69	A=24.3%; G=75.7%
3923755	rs1821431	chr21:46196728	3.40E-05	MEDU	AA=21; AG=61; GG=51	A=38.4%; G=61.6%
3923755	rs2294157	chr21:46197450	3.40E-05	MEDU	TT=21; TC=61; CC=51	T=38.4%; C=61.6%
3923755	rs8103	chr21:46189230	3.90E-05	MEDU	TT=22; TA=61; AA=51	T=39.2%; A=60.8%

3923755	rs2838678	chr21:46190842	3.90E-05	MEDU	GG=22; GA=61; AA=51	G=39.2%; A=60.8%
3923755	rs4818975	chr21:46191256	3.90E-05	MEDU	AA=22; AC=61; CC=51	A=39.2%; C=60.8%
3923755	rs1109280	chr21:46192733	3.90E-05	MEDU	TT=22; TC=61; AA=51	T=39.2%; A=60.8%
3923755	rs4239838	chr21:46202309	3.90E-05	MEDU	CC=22; CT=61; TT=51	C=39.2%; T=60.8%
3923709	rs2246417	chr21:46759503	4.80E-05	OCTX	CC=2; CT=34; TT=96	C=14.2%; T=85.8%
3923725	NA	chr21:46752046:CAGGC	1.80E-04	OCTX	NA	NA
3923727	rs2838861	chr21:46686619	2.60E-04	OCTX	TT=10; TC=61; CC=62	T=30.2%; C=69.8%
3923728	rs12483608	chr21:44800001	9.00E-05	OCTX	TT=0; TC=11; CC=113	T=4.1%; C=95.9%
3923733	rs59394517	chr21:45770725	2.80E-04	OCTX	TT=7; TG=47; GG=38	T=22.8%; G=77.2%
3923748	rs9978714	chr21:46395443	6.20E-05	OCTX	TT=0; TC=13; CC=113	T=4.9%; C=95.1%
3923749	rs74961332	chr21:46702822	6.70E-05	OCTX	GG=4; GA=27; AA=99	G=13.1%; A=86.9%
3923749	rs114822048	chr21:46702999	2.10E-04	OCTX	AA=2; AG=15; GG=117	A=7.1%; G=92.9%
3923749	rs56724325	chr21:46709555	2.70E-04	OCTX	CC=3; CA=23; AA=108	C=10.8%; A=89.2%
3923749	rs9306176	chr21:45663949	4.10E-04	OCTX	GG=2; GT=25; TT=107	G=10.8%; T=89.2%
3923750	rs76040172	chr21:46488959	4.70E-04	OCTX	AA=0; AG=19; GG=114	A=7.1%; G=92.9%
3923750	rs79585412	chr21:46487730	5.20E-04	OCTX	CC=0; CT=19, TT=114	C=7.1%; T=92.9%
3923758	NA	chr21:45051947:T_TCC	3.50E-04	OCTX	NA	NA
3923760	rs75185599	chr21:46759899	2.90E-04	OCTX	CC=0; CT=11; TT=119	C=4.1%; T=95.9%

3923703	rs76328697	chr21:45727098	2.30E-05	PUTM	AA=1; AG=8; GG=109	A=3.7%; G=96.3%
3923704	rs672226	chr21:44799734	1.20E-04	PUTM	TT=20: TC=55; CC=57	T=35.4%; C=64.5%
3923704	rs1034360	chr21:44798239	1.50E-04	PUTM	TT=20: AC=55; CC=57	T=35.4%; A=64.5%
3923704	rs34217534	chr21:44797907	1.50E-04	PUTM	CC=20; CA=55; AA=57	C=35.4%; A=64.5%
3923704	rs598771	chr21:44797204	1.80E-04	PUTM	AA=20; AG=54; GG=57	A=35.1%; G=64.9%
3923704	rs570905	chr21:44796008	2.50E-04	PUTM	TT=20; TC=55; CC=55	T=35.4%; C=64.6%
3923704	rs7281209	chr21:44813517	4.10E-04	PUTM	TT=8; TC=50; CC=74	T=24.6%; C=75.4%
3923722	NA	chr21:46799913	7.40E-05	PUTM	NA	NA
3923722	NA	chr21:46801313	1.10E-04	PUTM	NA	NA
3923722	NA	chr21:46785182	1.20E-04	PUTM	NA	NA
3923733	NA	chr21:46822508	8.10E-05	PUTM		
3923733	NA	chr21:46820082	2.70E-04	PUTM	NA	NA
3923733	NA	chr21:46820991	4.50E-04	PUTM	NA	NA
3923745	rs11701387	chr21:46417498	1.90E-04	PUTM	TT=10; TC=60; CC=11	T=29.9%; C=70.1%
3923748	rs41277544	chr21:45708197	3.50E-04	PUTM	AA=0; AC=12; CC=119	A=4.5%; G=95.5%
3923749	rs2155725	chr21:45689239	1.40E-04	PUTM	TT=25; TC=65; CC=44	T=42.9%; C=57.1%
3923755	rs76328697	chr21:45727098	3.70E-05	PUTM	AA=1; AG=8; GG=109	A=3.7%; G=96.3%
3923756	rs76328697	chr21:45727098	2.90E-04	PUTM	AA=1; AG=8; GG=109	A=3.7%; G=96.3%
3923761	NA	chr21:46822508	1.10E-04	PUTM	NA	NA
3923761	NA	chr21:46825723	1.30E-04	PUTM	NA	NA

3923761	NA	chr21:46832345	1.80E-04	PUTM	NA	NA
3923761	NA	chr21:46831693	2.00E-04	PUTM	NA	NA
3923761	NA	chr21:46832150:TTC_T	2.90E-04	PUTM	NA	NA
3923761	NA	chr21:46832148:ATTTC	2.90E-04	PUTM	NA	NA
3923761	NA	chr21:46832149:TTTC_	2.90E-04	PUTM	NA	NA
3923761	NA	chr21:46831922	3.30E-04	PUTM	NA	NA
3923703	NA	chr21:45993851	6.70E-05	SNIG	NA	NA
3923703	rs77242501	chr21:45353708	1.40E-04	SNIG	TT=0; TC=24; CC=100	T=9%; C=91%
3923703	rs458178	chr21:45991288	3.00E-04	SNIG	CC=3; GG=45; GG=86	C=19%; G=81%
3923703	rs465883	chr21:45991389	3.00E-04	SNIG	CC=3; GG=45; GG=86	C=19%; G=81%
3923703	rs458762	chr21:45992260	3.50E-04	SNIG	AA=3; AG=44; GG=87	A=18.7; G=81.3%
3923703	rs382478	chr21:45992140	3.60E-04	SNIG	AA=3; AG=44; GG=87	A=18.7; G=81.3%
3923704	rs186043129	chr21:46398720	3.90E-04	SNIG	CC=3; CG=38; GG=84	C=16.4%; C=83.6%
3923721	rs914204	chr21:46402548	3.80E-05	SNIG	CC=14; GG=66; GG=43	C=35.1%; G=64.9%
3923721	NA	chr21:46416165:CA_C	2.50E-04	SNIG	NA	NA
3923727	NA	chr21:46145360:AT_A	5.10E-05	SNIG	NA	NA
3923727	rs584779	chr21:46173340	3.50E-04	SNIG	AA=1; AG=16;GG=117	A=6.7%; G=93.3%
3923727	rs7282884	chr21:45686610	3.70E-04	SNIG	CC=36; CT=67; TT=31	C=51.9%; T=48.1%
3923727	rs8131710	chr21:45686859	3.70E-04	SNIG	TT=36; TC=67; CC=31	T=51.9%; C=48.1%
3923727	rs2838538	chr21:45687271	3.70E-04	SNIG	CC=36; CT=67; TT=31	C=51.9% T=48.1%

3923730	rs2742064	chr21:46170648	7.30E-05	SNIG	AA=0; AT=19; TT=67	A=7.1%; T=92.9%
3923730	rs584779	chr21:46173340	1.50E-04	SNIG	AA=1; AG=16;GG=117	A=6.7%; G=93.3%
3923730	rs690279	chr21:46173229	1.60E-04	SNIG	CC=1; CG=16; GG=117	C=6.7%; G=93.3%
3923730	rs690621	chr21:46171844	1.60E-04	SNIG	AA=1; AG=16; GG=117	A=6.7%; G=93.3%
3923730	rs437719	chr21:46169644	1.60E-04	SNIG	AA=1; AG=16; GG=117	A=6.7%; G=93.3%
3923730	rs2570976	chr21:46169387	1.60E-04	SNIG	TT=1; TA=16; AA=117	T=6.7%; A=93.3%
3923730	rs235347	chr21:46166663	1.60E-04	SNIG	GG=1; GA=16; AA=117	G=6.7%; A=93.3%
3923730	rs235349	chr21:46167718	1.60E-04	SNIG	AA=1; AG=16; GG=117	A=6.7%; G=93.3%
3923730	rs235345	chr21:46165122	1.60E-04	SNIG	AA=1; AC=16; GG=117	A=6.7%; G=93.3%
3923738	rs1051385	chr21:46646264	6.20E-04	SNIG	CC=3; CT=16; TT=115	C=8.2%; T=91.8%
3923748	rs150735593	chr21:46494920	7.30E-06	SNIG	CC=0, CT=12; TT=119	C=4.5%; T=95.5%
3923749	rs143667910	chr21:45533173	2.10E-04	SNIG	TT=1;. TC=22; CC=101	T=9%; C=91%
3923750	NA	chr21:46844350	5.70E-04	SNIG	NA	NA
3923750	NA	chr21:46847417	5.80E-04	SNIG	NA	NA
3923750	NA	chr21:46841925	6.10E-04	SNIG	NA	NA
3923752	rs9981225	chr21:45684199	1.40E-04	SNIG	AA=2; AT=42; TT=90	A=17.2%; T=82.8%
3923752	rs142072280	chr21:45696383	1.80E-04	SNIG	AA=3; AG=38; GG=91	A=16.4%; C=83.6%
3923752	rs5030670	chr21:46320403	2.50E-04	SNIG	TT=0; TC=16; CC=76	T=6%; C=94%

3923758	rs13051842	chr21:46117962	3.30E-04	SNIG	AA=10; AG=49; GG=72	A=25.7%; G=74.3%
3923758	rs2838642	chr21:46118157	3.50E-04	SNIG	CC=10; CG=49; GG=73	C=25.7%; G=74.3%
3923758	rs2838643	chr21:46118197	3.60E-04	SNIG	CC=10; CG=49; GG=74	C=25.7%; T=74.3%
3923759	rs9980281	chr21:46391635	5.40E-05	SNIG	TT=1; TC=51; CC=82	T=19.8%; C=80.2%
3923759	rs394531	chr21:46388665	1.20E-04	SNIG	GG=1; GA=50; AA=83	G=19.4%; A=80.6%
3923759	rs9978038	chr21:46366547	1.20E-04	SNIG	CC=1; CT=49; TT=83	C=19%, T=81%
3923759	rs17313439	chr21:46375354	1.20E-04	SNIG	GG=1; GA=50; AA=83	G=19.4%; A=80.6%
3923760	rs11539534	chr21:45168884	1.00E-04	SNIG	AA=2; AG=19; GG=107	A=8.6%; G=91.4%
3923760	rs62229219	chr21:45188783	1.70E-04	SNIG	AA=4; AG=27; GG=97	A=13.1%; G=86.9%
3923760	rs143483161	chr21:45165225	1.80E-04	SNIG	TT=2; TC=17; CC=110	T=7.8%; C=92.2%
3923760	rs74373568	chr21:45163867	1.80E-04	SNIG	TT=2; TC=17; CC=110	T=7.8%; C=92.2%
3923760	rs17004606	chr21:45176621	1.80E-04	SNIG	TT=4; TC=34; CC=96	T=15.7%; C=84.3%
3923760	rs73908381	chr21:45172007	1.90E-04	SNIG	CC=5; CT=44; TT=71	C=20.1%; T=79.9%
3923760	rs78198901	chr21:45186843	2.50E-04	SNIG	AA=4; AC=31; CC=98	A=14.6%; G=85.4%
3923760	rs2006288	chr21:45172860	2.70E-04	SNIG	TT=6; TG=47; GG=81	TT=22%; G=78%
3923723	NA	chr21:46775705	3.20E-04	TCTX	NA	NA
3923723	NA	chr21:46774574:TA_T	3.50E-04	TCTX	NA	NA
3923723	NA	chr21:46775677	3.90E-04	TCTX	NA	NA

3923723	NA	chr21:46775249	4.00E-04	TCTX	NA	NA
3923723	NA	chr21:46774822	4.00E-04	TCTX	NA	NA
3923723	rs3211245	chr21:45180206	5.00E-04	TCTX	AA=6; AC=44; CC=83	A=20.9%; C=79.1%
3923723	rs3194230	chr21:45181189	5.10E-04	TCTX	GG=6; GC=45; CC=45	G=21.3%; C=78.7%
3923723	NA	chr21:45177868:T_TA	5.40E-04	TCTX	NA	NA
3923726	rs432807	chr21:45974528	7.50E-05	TCTX	TT=5; TC=39; CC=81	T=18.3%; C=81.7%
3923726	NA	chr21:45974526:G_GT	7.90E-05	TCTX	NA	NA
3923726	NA	chr21:45974527:T_TTG	7.90E-05	TCTX	NA	NA
3923726	rs233249	chr21:45975187	8.10E-05	TCTX	AA=8; AG=44; GG=82	A=22.4%; G=77.6%
3923726	rs439043	chr21:45974529	8.70E-05	TCTX	GG=7; GA=40; AA=81	G=20.1%; A=79.9%
3923726	rs170846	chr21:45975519	9.80E-05	TCTX	GG=8; GA=43; AA=82	G=22%; A=78%
3923744	NA	chr21:46831693	1.10E-04	TCTX	NA	NA
3923744	rs9981625	chr21:44775278	1.60E-04	TCTX	CC=23; CG=60; GG=41	C=39.6%; G=60.4%
3923744	NA	chr21:46830449	1.80E-04	TCTX	NA	NA
3923745	rs9647232	chr21:45393449	2.00E-04	TCTX	AA=23; AG=48; GG=58	A=35.1%; G=64.9%
3923745	rs3788096	chr21:45393080	2.00E-04	TCTX	CC=26; CG=53; GG=53	C=39.2%; G=60.8%
3923745	rs7281359	chr21:45393542	2.00E-04	TCTX	AA=25; AG=53; GG=53	A=38.4%; G=61.6%
3923745	rs2838301	chr21:44838081	2.10E-04	TCTX	GG=0; GA=25; AA=108	G=9.3%; A=90.7%
3923745	rs762389	chr21:44837889	2.20E-04	TCTX	TT=0; TC=26; CC=108	T=9.7%; C=90.3%

3923745	rs2838300	chr21:44837359	2.30E-04	TCTX	AA=0; AG=26; GG=108	A=9.7%; G=90.3%
3923745	rs73380290	chr21:44835347	2.30E-04	TCTX	AA=0; AG=26; GG=108	A=9.7%; G=90.3%
3923748	rs73366550	chr21:45675904	1.70E-04	TCTX	GG=2; GT=31; TT=101	G=13.1%; A=86.9%
3923748	NA	chr21:45676496:C_CAG	1.80E-04	TCTX	NA	NA
3923748	rs2838534	chr21:45673649	2.20E-04	TCTX	CC=1; CT=24; TT=109	C=9.7%; T=90.3%
3923749	rs233285	chr21:45993819	4.50E-04	TCTX	CC=5; CT=37; TT=53	C=17.5%; T=82.5%
3923749	rs932281	chr21:46132885	4.70E-04	TCTX	TT=13; TG=53; GG=68	T=29.5%; G=70.5%
3923749	rs55854308	chr21:46142328	4.80E-04	TCTX	TT=11; TC=53; CC=68	T=28%; C=72%
3923749	rs12627028	chr21:45995154	5.70E-04	TCTX	TT=4; TC=40; CC=66	T=17.9%; C=82.1%
3923750	rs3916995	chr21:45128454	5.30E-04	TCTX	GG=23; GA=64; AA=47	G=41%; C=59%
3923752	rs2070572	chr21:45757905	7.80E-05	TCTX	TT=21; TC=57; CC=56	T=36.9%; C=63.1%
3923756	rs10854468	chr21:46407851	2.60E-04	TCTX	CC=19; CT=72; TT=43	C=41%; T=59%
3923756	rs11701193	chr21:46409441	2.60E-04	TCTX	GG=19; GA=72; AA=43	G=41%; A=59%
3923756	rs11088977	chr21:46410547	2.60E-04	TCTX	CC=19; CT=72; TT=43	C=41%; T=59%
3923756	rs9974719	chr21:46407392	2.80E-04	TCTX	TT=19; TC=71; CC=38	T=40.7%; C=59.3%
3923756	rs11088975	chr21:46407438	2.80E-04	TCTX	AA=19; AG=71; GG=38	A=40.7%; G=59.3%
3923756	rs9974964	chr21:46407009	2.90E-04	TCTX	CC=14; CT=73; TT=47	C=37.7%; T=62.3%

3923722	rs55927826	chr21:46276686	1.00E-04	THAL	GG=8; GA=45; AA=81	G=22.8%; A=77.2%
3923722	rs1344110	chr21:46272652	1.10E-04	THAL	CC=8; CT=44; TT=81	C=22.4%; T=77.6%
3923727	rs4819065	chr21:46762390	6.80E-05	THAL	AA=0; AG=14; GG=81	A=5.2%; G=94.8%
3923747	rs8133485	chr21:45180338	2.20E-04	THAL	AA=11; AG=63, GG=56	A=31.7%; G=68.3%
3923758	rs58697476	chr21:46482037	4.90E-04	THAL	TT=3; TC=29; CC=97	T=13.1%; C=86.9%
3923758	rs2838761	chr21:46481557	4.90E-04	THAL	GG=3; GA=29; AA=97	G=13.1%; A=86.9%
3923760	rs75384114	chr21:46261546	2.00E-04	THAL	CC=0; CT=8; TT=117	C=3%; T=97%
3923721	rs55831723	chr21:46294688	3.50E-04	WHMT	TT=1; TC=19; CC=114	T=7.8%; C=92.2%
3923721	NA	chr21:46294444:C_CA	3.50E-04	WHMT	NA	NA
3923723	rs66506615	chr21:46280140	6.80E-04	WHMT	TT=1; TC=17; CC=144	T=7.1%; C=92.9%
3923750	rs11701589	chr21:46404727	4.40E-04	WHMT	TT=0; TC=28; CC=104	T=10.4%; C=89.6%
3923752	rs179327	chr21:44846614	2.50E-04	WHMT	AA=10; AC=42; CC=75	A=23.1% C=76.9%
3923752	rs229347	chr21:44848070	2.50E-04	WHMT	GG=28; GA=65; AA=40	G=45.1%; A=54.9%
3923761	NA	chr21:46808884	2.60E-04	WHMT	NA	NA

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 27: Brain quantitative gene expression analyses for *CNTNAP1* gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency

3721996	rs115426537	chr17:39947520	4.40E-04	aveALL	TT=0; TC=19; CC=97	T=7.1%; C=92.9%
3722016	rs56162439	chr17:40249387	1.10E-03	aveALL	TT=0; TC=16; CC=110	T=6%; C=94%
3721992	NA	chr17:40878513:G_GAT	1.30E-04	CRBL	NA	NA
3721996	rs112666191	chr17:41377741	6.90E-04	CRBL	AA=8; AT=38; TT=70	A=20.1%; T=79.9%
3721996	rs4792972	chr17:41200537	8.60E-04	CRBL	CC=6; CT=43; TT=66	C=20.5%; T=79.5%
3722027	rs1973522	chr17:40838829	7.10E-04	CRBL	CC=0; CT=14; TT=120	C=5.2%; T=94.8%
3722030	rs76189032	chr17:40756882	2.60E-04	CRBL	TT=1; TC=21; CC=112	T=8.6%; C=91.4%
3722030	rs7209442	chr17:41540498	5.10E-04	CRBL	CC=7; CT=45; TT=76	C=22%; T=787%
3722030	rs184482331	chr17:40702760	7.30E-04	CRBL	TT=1; TC=320; CC=112	T=8.2%; C=91.8%
3721991	rs28736830	chr17:41680520	4.60E-04	FCTX	TT=20; TC=67; CC=40	T=39.9%; C=60.1%
3721991	rs7225125	chr17:41663900	4.90E-04	FCTX	AA=24; AG=66; GG=44	A=42.5%; G=57.5%
3721991	rs7217464	chr17:41663949	4.90E-04	FCTX	CC=24; CG=66; GG=44	C=42.5%; G=57.5%
3721991	rs939358	chr17:41666423	4.90E-04	FCTX	TT=24; TC=66; CC=44	T=42.5%; C=57.5%
3721991	rs11649769	chr17:41670704	5.00E-04	FCTX	TT=24; TC=66; CC=44	T=42.5%; C=57.5%
3721991	rs8077361	chr17:41679876	5.40E-04	FCTX	TT=22; TG=67; GG=44	T=41.4%; G=58.6%
3721991	rs11656735	chr17:41667085	6.40E-04	FCTX	GG=25; GT=63; TT=41	G=42.2%; T=57.8%
3721991	rs11655135	chr17:41667527	6.50E-04	FCTX	GG=25; GT=63; TT=41	G=42.2%; T=57.8%

3721991	rs11649707	chr17:41668581	6.50E-04	FCTX	GG=26; GC=67; CC=41	G=44.4%; C=55.6%
3721994	rs115426537	chr17:39947520	1.10E-04	FCTX	TT=0; TC=19; CC=97	T=7.1%; C=92.9%
3721996	rs62078395	chr17:40789841	6.30E-04	FCTX	AA=13; AG=52; GG=69	A=29.1%; G=70.9%
3721996	rs6503715	chr17:40788744	6.80E-04	FCTX	TT=13; TC=52; CC=69	T=29.1%; C=70.9%
3721996	rs62078394	chr17:40772967	7.20E-04	FCTX	AA=13; AC=52; CC=69	A=29.1%; C=70.9%
3721996	rs11653864	chr17:40782320	7.40E-04	FCTX	TT=13; TG=52; GG=69	T=29.1%; C=70.9%
3721997	rs117922651	chr17:39984746	1.90E-04	FCTX	AA=0; AG=29; GG=104	A=10.8%; G=89.2%
3721997	rs72835680	chr17:39969549	3.10E-04	FCTX	TT=0; TC=23; CC=104	T=8.6%; C=91.4%
3721997	rs115426537	chr17:39947520	3.70E-04	FCTX	TT=0; TC=19; CC=97	T=7.1%; C=92.9%
3721997	rs72837403	chr17:40018970	4.40E-04	FCTX	AA=0; AG=4; GG=114	A=1.5%; G=98.5%
3721997	rs112381903	chr17:41388250	5.60E-04	FCTX	TT=0; TA=13; AA=107	T=4.9%; A=95.15
3721999	rs115426537	chr17:39947520	1.20E-04	FCTX	TT=0; TC=19; CC=97	T=7.1%; C=92.9%
3721999	rs72837403	chr17:40018970	1.50E-04	FCTX	AA=0; AG=4; GG=114	A=1.5%; G=98.5%
3722007	rs115426537	chr17:39947520	2.80E-04	FCTX	TT=0; TC=19; CC=97	T=7.1%; C=92.9%
3722013	rs115426537	chr17:39947520	6.20E-05	FCTX	TT=0; TC=19; CC=97	T=7.1%; C=92.9%
3722013	rs72837403	chr17:40018970	2.00E-04	FCTX	AA=0; AG=4; GG=114	A=1.5%; G=98.5%
3722013	rs117922651	chr17:39984746	6.20E-04	FCTX	AA=0; AG=29; GG=104	A=10.8%; G=89.2%

3722014	rs112381903	chr17:41388250	4.70E-04	FCTX	TT=0; TA=13; AA=107	T=4.9%; A=95.15
3722016	rs115426537	chr17:39947520	5.30E-04	FCTX	TT=0; TC=19; CC=97	T=7.1%; C=92.9%
3722024	NA	chr17:41837660	1.80E-04	HIPP	NA	NA
3721991	rs72833177	chr17:41730185	1.70E-04	MEDU	CC=0; CT=15; TT=115	C=5.6%; T=94.4%
3721996	rs137909705	chr17:40305336	7.20E-04	MEDU	AA=0; AG=8; GG=114	A=3%; G=97%
3721996	rs55687905	chr17:40279061	1.00E-03	MEDU	CC=0; CA=7; AA=111	C=2.6%; A=97.4%
3721996	rs140569875	chr17:40276206	1.00E-03	MEDU	AA=0; AG=7; GG=111	A=2.6%; G=97.45
3721997	rs7213095	chr17:39940768	4.50E-04	MEDU	TT=28; TG=64; GG=30	T=44.8%; G=55.2%
t3721989	rs4372739	chr17:39995453	3.30E-04	OCTX	AA=10; AG=49; GG=72	A=25.7%; G=74.3%
t3721989	rs4514730	chr17:39996172	3.40E-04	OCTX	CC=10; CT=49; TT=72	C=25.7%; T=74.3%
t3721989	rs80064277	chr17:39996226	3.40E-04	OCTX	AA=10; AT=49; TT=72	A=25.7%; T=74.3%
t3721989	rs8069261	chr17:39996734	3.40E-04	OCTX	GG=10; GA=49; AA=72	G=25.7%; A=74.3%
t3721989	rs4513146	chr17:39995305	3.50E-04	OCTX	GG=10; GC=50; CC=74	G=26.1%; C=73.9%
t3721989	rs4796715	chr17:39993771	3.60E-04	OCTX	GG=10; GA=50; AA=74	G=26.1%; A=73.9%
t3721989	NA	chr17:40024868:AG_A	3.60E-04	OCTX	NA	NA
3721990	rs4796715	chr17:39993771	3.70E-04	OCTX	GG=10; GA=50; AA=74	G=26.1%; A=73.9%
3721990	rs4796714	chr17:39993748	3.70E-04	OCTX	TT=10; TC=50; CC=74	T=26.1%; C=73.9%

3721990	rs4513146	chr17:39995305	3.80E-04	OCTX	GG=10; GC=50; CC=74	G=26.1%; C=73.9%
3721990	rs57672173	chr17:39993485	3.80E-04	OCTX	CC=10; CT=50; TT=74	C=26.1%; T=73.9%
3721990	rs9899956	chr17:40032384	4.30E-04	OCTX	CC=9; CT=44; TT=72	C=23.1%; T=76.9%
3721990	rs7208199	chr17:40013497	4.50E-04	OCTX	GG=11; GA=49; AA=70	G=26.5%; A=73.5%
3721990	rs4372739	chr17:39995453	4.70E-04	OCTX	AA=10; AG=49; GG=72	A=25.7%; G=74.3%
3721990	rs9898328	chr17:40032356	5.00E-04	OCTX	GG=8; GA=43; AA=76	G=22%; A=78%
3721990	rs11871200	chr17:40012224	5.10E-04	OCTX	GG=11; GA=49; AA=71	G=26.5%; A=73.5%
3721994	rs4513146	chr17:39995305	2.40E-04	OCTX	GG=10; GC=50; CC=74	G=26.1%; C=73.9%
3721994	rs4372739	chr17:39995453	2.40E-04	OCTX	AA=10; AG=49; GG=72	A=25.7%; G=74.3%
3721994	rs4796715	chr17:39993771	2.40E-04	OCTX	GG=10; GA=50; AA=74	G=26.1%; A=73.9%
3721997	rs4513146	chr17:39995305	6.20E-04	OCTX	GG=10; GC=50; CC=74	G=26.1%; C=73.9%
3721997	rs4796715	chr17:39993771	6.20E-04	OCTX	GG=10; GA=50; AA=74	G=26.1%; A=73.9%
3721997	rs4796714	chr17:39993748	6.30E-04	OCTX	TT=10; TC=50; CC=74	T=26.1%; C=73.9%
3721998	rs60588087	chr17:39982432	1.90E-04	OCTX	AA=10; AC=54; CC=67	A=27.6%; C=72.4%
3721999	rs4372739	chr17:39995453	2.90E-04	OCTX	AA=10; AG=49; GG=72	A=25.7%; G=74.3%
3721999	rs80064277	chr17:39996226	2.90E-04	OCTX	AA=10; AT=49; TT=72	A=25.7%; T=74.3%
3721999	rs8069261	chr17:39996734	2.90E-04	OCTX	GG=10; AG=49; AA=72	G=25.7%; A=74.3%

3721999	rs4514730	chr17:39996172	2.90E-04	OCTX	CC=10; CT=49; TT=72	C=25.7%; T=74.3%
3721999	rs4513146	chr17:39995305	3.00E-04	OCTX	GG=10; GC=50; CC=74	G=26.1%; C=73.9%
3722004	rs60588087	chr17:39982432	1.30E-04	OCTX	AA=10; AC=54; CC=67	A=27.6%; C=72.4%
3722004	NA	chr17:39979267:GCTC_	1.50E-04	OCTX	NA	NA
3722004	rs4796715	chr17:39993771	1.60E-04	OCTX	GG=10; GA=50; AA=74	G=26.1%; A=73.9%
3722004	rs4796714	chr17:39993748	1.60E-04	OCTX	TT=10; AC=50; CC=74	T=26.1%; C=73.9%
3722004	rs4513146	chr17:39995305	1.60E-04	OCTX	GG=10; GC=50; CC=74	G=26.1%; C=73.9%
3722004	rs57672173	chr17:39993485	1.60E-04	OCTX	CC=10; CT=50; TT=74	C=26.1%; T=73.9%
3722004	rs4372739	chr17:39995453	1.80E-04	OCTX	AA=10; AG=49; GG=72	A=25.7%; G=74.3%
3722004	rs1836878	chr17:39986654	1.90E-04	OCTX	GG=10; GA=56; AA=68	G=28.4%; A=71.6%
3722004	rs9897034	chr17:39992584	1.90E-04	OCTX	CC=10; CT=56; TT=68	C=28.4%; T=71.6%
3722005	rs57825218	chr17:40159925	2.70E-04	OCTX	AA=0; AG=31; GG=103	A=11.6%; G=88.4%
3722005	rs4513146	chr17:39995305	3.10E-04	OCTX	GG=10; GC=50; CC=74	G=26.15; C=73.9%
3722005	rs4796715	chr17:39993771	3.10E-04	OCTX	GG=10; GA=50; AA=74	G=26.1%; A=73.9%
3722005	rs4796714	chr17:39993748	3.10E-04	OCTX	TT=10; TC=50; CC=74	T=26.1%; C=73.9%
3722005	rs57672173	chr17:39993485	3.20E-04	OCTX	CC=10; CT=50; TT=74	C=26.1%; T=73.9%
3722005	rs4372739	chr17:39995453	3.20E-04	OCTX	AA=10; AG=49; GG=72	A=25.7%; G=74.3%

3722005	rs60588087	chr17:39982432	3.30E-04	OCTX	AA=10; AC=54; CC=67	A=27.6%; C=72.4%
3722007	rs57825218	chr17:40159925	4.00E-04	OCTX	AA=0; AG=31; GG=103	A=11.6%; G=88.4%
3722007	rs4513146	chr17:39995305	4.40E-04	OCTX	GG=10; GC=50; CC=74	G=26.1%; C=73.9%
3722007	rs4372739	chr17:39995453	4.50E-04	OCTX	AA=10; AG=49; GG=72	A=25.7%; G=74.3%
3722007	rs4796715	chr17:39993771	4.50E-04	OCTX	GG=10; GA=50; AA=74	G=26.1%; A=73.9%
3722007	rs4796714	chr17:39993748	4.60E-04	OCTX	TT=10; TC=50; CC=74	T=26.1%; C=73.9%
3722007	rs4514730	chr17:39996172	4.60E-04	OCTX	CC=10; CT=49; TT=72	C=25.7%; T=74.3%
3722008	NA	chr17:41848317	4.10E-05	OCTX	NA	NA
3722008	NA	chr17:41846964	4.10E-05	OCTX	NA	NA
3722013	rs8066921	chr17:40131708	4.00E-04	OCTX	CC=1; CT=32; TT=86	C=12.7%; T=97.3%
3722013	rs4796751	chr17:40127537	5.00E-04	OCTX	TT=1; TC=30; CC=103	T=11.9%; C=88.1%
3722013	rs6503679	chr17:40146970	5.10E-04	OCTX	GG=1; GA=31; AA=102	G=12.3%; A=87.7%
3722013	rs8067085	chr17:40131805	5.70E-04	OCTX	CC=1; CG=30; GG=103	C=11.9%; G=88.1%
3722013	rs60588087	chr17:39982432	7.20E-04	OCTX	AA=10; AC=54; CC=67	A=27.6%; C=72.4%
3722013	rs56162439	chr17:40249387	7.30E-04	OCTX	TT=0; TC=16; CC=110	T=6%; C=94%
3722014	rs8066921	chr17:40131708	4.90E-04	OCTX	CC=1; CT=32; TT=86	C=12.7%; T=97.3%
3722014	rs56162439	chr17:40249387	5.00E-04	OCTX	TT=0; TC=16; CC=110	T=6%; C=94%

3722015	rs9905601	chr17:40015211	5.10E-04	OCTX	AA=0; AG=31; GG=103	A=11.6%; G=88.4%
3722015	rs57825218	chr17:40159925	5.10E-04	OCTX	AA=0; AG=31; GG=103	A=11.6%; G=88.4%
3722015	NA	chr17:40024868:AG_A	6.30E-04	OCTX	NA	NA
3722015	rs6503679	chr17:40146970	6.70E-04	OCTX	GG=1; GA=31; AA=102	G=12.3%; A=87.7%
3722015	rs4796751	chr17:40127537	7.00E-04	OCTX	TT=1; TC=30; CC=103	T=11.9%; C=88.1%
3722015	NA	chr17:40024867:AAG_A	7.40E-04	OCTX	NA	NA
3722016	rs56162439	chr17:40249387	5.40E-04	OCTX	TT=0; TC=16; CC=110	T=6%; C=94%
3722017	NA	chr17:41848317	8.50E-05	OCTX	NA	NA
3722017	NA	chr17:41846964	8.50E-05	OCTX	NA	NA
3722017	NA	chr17:41835215	5.30E-04	OCTX	NA	NA
3722019	rs9903458	chr17:40197021	1.80E-04	OCTX	TT=2; TC=30; CC=99	T=12.7%; C=87.3%
3722019	rs9905601	chr17:40015211	2.60E-04	OCTX	AA=0; AG=31; GG=103	A=11.6%; G=88.4%
3722019	rs57825218	chr17:40159925	3.20E-04	OCTX	AA=0; AG=31; GG=103	A=11.6%; G=88.4%
3722019	NA	chr17:40209517:C_CGT	3.90E-04	OCTX	NA	NA
3722019	rs8066921	chr17:40131708	4.10E-04	OCTX	CC=1; CT=32; TT=86	C=12.7%; T=87.3%
3722019	rs6503679	chr17:40146970	4.10E-04	OCTX	GG=1; GA=31; AA=102	G=12.3%; A=87.7%
3722019	rs4796751	chr17:40127537	4.60E-04	OCTX	TT=1; TC=30; CC=103	T=11.9%; C=88.1%

3722019	rs2240011	chr17:40193709	5.00E-04	OCTX	CC=2; CT=32; TT=100	C=13.4%; T=86.6%
3722020	NA	chr17:41835215	5.50E-04	OCTX	NA	NA
3722020	rs9905601	chr17:40015211	7.30E-04	OCTX	AA=0; AG=31; GG=103	A=11.6%; G=88.4%
3722027	NA	chr17:41848317	2.40E-05	OCTX	NA	NA
3722027	NA	chr17:41846964	2.40E-05	OCTX	NA	NA
3722027	NA	chr17:41839323	3.50E-04	OCTX	NA	NA
3722027	NA	chr17:41840056	3.50E-04	OCTX	NA	NA
3722027	NA	chr17:41842937	3.50E-04	OCTX	NA	NA
3722027	NA	chr17:41845235	3.50E-04	OCTX	NA	NA
3722027	NA	chr17:41845527	3.50E-04	OCTX	NA	NA
3722027	NA	chr17:41846508	3.50E-04	OCTX	NA	NA
3722027	NA	chr17:41835215	3.80E-04	OCTX	NA	NA
3722029	NA	chr17:41848317	1.30E-04	OCTX	NA	NA
3722029	NA	chr17:41846964	1.30E-04	OCTX	NA	NA
3722029	rs35490951	chr17:40250939	5.60E-04	OCTX	CC=0; CA=16; AA=112	C=6%; A=94%
3722030	rs4432296	chr17:40118807	8.90E-04	OCTX	CC=11; CT=52; TT=71	C=27.6%; T=72.4%
3722030	rs12602950	chr17:40123829	8.90E-04	OCTX	GG=11; GA=52; AA=71	G=27.6%; A=72.4%

3722030	rs11079026	chr17:40114049	8.90E-04	OCTX	GG=11; GA=52; AA=71	G=27.6%; A=72.4%
3722030	rs4796750	chr17:40114544	8.90E-04	OCTX	AA=11; AG=52; GG=71	A=27.6%; G=72.4%
3722030	rs9900219	chr17:40115017	8.90E-04	OCTX	GG=11; GA=52; AA=71	G=27.6%; A=72.4%
3722030	rs4480859	chr17:40118602	8.90E-04	OCTX	TT=11; TC=52; CC=71	T=27.6$; C=72.4%
3721997	NA	chr17:40505376:AAAAG	2.70E-04	PUTM	NA	NA
3722016	NA	chr17:40505376:AAAAG	9.50E-04	PUTM	NA	NA
3722017	NA	chr17:40505376:AAAAG	9.50E-04	PUTM	NA	NA
3722020	NA	chr17:40505376:AAAAG	4.50E-05	PUTM	NA	NA
3722020	rs11079012	chr17:39912880	4.70E-04	PUTM	GG=10; AG=22; GG=98	A=9%; G=91%
3722021	rs11079012	chr17:39912880	9.00E-05	PUTM	GG=10; GC=38; CC=45	G=21.6%; C=78.4%
3721992	rs8064555	chr17:39961246	8.50E-04	SNIG	GG=28; GA=66; AA=38	G=45.5%; A=54.5%
3722008	rs56162439	chr17:40249387	3.00E-05	SNIG	TT=0; TC=196; CC=110	T=6%; C=94%
3722008	rs11870415	chr17:40244007	8.80E-05	SNIG	CC=0; CT=24; TT=99	C=9%; T=91%
3722008	rs8064555	chr17:39961246	2.90E-04	SNIG	GG=28; GA=66; AA=38	G=45.5%; A=54.5%
3722008	NA	chr17:39959887:A_AG	3.40E-04	SNIG	NA	NA
3722008	rs3809877	chr17:39959511	3.50E-04	SNIG	CC=28; CT=68; TT=38	C=46.3%; T=53.7%
3722008	rs3809876	chr17:39959433	3.50E-04	SNIG	AA=28; AG=68; GG=38	A=46.3%;G=53.7%

3722008	rs28500587	chr17:39958179	3.50E-04	SNIG	AA=28; AG=68; GG=38	A=46.3%;G=53.7%
3722016	rs56162439	chr17:40249387	1.70E-03	SNIG	TT=0; TC=16; CC=110	T=6%; C=94%
3722016	rs799923	chr17:41251931	2.10E-03	SNIG	AA=8; AG=45; GG=81	A=22.8%; G=77.2%
3722017	rs56162439	chr17:40249387	2.40E-04	SNIG	TT=0; TC=16; CC=110	T=6%; C=94%
3722017	rs11870415	chr17:40244007	2.50E-04	SNIG	CC=0; CT=24; TT=99	C=9%; T=91%
3722017	rs8064555	chr17:39961246	1.20E-03	SNIG	GG=28; GA=66; AA=38	G=45.5%; A=54.5%
3722017	NA	chr17:39959887:A_AG	1.30E-03	SNIG	NA	NA
3722029	rs1865842	chr17:39986754	4.30E-04	SNIG	TT=11; TC=55; CC=43	T=28.7%; C=71.3%
3722029	rs8069503	chr17:39989662	4.30E-04	SNIG	GG=10; GA=55; AA=65	G=28%; A=72%
3722029	rs1043007	chr17:39979082	4.50E-04	SNIG	CC=10; CG=54; GG=65	C=27.6%; G=72.4%
3722029	rs4796713	chr17:39987361	4.50E-04	SNIG	GG=10; GA=55; AA=66	G=28%; A=72%
3722029	rs8075291	chr17:39989766	5.10E-04	SNIG	TT=10; TC=56; CC=63	T=28.4%; C=71.6%
3722029	NA	chr17:40105404:G_GAT	5.80E-04	SNIG	NA	NA
3722029	rs9902501	chr17:40050312	5.90E-04	SNIG	CC=11; CT=50; TT=67	C=26.9%; T=73.1%
3722030	rs62079762	chr17:41057462	8.00E-04	SNIG	TT=0; TC=15; CC=93	T=5.6%; C=94.4%
t3721989	rs117199298	chr17:40313106	2.40E-04	TCTX	AA=1; AG=22; GG=98	A=9%; G=91%
3721992	rs113366589	chr17:40516616	5.40E-04	TCTX	GG=0; GT=23; TT=111	G=8.6%; T=91.4%

3721992	NA	chr17:41225654:TA_T	6.20E-04	TCTX	NA	NA
3721998	NA	chr17:40060564:GAAGA	1.90E-04	TCTX	NA	NA
3721998	rs117199298	chr17:40313106	2.10E-04	TCTX	AA=1; AG=22; GG=98	A=9%; G=91%
3721998	rs76745238	chr17:39982550	2.20E-04	TCTX	GG=7; GA=32; AA=95	G=17.2%; A=82.8%
3721998	rs11079016	chr17:39976024	2.20E-04	TCTX	AA=7; AG=32; GG=95	A=17.2%; G=82.8%
3721998	rs35114175	chr17:39976877	2.20E-04	TCTX	AA=7; AG=32; GG=95	A=17.2%; G=82.8%
3721998	rs12936561	chr17:39985330	2.20E-04	TCTX	AA=7; AG=32; GG=95	A=17.2%; G=82.8%
3721998	rs17498604	chr17:39986378	2.20E-04	TCTX	AA=7; AG=32; GG=95	A=17.2%; G=82.8%
3721998	rs12952506	chr17:39989734	2.20E-04	TCTX	GG=7; GA=32; AA=95	G=17.2%; A=82.8%
3721998	rs71373456	chr17:39991801	2.20E-04	TCTX	GG=7; GT=32; TT=95	G=17.2%; T=82.8%
3721999	rs76745238	chr17:39982550	3.10E-04	TCTX	GG=7; GA=32; AA=95	G=17.2%; A=82.8%
3721999	rs11079016	chr17:39976024	3.10E-04	TCTX	AA=7; AG=32; GG=95	A=17.2%; G=82.8%
3722005	rs117199298	chr17:40313106	3.40E-04	TCTX	AA=1; AG=22; GG=98	A=9%; G=91%
3722008	rs3760385	chr17:40841906	4.20E-04	TCTX	AA=28; AG=62; GG=44	A=44%; G=56%
3722011	rs72826965	chr17:40841210	2.20E-04	TCTX	CC=0; CT=16; TT=118	C=6%; T=94%
3722011	rs34883538	chr17:40841818	2.20E-04	TCTX	AA=0; AG=16; GG=118	A=6%; G=94%
3722011	rs35855335	chr17:40842441	2.20E-04	TCTX	CC=0; CT=16; TT=118	C=6%; T=94%

3722011	rs1553469	chr17:40842762	2.20E-04	TCTX	AA=0; AC=16; CC=118	A=6%; C=94%
3722011	rs874640	chr17:40843392	2.20E-04	TCTX	TT=0; TG=16; GG=118	T=6%; G=94%
3722011	rs1973521	chr17:40840070	2.20E-04	TCTX	AA=0; AG=16; GG=118	A=6%; G=94%
3722011	rs117199298	chr17:40313106	2.80E-04	TCTX	AA=1; AG=22; GG=98	A=9%; G=91%
3722011	rs4792952	chr17:40871006	3.30E-04	TCTX	AA=0; AG=15; GG=119	A=5.6%; G=94.4%
3722011	rs113128311	chr17:40877432	3.30E-04	TCTX	GG=0; GA=15; AA=119	G=5.6%; A=94.4%
3722011	rs113025290	chr17:40893920	4.30E-04	TCTX	CC=0; CG=15; GG=117	C=5.6%; G=94.4%
3722012	rs117199298	chr17:40313106	1.70E-04	TCTX	AA=1; AG=22; GG=98	A=9%; G=91%
3722014	rs117199298	chr17:40313106	6.70E-05	TCTX	AA=1; AG=22; GG=98	A=9%; G=91%
3722014	NA	chr17:40060564:GAAGA	6.70E-04	TCTX	NA	NA
3722014	NA	chr17:40060566:AGAAG	7.50E-04	TCTX	NA	NA
3722014	rs76745238	chr17:39982550	7.90E-04	TCTX	GG=7; GA=32; AA=95	G=17.2%; A=82.8%
3722014	rs11079016	chr17:39976024	8.00E-04	TCTX	AA=7; AG=32; GG=95	A=17.2%; G=82.8%
3722015	rs117199298	chr17:40313106	1.70E-04	TCTX	AA=1; AG=22; GG=98	A=9%; G=91%
3722016	rs117199298	chr17:40313106	1.50E-03	TCTX	AA=1; AG=22; GG=98	A=9%; G=91%
3722016	rs2667940	chr17:41029029	1.70E-03	TCTX	CC=3; CT=35; TT=96	C=15.3%; T=84.7%
3722016	rs324075	chr17:41026523	1.70E-03	TCTX	GG=3; GA=35; AA=96	G=15.3%; A=84.7%

3722017	rs4793069	chr17:40801187	1.30E-03	TCTX	GG=1; GA=19; AA=112	G=7.8%; A=92.2%
3722018	NA	chr17:39989592:C_CA	2.40E-04	TCTX	NA	NA
3722018	rs60588087	chr17:39982432	2.90E-04	TCTX	AA=10; AC=54; CC=67	A=27.6%; C=72.4%
3722018	NA	chr17:40024868:AG_A	3.10E-04	TCTX	NA	NA
3722018	NA	chr17:40024867:AAG_A	3.10E-04	TCTX	NA	NA
3722018	NA	chr17:39979267:GCTC_	3.30E-04	TCTX	NA	NA
3722018	rs9897034	chr17:39992584	3.30E-04	TCTX	CC=10; AT=56; TT=68	C=28.4%; T=71.6%
3722018	rs1836878	chr17:39986654	3.30E-04	TCTX	GG=10; GA=56; AA=68	G=28.4%; A=71.6%
3722018	rs9913772	chr17:40055293	3.50E-04	TCTX	CC=12; CT=50; TT=71	C=27.6%; T=72.4%
3722018	rs7212972	chr17:39980819	3.70E-04	TCTX	CC=10; CT=56; TT=68	C=28.4%; T=71.6%
3722018	rs1436440	chr17:39981131	3.70E-04	TCTX	GG=10; GA=56; AA=68	G=28.4%; A=71.6%
3722019	rs117199298	chr17:40313106	1.50E-04	TCTX	AA=1; AG=22; GG=98	A=9%; G=91%
3722020	rs117199298	chr17:40313106	1.30E-04	TCTX	AA=1; AG=22; GG=98	A=9%; G=91%
3722020	rs8072862	chr17:39870477	9.70E-04	TCTX	AA=2; AT=18; TT=113	A=8.2%; T=91.8%
3722020	rs4796691	chr17:39883789	1.00E-03	TCTX	AA=2; AG=18; GG=114	A=8.2%; G=91.8%
3722020	NA	chr17:40060564:GAAGA	1.10E-03	TCTX	NA	NA
3721990	rs56387576	chr17:40557693	4.60E-04	THAL	TT=1. TG=32; GG=70	T=12.7%; G=87.3%

3721992	rs56387576	chr17:40557693	4.90E-04	THAL	TT=1; TG=32; GG=70	T=12.7%; G=87.3%
3721999	rs56387576	chr17:40557693	9.10E-05	THAL	TT=1; TG=32; GG=70	T=12.7%; G=87.3%
3722013	rs75771390	chr17:40194054	5.20E-04	THAL	GG=0; GA=23; AA=110	G=8.6%; A=91.4%
3722014	rs56387576	chr17:40557693	7.20E-04	THAL	TT=1; TG=32; GG=70	T=12.7%; G=87.3%
3722015	rs56387576	chr17:40557693	3.50E-04	THAL	TT=1; TG=32; GG=70	T=12.7%; G=87.3%
3722016	rs56387576	chr17:40557693	8.90E-04	THAL	TT=1; TG=32; GG=70	T=12.7%; G=87.3%
3722017	rs56387576	chr17:40557693	7.10E-04	THAL	TT=1; TG=32; GG=70	T=12.7%; G=87.3%
3722020	NA	chr17:40582365:A_AT	8.80E-04	THAL	NA	NA
3722020	rs56001200	chr17:40587919	1.10E-03	THAL	CC=4; CT=39; TT=88	C=17.5%; T=82.5%
t3721989	NA	chr17:40270051:G_GAA	1.00E-04	WHMT	NA	NA
t3721989	NA	chr17:40270053:C_CAA	1.70E-04	WHMT	NA	NA
3721992	rs2074165	chr17:40267299	3.90E-04	WHMT	CC=2; CT=33; TT=97	C=13.8%; T=86.2%
3721992	NA	chr17:40270053:C_CAA	4.10E-04	WHMT	NA	NA
3721992	NA	chr17:40270051:G_GAA	5.50E-04	WHMT	NA	NA
3721992	rs2277621	chr17:40264661	7.00E-04	WHMT	GG=2; GC=31; CC=101	G=13.1%; C=86.9%
3721992	rs2074166	chr17:40267255	9.60E-04	WHMT	CC=2; CT=33; TT=99	C=13.8%; T=86.2%
3721993	rs2277621	chr17:40264661	5.00E-05	WHMT	GG=2; GC=31; CC=101	G=13.1%; C=86.9%

3721993	rs2074165	chr17:40267299	6.70E-05	WHMT	CC=2; CT=33; TT=97	C=13.8%; T=86.2%
3721993	rs2074166	chr17:40267255	7.80E-05	WHMT	CC=2; CT=33; TT=97	C=13.8%; T=86.2%
3721993	rs4796771	chr17:40268416	7.80E-05	WHMT	GG=2. GA=33; AA=99	G=13.8%; A=86.2%
3721993	NA	chr17:40270053:C_CAA	8.40E-05	WHMT	NA	NA
3721993	rs2074164	chr17:40270238	8.60E-05	WHMT	CC=2; CG=33; GG=99	C=13.8%; G=86.2%
3721993	rs3744484	chr17:40264125	8.60E-05	WHMT	TT=2; TA=33; AA=99	T=13.8%; A=86.2%
3721993	rs4796772	chr17:40268453	8.60E-05	WHMT	CC=2; CT=33; TT=99	C=13.8%; T=86.2%
3721993	rs35478347	chr17:40270053	1.10E-04	WHMT	AA=2; AC=32; CC=100	A=13.4%; C=86.6%
3721993	NA	chr17:40270119:GGAGA	1.10E-04	WHMT	NA	NA
3721994	rs72831101	chr17:41488718	1.60E-04	WHMT	TT=16; TC=61; CC=56	T=34.7%; C=65.3%
3721994	rs72831100	chr17:41488651	1.60E-04	WHMT	CC=16; CG=61; GG=56	C=34.7%; G=65.3%
3721994	rs57804968	chr17:41488496	1.60E-04	WHMT	GG=16; GC=61; CC=56	G=34.7%; C=65.3%
3721994	rs12603967	chr17:41489793	2.40E-04	WHMT	TT=17; TC=60; CC=56	T=35.1%; C=64.9%
3721994	rs35122535	chr17:41489319	2.40E-04	WHMT	CC=17; CA=60; AA=56	C=35.1%; A=64.9%
3721994	NA	chr17:41489738:TC_T	2.40E-04	WHMT	NA	NA
3722004	NA	chr17:40270051:G_GAA	1.00E-04	WHMT	NA	NA
3722005	NA	chr17:40270051:G_GAA	1.30E-04	WHMT	NA	NA

3722005	NA	chr17:40270053:C_CAA	2.60E-04	WHMT	NA	NA
3722007	NA	chr17:40270051:G_GAA	2.10E-04	WHMT	NA	NA
3722007	NA	chr17:40270053:C_CAA	3.10E-04	WHMT	NA	NA
3722007	rs2074165	chr17:40267299	3.10E-04	WHMT	CC=2; CT=33; TT=97	C=13.8%; T=86.2%
3722012	NA	chr17:40270053:C_CAA	9.80E-05	WHMT	NA	NA
3722012	rs2277621	chr17:40264661	1.90E-04	WHMT	GG=2; GC=31; CC=101	G=13.1%; C=86.9%
3722012	rs4796771	chr17:40268416	2.50E-04	WHMT	GG=2; GA=33; AA=99	G=13.8%; A=86.2%
3722012	rs2074166	chr17:40267255	2.50E-04	WHMT	CC=2; CT=33; TT=99	C=13.8%; T=86.2%
3722012	rs2074164	chr17:40270238	2.70E-04	WHMT	CC=2; CG=33; GG=99	C=13.8%; G=86.2%
3722012	rs3744484	chr17:40264125	2.70E-04	WHMT	TT=2; TA=33; AA=99	T=13.8%; A=86.2%
3722012	rs4796772	chr17:40268453	2.70E-04	WHMT	CC=2; CT=33; TT=99	C=13.8%; T=86.2%
3722012	rs2074165	chr17:40267299	2.70E-04	WHMT	CC=2; CT=33; TT=97	C=13.8%; T=86.2%
3722012	rs35478347	chr17:40270053	2.90E-04	WHMT	AA=2; AC=32; CC=100	A=13.4%; C=86.6%
3722014	NA	chr17:40270051:G_GAA	6.30E-04	WHMT	NA	NA
3722015	NA	chr17:40270051:G_GAA	3.00E-04	WHMT	NA	NA
3722015	NA	chr17:40270053:C_CAA	5.90E-04	WHMT	NA	NA
3722019	NA	chr17:40270051:G_GAA	4.30E-04	WHMT	NA	NA

3722021	rs2074165	chr17:40267299	4.30E-05	WHMT	CC=2; CT=33; TT=97	C=13.8%; T=86.2%
3722021	rs2074166	chr17:40267255	1.20E-04	WHMT	CC=2; CT=33; TT=99	C=13.8%; T=86.2%
3722021	rs4796771	chr17:40268416	1.20E-04	WHMT	GG=2; GA=33; AA=99	G=13.8%; A=86.2%
3722021	rs2277621	chr17:40264661	1.20E-04	WHMT	GG=2; GC=31; CC=101	G=13.1%; C=86.9%
3722021	NA	chr17:40270051:G_GAA	1.20E-04	WHMT	NA	NA
3722021	rs4796772	chr17:40268453	1.30E-04	WHMT	CC=2; CT=33; TT=99	C=13.8%; T=86.2%
3722021	rs3744484	chr17:40264125	1.30E-04	WHMT	TT=2; TA=33; AA=99	T=13.8%; A=86.2%
3722021	rs2074164	chr17:40270238	1.40E-04	WHMT	CC=2; CG=33; GG=99	C=13.8%;G=86.2 %
3722021	NA	chr17:40270053:C_CAA	1.50E-04	WHMT	NA	NA
3722022	rs2277621	chr17:40264661	2.80E-07	WHMT	GG=2; GC=31; CC=101	G=13.1%; C=86.9%
3722022	rs4796771	chr17:40268416	9.10E-07	WHMT	GG=2; GA=33; AA=99	G=13.8%; A=86.2%
3722022	rs2074166	chr17:40267255	9.10E-07	WHMT	CC=2; CT=33; TT=99	C=13.8%; T==86.2%
3722022	rs2074164	chr17:40270238	1.10E-06	WHMT	CC=2; CG=33; GG=99	C=13.8%; G==86.2%
3722022	rs3744484	chr17:40264125	1.10E-06	WHMT	TT=2; TA=33; AA=99	T=13.8%; A=86.2%
3722022	rs4796772	chr17:40268453	1.10E-06	WHMT	CC=2; CT=33; TT=99	C=13.8%; T=86.2%
3722022	rs2074165	chr17:40267299	1.20E-06	WHMT	CC=2; CT=33; TT=97	C=13.8%; T=86.2%
3722022	rs35478347	chr17:40270053	1.40E-06	WHMT	AA=2; AC=32; CC=100	A=13.4%; C=86.6%

3722022	NA	chr17:40270119:GGAGA	1.50E-06	WHMT	NA	NA
3722022	rs2074163	chr17:40270957	1.60E-06	WHMT		
3722024	NA	chr17:40270053:C_CAA	7.40E-05	WHMT	NA	NA
3722024	NA	chr17:40270051:G_GAA	1.10E-04	WHMT	NA	NA
3722024	rs2074159	chr17:40256498	1.90E-04	WHMT	CC=1; CG=23; GG=110	C=9.3%; G=90.7%
3722024	rs12952244	chr17:40270081	1.90E-04	WHMT	GG=1; GA=24; AA=109	G=9.7%; A=90.3%
3722024	rs35370188	chr17:40258127	2.50E-04	WHMT	CC=1; CT=23; TT=110	C=9.3%; T=90.7%
3722024	rs35493105	chr17:40260728	2.50E-04	WHMT	AA=1; AG=23; GG=110	A=9.3%; G=90.7%
3722024	rs2158067	chr17:40260865	2.50E-04	WHMT	CC=1; CA=23; AA=110	C=9.3%; A=90.7%
3722024	rs12600570	chr17:40261545	2.50E-04	WHMT	TT=1; TC=23; CC=110	T=9.3%; C=90.7%
3722024	NA	chr17:40259383:A_AT	2.60E-04	WHMT	NA	NA

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 28: Brain quantitative gene expression analyses for *UNC13D* gene variants.

Expr ID	rsID	Variant	*P-value*	tissue	Genotype_counts	Allele_frequency
3770988	rs11077824	chr17:74515405	4.60E-04	aveALL	CC=2; CA=10; AA=122	C=5.2%; A=94.8%

3770989	NA	chr17:73903487:GT_G	3.10E-05	aveALL	NA	NA
3770989	rs7218058	chr17:73834948	1.20E-04	aveALL	GG=6; GA=41; AA=85	G=19.%; A=80.%
3770989	rs8068749	chr17:73885161	1.40E-04	aveALL	GG=6; GA==37; AA=81	G=18.3%; A=81.7%
3770989	NA	chr17:73903481:AT_A	1.60E-04	aveALL	NA	NA
3770997	NA	chr17:74500379:GC_G	1.50E-04	aveALL	NA	NA
3770997	NA	chr17:74500404:G_GT	2.30E-04	aveALL	NA	NA
3771002	NA	chr17:73079547:A_AT	7.80E-04	aveALL	NA	NA
3771005	rs4238992	chr17:74498585	2.20E-05	aveALL	CC=40; CT=58; TT=36	C=51.5%; T=48.5%
3771005	rs895158	chr17:74500380	1.00E-04	aveALL	GG=41; GC=58; CC=30	G=52.2%; C=57.8%
3771005	rs895159	chr17:74500384	1.00E-04	aveALL	CC=41; CG=58; GG=30	C==52.2%; G=47.8%
3771005	NA	chr17:74500404:G_GT	1.60E-04	aveALL	NA	NA
3771005	NA	chr17:74456211:AATTT	1.60E-04	aveALL	NA	NA
3771005	rs71384112	chr17:74515080	2.50E-04	aveALL	AA=1; AG=16; GG=108	A=6.7%; G=93.3%
3771010	rs743554	chr17:73754248	8.80E-05	aveALL	AA=3; AG=27; GG=103	A=12.3%; G=87.7%
3771010	rs112308072	chr17:73442853	3.40E-04	aveALL	AA=0; AG=21; GG=103	A=7.8%; G=92.2%
3771014	rs78044548	chr17:74019680	2.30E-04	aveALL	TT=0; TC=22; CC=110	T=8.2%; C=91.8%
3771014	rs146556419	chr17:74024205	2.40E-04	aveALL	AA=0; AC=21; CC=110	A=7.8%; C=92.2%

3771014	rs141099275	chr17:73984478	2.40E-04	aveALL	AA=0; AC=23; CC=111	A=8.6%; C=91.4%
3771014	rs138332531	chr17:73985203	2.40E-04	aveALL	TT=0; TC=23; CC=111	T=8.6%; C=91.4%
3771016	rs8067275	chr17:73884249	2.10E-04	aveALL	TT=0; TA=9; AA=105	T=3.4%; A=96.6%
3771016	rs73995995	chr17:73739121	2.80E-04	aveALL	GG=0; GA=17; AA=110	G=6.3%; A=93.7%
3771016	rs9894318	chr17:73740452	2.80E-04	aveALL	CC=0; CT=17; TT=110	C=6.3%; T=93.7%
3771023	rs743554	chr17:73754248	4.20E-04	aveALL	AA=3; AG=27; GG=103	A=12.3%; G=87.7%
3771024	rs9894765	chr17:74456426	6.70E-05	aveALL	GG=5; GC=41; CC=66	G=19%; C=81%
3771024	rs62084967	chr17:74420094	7.40E-05	aveALL	GG=3; GA=32; AA=97	G=14.2%; A=85.8%
3771024	rs346809	chr17:74405280	9.50E-05	aveALL	AA=3; AG=33; GG=97	A=14.6%; G=85.4%
3771024	rs423130	chr17:74416189	1.10E-04	aveALL	AA=3; AG=33; GG=98	A=14.6%; G=85.4%
3771024	rs62084971	chr17:74425318	1.30E-04	aveALL	TT=3; TG=33; GG=98	T=14.6%; G=85.4%
3771024	rs12950218	chr17:74409547	1.30E-04	aveALL	AA=3; AG=33; GG=98	A=14.6%; G=85.4%
3771024	rs346811	chr17:74403926	1.30E-04	aveALL	TT=3; TC=33; CC=98	T=14.6%; C=85.4%
3771024	rs452868	chr17:74421483	1.30E-04	aveALL	CC=3; CA=33; AA=98	C=14.6%; A=85.4%
3771024	rs4419085	chr17:74443683	1.30E-04	aveALL	CC=3; CT=33; TT=98	C=14.6%; T=85.4%
3771024	rs12949638	chr17:74444758	1.30E-04	aveALL	TT=3; TC=33; CC=98	T=14.6%; C=85.4%
3771027	rs28715905	chr17:74448063	3.20E-04	aveALL	AA=3; AC=33; CC=96	A=14.6%; C=85.4%

3771027	rs4647868	chr17:74513961	3.30E-04	aveALL	AA=16; AC=53; CC=65	A=31.7%; C=68.3%
3770982	rs71384112	chr17:74515080	1.70E-04	CRBL	AA=1; AG=16; GG=108	A=6.7%; G=93.3%
3770982	rs4611488	chr17:74499266	2.10E-04	CRBL	TT=10; TG=39; GG=85	T=22%; G=78%
3770982	rs10852758	chr17:72981775	2.60E-04	CRBL	GG=1; GA=15; AA=118	G=6.3%; A=93.7%
3770982	rs74721266	chr17:74423288	2.60E-04	CRBL	TT=1; TC=10; CC=116	T=4.5%; C=95.5%
3770982	rs117222111	chr17:74603533	2.70E-04	CRBL	GG=0; GT=17; TT=90	G=6.3%; A=93.7%
3770982	rs117771877	chr17:74378028	2.80E-04	CRBL	GG=1; GT=10; TT=116	G=4.5%; T=95.5%
3770990	rs902728	chr17:72955310	1.50E-05	CRBL	AA=4; AT=38; TT=91	A=17.2%; T=82.8%
3770990	rs59170636	chr17:72957007	1.50E-05	CRBL	TT=4; TA=38; AA=91	T=17.2%; A=82.8%
3770990	rs3744199	chr17:72956399	1.60E-05	CRBL	AA=4; AC=38; CC=91	A=17.2%; C=82.8%
3770991	rs449446	chr17:74365663	9.00E-05	CRBL	AA=1; AG=17; GG=102	A=7.1%; G=92.9%
3770996	rs4789251	chr17:74198818	8.40E-05	CRBL	TT=29; TC=56; CC=49	T=42.5%; C=57.5%
3770996	rs9913054	chr17:74205023	8.40E-05	CRBL	AA=29; AC=56; CC=49	A=42.5%; C=57.5%
3770996	rs4505373	chr17:74204592	8.60E-05	CRBL	GG=29; GT=56; TT=49	G=42.5%; T=57.5%
3770996	rs9901431	chr17:74206638	1.00E-04	CRBL	CC=24; CT=47; TT=45	C=35.4%; T=64.6%
3771012	rs62088545	chr17:73538318	1.30E-04	CRBL	TT=9; TC=56; CC=53	T=27.6%; C=72.4%
3771014	rs67017503	chr17:74280991	1.50E-04	CRBL	AA=1; AC=13; CC=118	A=5.6%; C=94.4%

3771014	rs9674537	chr17:74264054	2.10E-04	CRBL	AA=1; AG=18; GG=115	A=7.5%; G=92.5%
3771014	rs9674642	chr17:74264304	2.20E-04	CRBL	GG=1; GA=18; AA=115	G=7.5%; A=92.5%
3771017	NA	chr17:74022795:GCCAG	1.90E-05	CRBL	NA	NA
3771017	rs146556419	chr17:74024205	1.90E-05	CRBL	AA=0; AC=21; CC=110	A=7.8%; C=92.2%
3771017	rs78044548	chr17:74019680	3.40E-05	CRBL	TT=0; TC=22; CC=110	T=8.2%; C=91.8%
3771017	rs1806914	chr17:74018640	5.30E-05	CRBL	GG=0; GC=23; CC=111	G=8.6%; C=91.4%
3771017	rs8071298	chr17:74014228	5.60E-05	CRBL	AA=0; AG=23; GG=111	A=8.6%; G=91.4%
3771017	rs117028962	chr17:73990066	5.80E-05	CRBL	TT=0; TA=23; AA=111	T=8.6%; A=91.4%
3771017	rs7220365	chr17:73987162	5.80E-05	CRBL	TT=0; TC=23; CC=111	T=8.6%; C=91.4%
3771017	rs138332531	chr17:73985203	5.80E-05	CRBL	TT=0; TC=23; CC=111	T=8.6%; C=91.4%
3771017	rs141099275	chr17:73984478	5.90E-05	CRBL	AA=0; AC=23; CC=111	A=8.6%; C=91.4%
3771017	rs2665976	chr17:74027906	7.30E-05	CRBL	TT=0; TC=12; CC=115	T=4.5%; C=95.5%
3771027	rs72860367	chr17:73784780	5.40E-04	CRBL	TT=1; TC=10; CC=115	T=4.5%; C=95..5%
3771034	rs60037565	chr17:74618280	4.60E-04	CRBL	TT=4; TA=33; AA=83	T=15.3%; A=84.7%
3770983	rs77860123	chr17:73274558	4.50E-04	FCTX	AA=4; AG=16; GG=112	A=9%; G=91%
3770983	rs113909053	chr17:73274800	4.50E-04	FCTX	TT=4; TC=16; CC=112	T=9%; C=91%
3770983	NA	chr17:73274500:T_TA	4.60E-04	FCTX	NA	NA

3770985	rs78829815	chr17:73978831	7.10E-04	FCTX	AA=0; AG=21; GG=98	A=7.8%; G=92.2%
3771003	rs12939461	chr17:72996791	6.90E-05	FCTX	TT=14; TC=52; CC=66	T=29.9%; C=70.1%
3771003	rs34063142	chr17:72992655	7.50E-05	FCTX	TT=15; TC=52; CC=66	T=30.6%; C=69.4%
3771003	NA	chr17:72997364:T_TAG	7.70E-05	FCTX	NA	NA
3771003	rs8066760	chr17:72993780	9.70E-05	FCTX	AA=15; AG=53; GG=66	A=31%; G=69%
3771003	rs8065063	chr17:72993707	9.70E-05	FCTX	GG=15; GA=53; AA=66	G=31%; A=69%
3771005	rs516035	chr17:72862155	2.40E-04	FCTX	GG=5; GT=50; TT=76	G=22.4%; T=77.6%
3771018	rs11077798	chr17:73953404	1.20E-03	FCTX	TT=5; TC=35; CC=94	T=16.85; C=83.2%
3771018	rs2598416	chr17:74021369	1.30E-03	FCTX	TT=7; TC=49; CC=78	T=23.5%; C=76.5%
3771018	rs2665964	chr17:74021304	1.30E-03	FCTX	AA=7; AG=49; GG=78	A=23.5%; G=76.5%
3771018	rs2467099	chr17:73949045	1.30E-03	FCTX	TT=5; TC=35; CC=94	T=16.5%; C=83.2%
3771018	rs113789309	chr17:73904155	1.30E-03	FCTX	AA=5; AG=35; GG=94	A=16.8%; G=83.2%
3771023	rs11654531	chr17:73084344	8.00E-04	FCTX	TT=15; TG=50; GG=61	T=29.9%; G=70.1%
3771023	rs12947426	chr17:73085662	8.10E-04	FCTX	AA=15; AG=49; GG=61	A=29.5%; G=70.55
3771034	NA	chr17:73963716:C_CAT	2.20E-04	FCTX	NA	NA
3771034	rs820142	chr17:73609112	3.10E-04	FCTX	GG=35; GA=66; AA=31	G=50.7%; A=49.3%
3771034	rs820140	chr17:73608203	3.70E-04	FCTX	TT=35; TC=66; CC=31	T=50.7%; C=49.3%
3771034	rs78829815	chr17:73978831	5.00E-04	FCTX	AA=0; AG=21; GG=98	A=7.8%; G=92.2%

3771034	rs4789221	chr17:73610203	6.10E-04	FCTX	TT=20; TC=62; CC=51	T=38.1%; C=61.9%
3771034	rs3803728	chr17:73609139	6.10E-04	FCTX	TT=20; TC=62; CC=51	T=38.1%; C=61.9%
3771034	NA	chr17:73066937:GGCTT	6.60E-04	FCTX	NA	NA
3771034	rs8065144	chr17:73959857	6.70E-04	FCTX	GG=13; GA=54; AA=64	G=29.9%; A=70.1%
3770985	rs113769601	chr17:74130237	5.70E-04	HIPP	AA=3; AG=21; GG=102	A=10.1%; G=89.9%
3770997	rs11870242	chr17:74824168	2.70E-04	HIPP	AA=11; AG=46; GG=72	A=25.4%; G=74.6%
3770997	rs12945478	chr17:74824376	2.70E-04	HIPP	CC=8; CG=46; GG=72	C=23.1%; G=76.9%
3770997	rs11870421	chr17:74824161	3.50E-04	HIPP	TT=11; TC=47; CC=72	T=25.7%; C=74.3%
3771009	rs16968673	chr17:74168831	1.60E-04	HIPP	TT=1; TA=15; AA=113	T=6.3%; A=93.7%
3771009	rs72868716	chr17:74163247	2.00E-04	HIPP	TT=1; TC=13; CC=117	T=5.6%; C=94.4%
3771009	NA	chr17:74431487:CACAC	2.80E-04	HIPP	NA	NA
3771009	rs874530	chr17:74377307	4.30E-04	HIPP	CC=19; CT=59; TT=37	C=36.2%; T=63.8%
3771012	rs112336265	chr17:74579215	3.10E-06	HIPP	GG=0; GT=12; TT=121	G=4.5%; T=95.5%
3771012	rs60276435	chr17:74580142	1.00E-05	HIPP	TT=0; TC=10; CC=122	T=3.7%; C=96.3%
3771012	rs8076344	chr17:74568303	1.10E-05	HIPP	TT=0; TC=16; CC=118	T=6%; C=94%
3771012	rs76538582	chr17:74566170	1.10E-05	HIPP	CC=0; CT=16; TT=118	C=6%; T=94%
3771012	rs78084209	chr17:74566132	1.30E-05	HIPP	TT=0; TC=16; CC=118	T=6%; C=94%

3771014	rs76114178	chr17:72933993	3.60E-05	HIPP	GG=1; GC=32; CC=88	G=12.7%; C=87.3%
3771023	rs36089184	chr17:72866377	8.10E-04	HIPP	TT=1; TC=25; CC=96	T=10.1; C=89.9%
3771027	rs72868716	chr17:74163247	5.50E-05	HIPP	TT=1; TC=13; CC=117	T=5.6%; C=94.4%
3771027	rs76114178	chr17:72933993	1.10E-04	HIPP	GG=1; GC=32; CC=88	G=12.7%; C=87.3%
3771027	rs16968673	chr17:74168831	1.40E-04	HIPP	TT=1; TA=15; AA=113	T=6.3%; A=93.7%
t3770979	rs419793	chr17:74313086	3.20E-04	MEDU	TT=2; TC=27; CC=105	T=11.6%; C=88.4%
t3770979	rs8073728	chr17:74311942	3.30E-04	MEDU	TT=2; TC=27; CC=105	T=11.6%; C=88.4%
t3770979	rs453605	chr17:74310362	3.40E-04	MEDU	AA=2; AG=27; GG=105	A=11.6%; G=88.4%
t3770979	rs58119532	chr17:74308734	3.50E-04	MEDU	CC=2; CT=27; TT=105	C=11.6%; T=88.4%
t3770979	rs447294	chr17:74308125	4.40E-04	MEDU	AA=2; AG=27; GG=105	A=11.6%; G=88.4%
3770985	rs12941950	chr17:74416393	4.80E-04	MEDU	GG=1; GT=18; TT=109	G=7.5%; T=92.5%
3770985	rs35720705	chr17:74459686	5.40E-04	MEDU	AA=1; AG=22; GG=108	A=9%; G=91%
3770985	rs28507667	chr17:74433601	5.90E-04	MEDU	CC=0; CA=17; AA=111	C=6.3%; A=93.7%
3770985	rs144334645	chr17:74376428	7.10E-04	MEDU	AA=0; AG=13; GG=111	A=4.9%; G=95.1%
3770985	NA	chr17:74385111:AG_A	7.20E-04	MEDU	NA	NA
3770988	rs71380857	chr17:73026463	6.00E-05	MEDU	AA=1; AG=11; GG=120	A=4.9%; G=95.1%
3770988	rs35552011	chr17:73029764	2.40E-04	MEDU	TT=1; TA=11; AA=121	T=4.9%; A=95.1%

3770988	rs7208154	chr17:73021567	3.30E-04	MEDU	AA=1; AG=16; GG=115	A=6.7%; G=93.3%
3770988	rs113682539	chr17:73067364	3.30E-04	MEDU	TT=1; TC=15; CC=117	T=6.3%; C=93..7%
3770988	rs902723	chr17:73003195	3.40E-04	MEDU	TT=1; TC=22; CC=109	T=9%; C=91%
3770988	rs9912723	chr17:73004228	3.80E-04	MEDU	CC=1; CA==22; AA=109	C=9%; A=91%
3770997	rs2665971	chr17:74010038	1.50E-04	MEDU	TT=23; TC=54; CC=56	T=37.3%; C=63.7%
3770997	rs4561495	chr17:73983684	2.20E-04	MEDU	TT=1; TC=34; CC=99	T=13.4%; C=86.6%
3771000	NA	chr17:73461758:ATATT	2.50E-04	MEDU	NA	NA
3771002	NA	chr17:74319434:AG_A	5.90E-04	MEDU	NA	NA
3771002	rs3988166	chr17:74321217	6.70E-04	MEDU	GG=3; GA=35; AA=94	G=15.3%; A=84.7%
3771002	rs438481	chr17:74321077	7.90E-04	MEDU	AA=3; AG=35; GG=96	A=15.3%; G=84.7%
3771002	rs1713398	chr17:74319435	7.90E-04	MEDU	AA=3; AG=35; GG=96	A=15.3%; G=84.7%
3771008	rs56298033	chr17:73588233	3.50E-05	MEDU	TT=9; TG=35; GG=85	T=19.8%; G=80.2%
3771008	rs820250	chr17:73589558	3.70E-05	MEDU	AA=11; AG=36; GG=87	A=21.6%; G=78.4%
3771008	rs1661693	chr17:73596956	5.90E-05	MEDU	TT=2; TC=12; CC=119	T=6%; C=94%
3771008	rs56144802	chr17:73702135	6.00E-05	MEDU	AA=0; AG=1; GG=120	A=0.4%; G=99.6%
3771008	rs55853884	chr17:73647429	7.70E-05	MEDU	TT=1; TC=10; CC=120	T=4.5%; C=95.5%
3771008	rs12943907	chr17:73595658	7.80E-05	MEDU	AA=12; AG=33; GG=88	A=21.3%; G=78.7%
3771008	rs72854940	chr17:73630721	7.90E-05	MEDU	AA=2; AG=10; GG=120	A=5.2%; G=94.8%

3771008	rs820251	chr17:73589643	8.20E-05	MEDU	GG=2; GA=12; AA=120	G=6%; A=94%
3771008	rs820256	chr17:73590830	8.30E-05	MEDU	TT=2; TG=12; GG=120	T=6%; G=94%
3771008	rs1670993	chr17:73603086	8.40E-05	MEDU	TT=2; TC=12; CC=120	T=6%; C=94%
3771027	rs59467367	chr17:74487666	3.90E-05	MEDU	CC=28; CT=54; TT=43	C=41%; T=59%
3771027	rs4788926	chr17:74487735	6.20E-04	MEDU	TT=24; TC=54; CC=53	T=39.2%; C=60.8%
t3770979	rs9904343	chr17:74156332	4.80E-04	OCTX	CC=9; CA=39; AA=83	C=22.3%; A=78.7%
3770985	NA	chr17:73318902:GCA_G	3.40E-04	OCTX	NA	NA
3770985	rs4402606	chr17:73319892	7.60E-04	OCTX	TT=9; TC=41; CC=45	T=22%; C=78%
3770987	rs9904343	chr17:74156332	6.20E-06	OCTX	CC=9; CA=39; AA=83	C=21.3%; A=78.7%
3770987	rs2289605	chr17:74156752	8.70E-06	OCTX	CC=9; CG=40; GG=84	C=21.6%; G=78.4%
3770987	rs9893558	chr17:74159763	1.20E-05	OCTX	GG=10; GT=40; TT=84	G=22.4; T=777.6%
3770987	rs4788916	chr17:74169223	2.30E-05	OCTX	TT=10; TC=41; CC=83	T=22.8%; C=77.2%
3770987	rs4789247	chr17:74169093	2.30E-05	OCTX	TT=10; TC=41; CC=83	T=22.8%; C=77.2%
3770987	rs34995888	chr17:74166263	2.30E-05	OCTX	GG=10; GA=41; AA=83	G=22.8%; A=77.2%
3770987	rs2278826	chr17:74162997	2.30E-05	OCTX	GG=10; GA=41; AA=83	G=22.8%; A=77.2%
3770987	rs2278824	chr17:74163490	2.30E-05	OCTX	AA=10; AG=41; GG=83	A=22.8%; G=77.2%
3770987	rs8077046	chr17:74166869	2.30E-05	OCTX	AA=10; AG=41; GG=83	A=22.8%; G=77.2%

3770987	rs8076990	chr17:74165601	2.50E-05	OCTX	CC=10; CT=41; TT=83	C=22.8%; T=77..2%
3770988	NA	chr17:73069185:T_TAC	3.00E-04	OCTX	NA	NA
3770988	rs77692739	chr17:73108433	4.40E-04	OCTX	GG=0; GA=16; AA=118	G=6%; A=94%
3770995	rs148546283	chr17:74604409	1.20E-04	OCTX	GG=0; GA=13; AA=83	G=4.9%; A=95.1%
3770995	rs4789328	chr17:74613047	2.00E-04	OCTX	AA=0; AC=10; CC=112	A=3.7%; C=96.3%
3771009	rs71384112	chr17:74515080	5.90E-04	OCTX	AA=1; AG=16; GG=108	A=6.7%; G=93.3%
3771010	rs4402606	chr17:73319892	3.70E-04	OCTX	TT=9; TC=41; CC=45	T=22%; C=78%
3771016	rs2665984	chr17:74134653	2.00E-04	OCTX	CC=11; CG=50; GG=63	C=26.9%; G=73.1%
3771016	rs1868824	chr17:74134628	2.50E-04	OCTX	GG=9; GC=50; CC=63	G=25.4%; C=74.6%
3771016	NA	chr17:74134320:G_GC	3.70E-04	OCTX	NA	NA
3771016	rs754707	chr17:74150148	3.80E-04	OCTX	TT=12; TC=59; CC=63	T=31%; C=69%
3771016	rs2598427	chr17:74139694	4.00E-04	OCTX	GG=12; GA=59; AA=63	G=31%; A=69%
3771016	rs1465960	chr17:74139264	4.00E-04	OCTX	AA=12; AG=59; GG=63	A=31%; G=69%
3771016	rs2585738	chr17:74146733	4.00E-04	OCTX	GG=12; GA=59; AA=63	G=31%; A=69%
3771018	rs4789250	chr17:74190835	8.30E-04	OCTX	GG=21; GA=51; AA=51	G=34..7%; A=65.3%
3771018	rs10048213	chr17:74198211	1.10E-03	OCTX	TT=4; TA=37; AA=38	T=16.8%; A=83.2%
3771018	rs8067947	chr17:74195151	1.30E-03	OCTX	TT=26; TC=55; CC=53	T=39.9%; C=60.1%
3771018	rs4525514	chr17:74194359	1.30E-03	OCTX	TT=26; TC=55; CC=52	T=39.9%; C=60.1%

3771027	rs11654510	chr17:74677362	1.20E-04	OCTX	AA=0; AC=27; CC=86	A=10.1;%; C=89.9%
t3770979	rs7211678	chr17:74619884	2.00E-04	PUTM	GG=2; GT=26; TT=106	G=11.2%; T=88.8%
3770988	rs820240	chr17:73583027	4.10E-04	PUTM	AA=6; AG=33; GG=94	A=16.8%; G=83.2%
3770995	rs2279057	chr17:74309425	1.10E-04	PUTM	CC=9; CT=49; TT=76	C=25%; T=75%
3770995	rs2279056	chr17:74309474	1.10E-04	PUTM	GG=9; GA=49; AA=76	G=25%; A=75%
3770995	rs4789276	chr17:74294598	1.10E-04	PUTM	CC=7; CT=46; TT=75	C=22.4%; T=77.6%
3770995	rs407281	chr17:74311343	1.10E-04	PUTM	TT=9; TC=49; CC=76	T=25%; C=75%
3770995	rs379503	chr17:74308358	1.20E-04	PUTM	CC=9; CA=48; AA=76	C=24.6%; A=75.4%
3770995	rs446662	chr17:74313542	1.30E-04	PUTM	CC=9; CA=48; AA=76	C=24.6%; A=75.4%
3770995	rs2585747	chr17:74298257	1.40E-04	PUTM	GG=9; GC=46; CC=75	G=23.9%; C=76.1%
3770995	rs186985	chr17:74293388	2.90E-04	PUTM	GG=9; GA=45; AA=73	G=23.5%; A=76.5%
3771009	NA	chr17:74543994:TCA_T	5.60E-04	PUTM	NA	NA
3771009	rs12949102	chr17:74548115	8.30E-04	PUTM	TT=9; TC=47; CC=78	T=24.3%; C=75.7%
3771009	rs3744049	chr17:74547398	8.40E-04	PUTM	AA=9; AC=47; CC=78	A=24.3%; C=75.7%
3771009	rs752049	chr17:74546939	8.40E-04	PUTM	TT=9; TC=47; CC=78	T=24.3%; C=75.7%
3771009	rs5742903	chr17:74541171	8.50E-04	PUTM	CC=9; CT=47; TT=78	C=24.3%; T=75.7%
3771010	NA	chr17:74552531:A_AT	2.50E-04	PUTM	NA	NA
3771012	rs146663558	chr17:73067299	1.60E-04	PUTM	TT=0; TC=9; CC=113	T=3.4%; C=96.6%

3771013	NA	chr17:73273302:A_AC	8.10E-04	PUTM	NA	NA
3771027	rs148546283	chr17:74604409	5.00E-04	PUTM	GG=0; GA=13; AA=83	G=4.9%; A=95.1%
3771030	rs60764842	chr17:74485208	1.10E-04	PUTM	AA=20; AG=64; GG=38	A=38.8%; G=61.2%
3770985	rs689882	chr17:72876818	7.60E-04	SNIG	AA=9; AG=48; GG=59	A=24.6%; G=75.4%
3770990	rs12947009	chr17:74460301	6.10E-05	SNIG	TT=0; TG=10; GG=113	T=3.7%; G=96.3%
3770990	rs12947725	chr17:74451362	1.20E-04	SNIG	TT=0; TC=10; CC=114	T=3.7%; C=96.3%
3770990	rs35177607	chr17:74389476	2.70E-04	SNIG	TT=0; TC=11; CC=112	T=4.1%; C=95.9%
3770990	rs12450432	chr17:74692908	3.30E-04	SNIG	AA=2; AC=23; CC=109	A=10.1%; C=89.9%
3770990	rs59953252	chr17:74688824	3.50E-04	SNIG	GG=2; GT=23; TT=109	G=10.1%; T=89..9%
3770990	rs73357371	chr17:74689278	3.50E-04	SNIG	AA=2; AG=23; GG=109	A=10.1%; G=89.9%
3770990	rs73357369	chr17:74685836	3.60E-04	SNIG	AA=2; AC=23; CC=109	A=10.1%; C=89.9%
3770997	rs57087153	chr17:74513025	2.70E-04	SNIG	CC=13; CA=46; AA=75	C=26.9%; A=73.1%
3770997	rs71384111	chr17:74513624	2.70E-04	SNIG	GG=13; GA=46; AA=75	G=26.9%; A=73.1%
3770997	rs35780150	chr17:74509153	2.70E-04	SNIG	TT=12; TC=46; CC=76	T=26.1%; C=73.9%
3771000	rs4789255	chr17:74220911	3.00E-04	SNIG	GG=26; GA=57; AA=51	G=40.7%; A=59.3%
3771000	rs6501868	chr17:74222490	3.00E-04	SNIG	GG=26; GA=57; AA=51	G=40.7%; A=59.3%
3771000	rs7225855	chr17:74224405	3.00E-04	SNIG	CC=26; CT=57; TT=51	C=40.7%; T=59.3%

3771000	rs3859178	chr17:74213775	3.00E-04	SNIG	AA=26; AG=57; GG=51	A=40.7; G=59.3%
3771000	rs9896553	chr17:74212788	3.00E-04	SNIG	CC=26; CT=57; TT=51	C=40.7%; T=59.3%
3771000	rs3859181	chr17:74234658	3.00E-04	SNIG	GG=26; GA=57; AA=51	G=40.7%; A=59.3%
3771000	rs9903178	chr17:74235205	3.30E-04	SNIG	CC=20; CA=51; AA=62	C=34%; A=66%
3771000	rs9901220	chr17:74235428	3.30E-04	SNIG	AA=20; AG=51; GG=62	A=34; G=66%
3771002	rs12453974	chr17:73068382	1.20E-04	SNIG	AA=12; AG=40; GG=82	A=23.9%; G=76.1%
3771002	NA	chr17:73069185:T_TAC	2.40E-04	SNIG	NA	NA
3771002	rs13342015	chr17:73067482	3.00E-04	SNIG	AA=11; AG=41; GG=78	A=23.5%; G=76.5%
3771002	NA	chr17:73069183:T_TAC	5.50E-04	SNIG	NA	NA
3771003	NA	chr17:74336580:GT_G	2.20E-05	SNIG	NA	NA
3771005	rs4442849	chr17:74506729	9.60E-05	SNIG	AA=2; AG==36; GG=37	A=14.9%; G=85.1%
3771005	rs62086562	chr17:74494492	1.50E-04	SNIG	GG=29; GA=52; AA=46	G=41%; A=59%
3771005	rs4238992	chr17:74498585	2.30E-04	SNIG	CC=40; CT=58; TT=36	C=51.5%; T=48.5%
3771010	rs12450432	chr17:74692908	3.90E-04	SNIG	AA=2; AC=23; CC=109	A=10.1%; C=89.9%
3771010	rs59953252	chr17:74688824	3.90E-04	SNIG	GG=2; GT=23; TT=109	G=10.1%; T=89..9%
3771010	rs73357371	chr17:74689278	3.90E-04	SNIG	AA=2; AG=23; GG=109	A=10.1%; G=89.9%
3771010	rs73357369	chr17:74685836	4.00E-04	SNIG	AA=2; AC=23; CC=109	A=10.1%; C=89.9%
3771014	NA	chr17:74688299:AG_A	1.70E-04	SNIG	NA	NA

3771014	rs181899376	chr17:74624133	1.90E-04	SNIG	GG=1; GT=19; TT=111	G=7.8%; T=92.2%
3771023	rs9903414	chr17:72951845	3.20E-04	SNIG	GG=1; GA=14; AA=117	G=6%; A=94%
3771023	NA	chr17:72950951:CA_C	3.90E-04	SNIG	NA	NA
3771023	rs9897379	chr17:72950874	4.10E-04	SNIG	CC=1; CT=16; TT=117	C=6.7%; T=93.3%
3771023	rs9891655	chr17:72950826	4.60E-04	SNIG	CC=1; CT=16; TT=117	C=6.7%; T=93.3%
3771023	rs4789114	chr17:72950927	4.60E-04	SNIG	TT=1; TC=16; CC=117	T=6.7%; C=93.3%
3771023	rs9895930	chr17:72984778	5.00E-04	SNIG	AA=1; AT=18; YTT=113	A=7.5%; T=92.5%
t3770979	NA	chr17:73903481:AT_A	4.10E-04	TCTX	NA	NA
t3770979	rs73362233	chr17:73512386	4.20E-04	TCTX	TT=3; TC=38; CC=91	T=16.4%; C=83.6%
3770983	rs35103294	chr17:73810937	1.70E-04	TCTX	CC=9; CT=54; TT=68	C=26.9%; T=73.1%
3770983	rs11658385	chr17:73810400	1.70E-04	TCTX	CC=9; CT=54; TT=68	C=26.9%; T=73.1%
3770983	rs878371	chr17:73816844	1.80E-04	TCTX	GG=9; GA=56; AA=69	G=27.6%; A=72.4%
3770983	rs62088246	chr17:73807961	2.70E-04	TCTX	AA=18; AG=54; GG=20	A=33.6%; G=66.4%
3770983	rs35757209	chr17:73793504	3.20E-04	TCTX	TT=9; TC=50; CC=73	T=25.4%; C=74.6%
3770983	NA	chr17:73822597:G_GC	4.60E-04	TCTX	NA	NA
3770983	rs9900933	chr17:73801154	4.80E-04	TCTX	CC=7; CT=48; TT=72	C=23.1%; T=76.9%
3770992	rs12937813	chr17:74173135	3.90E-04	TCTX	CC=3; CT=19; TT=112	C=9.3%; T=90.7%
3770992	rs35964589	chr17:74173374	3.90E-04	TCTX	TT=3; TC=19; CC=112	T=9.3%; C=90.7%

3770992	rs36032105	chr17:74173394	3.90E-04	TCTX	GG=3; GC=19; CC=112	G=9.3%; C=90.7%
3770992	rs920713	chr17:74174885	3.90E-04	TCTX	CC=3; CG=19; GG=112	C=9.3%; G=90.7%
3770992	rs1868827	chr17:74175017	3.90E-04	TCTX	AA=3; AG=19; GG=112	A=.3%; G=90.7%
3770996	rs62088463	chr17:73514316	5.80E-05	TCTX	CC=4; CT=46; TT=84	C=20.1%; T=79.9%
3770996	rs62088464	chr17:73514607	5.80E-05	TCTX	GG=4; GA=46; AA=84	G=20.1%; A=79.9%
3770996	rs1133934	chr17:73518850	5.80E-05	TCTX	TT=4; TC=46; CC=84	T=20.1%; C=79.9%
3770996	rs62088469	chr17:73519589	5.80E-05	TCTX	CC=4; CT=46; TT=84	C=20.1%; T=79.9%
3770996	rs62088461	chr17:73512305	7.40E-05	TCTX	GG=6; GA=52; AA=75	G=23.9%; A=76.1%
3770996	rs62088462	chr17:73512354	7.50E-05	TCTX	CC=6; CA=52; AA=75	C=23.9%; A=76.1%
3771010	rs9367	chr17:73753661	1.10E-04	TCTX	CC=4; CT=35; TT=95	C=16%; T=84%
3771010	rs743554	chr17:73754248	3.80E-04	TCTX	AA=3; AG=27; GG=103	A=12.3%; G=87.7%
3771013	rs4789112	chr17:72943929	1.60E-05	TCTX	TT=40; TC=59; CC=35	T=51.9%; C=48.1%
3771013	rs8069015	chr17:72939663	5.60E-04	TCTX	GG=20; GA=65; AA=49	G=39.2%; A=60.8%
3771013	rs4789110	chr17:72939446	5.70E-04	TCTX	CC=20; CT=65; TT=49	C=39.2%; T=60.8%
3771013	rs11649883	chr17:72944972	6.90E-04	TCTX	AA=43; AG=58; GG=33	A=53.7%; G=46.3%
3771013	rs62086795	chr17:74757144	8.60E-04	TCTX	AA=0; AG=11; GG=119	A=4.1%; G=95.9%
3771034	rs12948967	chr17:74506719	7.10E-04	TCTX	AA=0; AG=13; GG=85	A=4.9%; G=95.1%

3770989	rs144094561	chr17:74345784	3.30E-05	THAL	AA=0; AG=18; GG=116	A=6.7%; G=93.3%
3770989	NA	chr17:74355252:A_AAA	3.70E-05	THAL	NA	NA
3770989	rs8069918	chr17:74374536	1.60E-04	THAL	AA=1; AC=21; CC=112	A=8.6%; C=91.4%
3770989	rs4789288	chr17:74373536	1.60E-04	THAL	TT=1; TA=21; AA=112	T=8.6%; A=91.4%
3770989	rs143928125	chr17:74372292	1.60E-04	THAL	GG=1; GA=21; AA=112	G=8.6%; A=91.4%
3771002	rs113698410	chr17:74320858	7.60E-04	THAL	AA=0; AG=11; GG=109	A=4.1%; G=95.9%
3771003	NA	chr17:74536335:G_GT	1.70E-04	THAL	NA	NA
3771003	rs71384112	chr17:74515080	1.90E-04	THAL	AA=1; AG=16; GG=108	A=6.7%; G=93.3%
3771012	NA	chr17:74489587:TG_T	1.60E-04	THAL	NA	NA
3771012	rs4611488	chr17:74499266	1.70E-04	THAL	TT=10; TG=39; GG=85	R=22%; G=78%
3771012	rs56339449	chr17:74493752	1.80E-04	THAL	TT=40; TC=59; CC=35	T=51.9%; C=48.1%
3771013	NA	chr17:74346291:CG_C	7.80E-04	THAL	NA	NA
3771013	rs60470662	chr17:74360311	9.00E-04	THAL	CC=1; CT=19; TT=114	C=7.8%; T=92.2%
3771013	rs58844327	chr17:74360550	9.00E-04	THAL	CC=1; VT=19; TT=114	C=7..8%; T=92.2%
t3770979	NA	chr17:74022795:GCCAG	4.10E-04	WHMT	NA	NA
3770982	rs113698410	chr17:74320858	1.40E-04	WHMT	AA=0; AG=11; GG=109	A=4.1%; G=95.9%
3770982	rs879108	chr17:74126805	2.10E-04	WHMT	CC=11; CG=44GG=76	C=24.6%; G=75.4%
3770982	rs62088258	chr17:73979075	2.60E-04	WHMT	AA=28; AG=62; GG=25	A=44%; G=56%

3770982	rs881564	chr17:74128844	2.70E-04	WHMT	AA=12; AG=46; GG=76	A=26.1%; G=73.9%
3770989	rs113698410	chr17:74320858	1.60E-04	WHMT	AA=0; AG=11; GG=109	A=4.1%; G=95.9%
3770991	rs9904658	chr17:74806163	2.20E-04	WHMT	GG=0; GA=13; AA=120	G=4.9%; A=95.1%
3770991	rs4789355	chr17:74807061	2.20E-04	WHMT	AA=0; AT=13; TT=120	A=4.9%; T=95.1%
3770991	NA	chr17:74806261:C_CT	2.20E-04	WHMT	NA	NA
3770991	NA	chr17:74813883:TTC_T	3.40E-04	WHMT	NA	NA
3770991	rs35719246	chr17:74805783	3.50E-04	WHMT	GG=4; GA=38; AA=87	G=17.2%; A=82.8%
3770991	NA	chr17:74820036:C_CT	3.50E-04	WHMT	NA	NA
3770991	rs11869340	chr17:74817711	3.90E-04	WHMT	CC=0; CT=13; TT=121	C=4.9%; T=95.1%
3770991	rs4605193	chr17:74797290	4.30E-04	WHMT	AA=0; AG=15; GG=118	A=5.6%; G=94.4%
3770991	rs8079262	chr17:74800132	4.40E-04	WHMT	TT=0; TC=15; CC=118	T=5.6%; C=94.4%
3770992	rs4412997	chr17:73125774	3.30E-05	WHMT	TT=1; TC=16; CC=117	T=6,7%; C=93.3%
3770992	rs111392577	chr17:73179611	7.10E-05	WHMT	TT=0; TC=15; CC=117	T=5.6%; C=94.4%
3770992	NA	chr17:73190040:T_TA	7.30E-05	WHMT	NA	NA
3770992	NA	chr17:73190039:T_TTA	7.30E-05	WHMT	NA	NA
3770992	rs80333846	chr17:73197028	9.00E-05	WHMT	TT=0; TC=14; CC=115	T=5.2%; C=94.8%
3771000	rs7212960	chr17:73417662	2.40E-04	WHMT	TT=2; TC=24; CC=97	T=10,4%; C=89.6%
3771003	rs113698410	chr17:74320858	4.30E-05	WHMT	AA=0; AG=11; GG=109	A=4.1%; G=95.9%
3771003	NA	chr17:74412117:ATG_A	2.10E-04	WHMT	NA	NA

3771013	rs820196	chr17:73627539	1.50E-04	WHMT	CC=6; CT=43; TT=80	C=20.5%; T=79.5%
3771018	rs17881630	chr17:74002655	8.70E-04	WHMT	AA=0; AG=27; GG=107	A=10.1%; G=89..9%
3771030	rs146556419	chr17:74024205	9.80E-05	WHMT	AA=0; AC=21; CC=110	A=7.8%; C=92.2%
3771030	rs78044548	chr17:74019680	1.20E-04	WHMT	TT=0; TC=22; CC=110	T=.2%; C=91.8%
3771030	rs1806914	chr17:74018640	1.30E-04	WHMT	GG=0; GC=23; CC=111	G=8.6%; C=91.4%
3771030	rs8071298	chr17:74014228	1.40E-04	WHMT	AA=0; AG=23; GG=111	A=8.6%; G=91.4%
3771030	rs117028962	chr17:73990066	1.40E-04	WHMT	TT=0; TA=23; AA=111	T=8.6%; A=91.4%
3771030	rs7220365	chr17:73987162	1.40E-04	WHMT	TT=0; TC=23; CC=111	T=8.6%; C=91.4%
3771030	rs138332531	chr17:73985203	1.50E-04	WHMT	TT=0; TC=23; CC=111	T=8.6%; C=91.4%
3771030	rs141099275	chr17:73984478	1.50E-04	WHMT	AA=0; AC=23; CC=111	A=8.6%; C=91.4%
3771030	NA	chr17:74022795:GCCAG	2.00E-04	WHMT	NA	NA

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 29: Brain quantitative gene expression analyses for *ANO8* gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
3854378	rs28510435	chr19:17756994	3.10E-04	aveALL	AA=9; AG=30; GG=93	A=17.9%; G=82.1%

3854384	NA	chr19:17694577:AACAG	9.20E-05	aveALL	NA	NA
3854385	rs971694	chr19:17422833	1.60E-05	aveALL	TT=2; TC=22; CC=110	T=9.7%; C=90.3%
3854385	rs7245725	chr19:17428176	2.40E-05	aveALL	CC=2; CG=22; GG=110	C=9.7%; G=90.3%
3854385	rs111707632	chr19:17284974	1.40E-04	aveALL	AA=1; AG=18; GG=115	A=7.5%; G=92.5%
3854387	NA	chr19:17512366:GGT_G	1.50E-04	aveALL	NA	NA
3854388	rs35098701	chr19:17757820	5.40E-07	aveALL	AA=16; AC=38; CC=32	A=26.1%; C=73.9%
3854388	rs34575473	chr19:17757702	5.50E-07	aveALL	GG=16; GC=38; CC=32	G=26.1%; C=73.9%
3854388	rs35696404	chr19:17756094	6.40E-07	aveALL	GG=1; GA=39; AA=31	G=25%; A=75%
3854388	rs28510435	chr19:17756994	1.90E-06	aveALL	AA=9; AG=30; GG=39	A=17.9%; G=82.1%
3854388	rs73009918	chr19:17757459	2.10E-06	aveALL	TT=10; TC=30; CC=93	T=19.7%; C=81.3%
3854388	rs4808089	chr19:17758554	2.40E-06	aveALL	AA=10; AT=31; TT=93	A=19%; T=81%
3854388	rs4808675	chr19:17758368	2.40E-06	aveALL	GG=10; GA=31; AA=93	G=19%; A=81%
3854396	rs11883013	chr19:16746005	2.90E-04	aveALL	TT=1; TC=18; CC=111	T=7.5%; C=92.5%
3854396	rs3786598	chr19:16729515	3.80E-04	aveALL	GG=1; GC=19; CC=113	G=7.8%; C=92.2%
3854396	rs56357407	chr19:16697906	4.60E-04	aveALL	AA=1; AG=20; GG=113	A=8.2%; G=91.8%
3854396	rs56200267	chr19:16723993	4.60E-04	aveALL	TT=1; TC=20; CC=113	T=8.2%; C=91.8%
3854396	rs7246513	chr19:16723583	4.60E-04	aveALL	GG=1; GA=20; AA=113	G=8.2%; A=91.8%

3854396	rs1020723	chr19:16727129	4.60E-04	aveALL	GG=1; GA=20; AA=113	G=8.2%; A=91.8%
3854396	rs7246160	chr19:16685120	4.70E-04	aveALL	GG=1; GC=20; CC=113	G=8.2%; C=91.8%
3854399	rs2241351	chr19:18433225	1.10E-04	aveALL	TT=1; TC=20; CC=108	T=8.2%; C=91.8%
3854399	rs62120446	chr19:18416399	2.30E-04	aveALL	AA=0; AG=13; GG=118	A=4.9%; G=95.1%
3854401	rs2303745	chr19:17420289	2.40E-04	aveALL	GG=3; GT=30; TT=100	G=13.4%; T=86.6%
3854401	rs12710307	chr19:17395720	5.70E-04	aveALL	GG=2; GA=28; AA=103	G=11.9%; A=88.1%
t3854376	rs12985511	chr19:17594473	2.10E-04	CRBL	GG=1; GA=27; AA=106	G=10.8%; A=89.2%
3854377	rs2110586	chr19:17957309	1.80E-05	CRBL	TT=4; TC=35; CC=95	T=16%; C=84%
3854378	rs11881707	chr19:17150993	3.10E-04	CRBL	TT=1; TG=15; GG=106	T=6.3%; G=93.7%
3854382	NA	chr19:16441799	1.40E-04	CRBL	NA	NA
3854382	NA	chr19:16441043	3.20E-04	CRBL	NA	NA
3854386	rs111774730	chr19:17585619	5.20E-04	CRBL	GG=11; GA=56; AA=63	G=29.1%; A=70.9%
3854396	rs58997823	chr19:18398720	3.50E-04	CRBL	GG=1; GA=24; AA=106	G=9.7%; A=990.3%
3854396	rs7256111	chr19:18394761	3.70E-04	CRBL	AA=19; AG=55; GG=53	A=34.7%; G=65.3%
3854402	rs11668584	chr19:17391787	3.30E-04	CRBL	GG=4; GA=42; AA=71	G=18.7%; A=81.3%
3854378	rs62120446	chr19:18416399	2.80E-04	FCTX	AA=0; AG=13; GG=118	A=4.9%; G=95.1%
3854379	rs57342349	chr19:18006792	8.70E-05	FCTX	GG=7; GA=32; AA=75	G=17.2%; A=82.8%
3854379	rs4808708	chr19:18001686	1.50E-04	FCTX	AA=11; AG=42; GG=80	A=23.9%; G=76.1%

3854379	rs75600833	chr19:18000641	2.00E-04	FCTX	AA=11; AG=42; GG=80	A=23.9%; G=76.1%
3854379	rs2159330	chr19:18012141	2.50E-04	FCTX	CC=1; CT=45; TT=72	C=25%; T=75%
3854379	rs4808712	chr19:18011924	2.50E-04	FCTX	CC=11; CT=45; TT=72	C=25%; T=75%
3854384	rs188309744	chr19:17124262	5.80E-06	FCTX	GG=0; GC=14; CC=85	G=5.2%; C=94.8%
3854384	rs192943660	chr19:17124263	5.80E-06	FCTX	GG=0; GA=16; AA=80	G=6%; A=94%
3854384	NA	chr19:17124793:CCTA_	2.80E-05	FCTX	NA	NA
3854384	rs62126009	chr19:17124587	4.10E-05	FCTX	CC=0; CT=19; TT=84	C=7.1%; T=92.9%
3854384	rs62126008	chr19:17124581	4.10E-05	FCTX	GG=0; GA=19; AA=84	G=7.1%; A=92.9%
3854384	rs62126007	chr19:17124372	4.20E-05	FCTX	CC=0; CT=19; TT=84	C=7.1%; T=92.9%
3854384	rs73018336	chr19:17124750	4.50E-05	FCTX	TT=0; TC=19; CC=84	T=7.1%; C=92.9%
3854384	rs6512124	chr19:16749445	5.70E-05	FCTX	TT=1; TC=8; CC=103	T=3.7%; C=96.3%
3854384	NA	chr19:17124850:T_TCT	5.90E-05	FCTX	NA	NA
3854396	rs8100862	chr19:17635484	1.20E-04	FCTX	AA=2; AG=28; GG=96	A=11.9%; G=88.1%
3854397	rs8100862	chr19:17635484	8.50E-06	FCTX	AA=2; AG=28; GG=96	A=11.9%; G=88.1%
3854397	rs7252312	chr19:17681997	3.00E-05	FCTX	TT=2; TC=37; CC=92	T=15.3%; C=84.7%
3854397	rs8100092	chr19:17692324	3.40E-05	FCTX	TT=1; TG=27; GG=102	T=10.8%; G=89.2%
3854397	rs3943858	chr19:17686781	3.40E-05	FCTX	AA=1; AG=29; GG=102	A=11.6%; G=88.4%
3854397	rs10412002	chr19:17665109	3.90E-05	FCTX	CC=1; CT=30; TT=103	C=11.9%; T=88.1%

3854397	rs6512203	chr19:17682142	4.00E-05	FCTX	TT=1; TC=30; CC=102	T=11.9%; C=88.1%
3854397	rs4808665	chr19:17658722	4.10E-05	FCTX	AA=1; AC=30; CC=102	A=11.9%; C=88.1%
3854397	rs6512202	chr19:17676804	4.10E-05	FCTX	CC=1; CT=30; TT=102	C=11.9%; T=88.1%
3854397	rs4524058	chr19:17675726	4.30E-05	FCTX	TT=1; TC=30; CC=102	T=11.9%; C=88.1%
3854401	NA	chr19:18435661:ATG_A	1.50E-04	FCTX	NA	NA
3854402	rs11672396	chr19:16718713	1.80E-04	FCTX	GG=0; GA=23; AA=111	G=8.6%; A=91.4%
3854402	rs73006531	chr19:16710008	2.20E-04	FCTX	TT=0; TC=23; CC=111	T=8.6%; C=91.4%
3854406	rs12462622	chr19:17927285	1.80E-05	FCTX	GG=2; GT=12; TT=120	G=6%; T=94%
3854406	NA	chr19:17934899:CT_C	2.10E-05	FCTX	NA	NA
3854406	rs12463004	chr19:17932897	2.20E-05	FCTX	AA=2; AG=11; GG=121	A=5.6%; G=94.4%
3854406	rs2286663	chr19:17932289	2.20E-05	FCTX	TT=2; TC=11; CC=121	T=5.6%; C=94.4%
3854406	rs8107831	chr19:17931350	2.30E-05	FCTX	TT=2; TC=11; CC=121	T=5.6%; C=94.4%
3854406	rs28403613	chr19:17923738	2.60E-05	FCTX	TT=4; TC=25; CC=95	T=12.3%; C=87.7%
3854406	rs1006853	chr19:17921888	2.60E-05	FCTX	TT=5; TC=32; CC=96	T=15.7%; C=84.3%
3854406	rs10401372	chr19:17921097	2.70E-05	FCTX	TT=5; TC=32; CC=96	T=15.7%; C=84.3%
3854406	rs2240813	chr19:17919024	4.80E-05	FCTX	TT=3; TA=15; AA=116	T=7.8%; A=92.2%
3854406	rs12461460	chr19:17932855	6.30E-05	FCTX	GG=2; GT=11; TT=120	G=5.6%; T=94.4%

3854409	rs56200267	chr19:16723993	2.50E-05	FCTX	TT=1; TC=20; CC=113	T=8.2%; C=91.8%
3854409	rs1020723	chr19:16727129	2.50E-05	FCTX	GG=1; GA=20; AA=113	G=8.2%; A=91.8%
3854409	rs7246513	chr19:16723583	2.50E-05	FCTX	GG=1; GA=20; AA=113	G=8.2%; A=91.8%
3854409	rs56357407	chr19:16697906	2.50E-05	FCTX	AA=1; AG=20; GG=113	A=8.2%; G=91.8%
3854409	rs56003264	chr19:16670075	2.50E-05	FCTX	TT=1; TC=20; CC=112	A=8.2%; G=91.8%
3854409	rs114584410	chr19:16671545	2.50E-05	FCTX	TT=1; TC=20; CC=112	A=8.2%; G=91.8%
3854409	rs8104501	chr19:16672410	2.50E-05	FCTX	CC=1; CT=20; TT=112	C=8.2%; T=91.8%
3854409	rs62116871	chr19:16682261	2.50E-05	FCTX	AA=1; AG=20; GG=113	A=8.2%; G=91.8%
3854409	rs10409339	chr19:16655808	2.50E-05	FCTX	TT=1; TC=21; CC=112	T=8.6%; C=91.4%
t3854376	rs4549004	chr19:17756029	2.60E-05	HIPP	AA=1; AG=21; GG=64	A=8.6%; G=91.4%
t3854376	rs4541187	chr19:17756179	3.80E-05	HIPP	CC=1; CT=23; TT=62	C=9.3%; T=90.7%
3854378	rs113502859	chr19:18019349	2.10E-04	HIPP	AA=1; AG=11; GG=119	A=4.9%; G=95.1%
3854378	rs4808102	chr19:18020685	2.70E-04	HIPP	GG=2; GA=10; AA=119	G=5.2%; A=94.8%
3854379	rs3212770	chr19:17944900	4.30E-05	HIPP	TT=2; TA=31; AA=54	T=13.1%; A=86.9%
3854379	rs2302601	chr19:17941173	1.10E-04	HIPP	GG=2; GC=35; CC=52	G=14.6%; C=85.4%
3854379	rs2302600	chr19:17941143	1.10E-04	HIPP	CC=2; CA=35; AA=52	C=14.6%; A=85.4%
3854379	rs2302603	chr19:17941294	2.40E-04	HIPP	CC=3; CT=39; TT=41	C=16.8%; T=83.2%

3854386	NA	chr19:17519240:T_TTT	4.40E-04	HIPP	NA	NA
3854400	rs62126776	chr19:17581948	6.30E-05	HIPP	TT=1; TC=15; CC=102	T=6.3%; C=93.7%
3854400	NA	chr19:16437048	1.30E-04	HIPP	NA	NA
3854400	rs55714539	chr19:18207397	2.30E-04	HIPP	CC=12; CA=53; AA=55	C=28.7%; A=71.3%
3854400	NA	chr19:16434454	2.40E-04	HIPP	NA	NA
3854408	rs6512254	chr19:18381328	3.30E-07	HIPP	GG=5; GT=55; TT=72	G=24.3%; T=75.7%
3854408	rs2080831	chr19:18409268	1.40E-05	HIPP	TT=6; TG=51; GG=11	T=23.5%; G=76.5%
3854408	rs41446250	chr19:18390253	3.70E-05	HIPP	AA=2; AG=25; GG=107	A=10.8%; G=89.2%
3854408	rs4549004	chr19:17756029	5.10E-05	HIPP	AA=1; AG=21; GG=64	A=8.6%; G=91.4%
3854408	rs60235938	chr19:18396394	6.10E-05	HIPP	AA=2; AG=24; GG=108	A=10.4%; G=89.6%
3854408	rs113451170	chr19:18397062	6.10E-05	HIPP	CC=2; CT=24; TT=108	C=10.4%; T=89.6%
3854408	rs4541187	chr19:17756179	6.20E-05	HIPP	CC=1; CT=23; TT=62	C=9.3%; T=90.7%
3854408	rs58997823	chr19:18398720	8.60E-05	HIPP	GG=1; GA=24; AA=106	G=9.7%; A=90.3%
3854408	rs56069717	chr19:18383482	9.20E-05	HIPP	GG=2; GA=26; AA=105	G=11.2%; A=88.8%
3854408	rs16982288	chr19:18383293	1.10E-04	HIPP	CC=2; CG=27; GG=105	C=11.6%; A=88.4%
3854382	NA	chr19:16539355:AC_A	1.10E-04	MEDU	NA	NA
3854382	NA	chr19:16511170:A_AC	3.30E-04	MEDU	NA	NA
3854388	NA	chr19:18132350:A_AC	1.70E-05	MEDU	NA	NA
3854388	rs408484	chr19:18139771	2.50E-05	MEDU	TT=2; TC=31; CC=101	T=13.1%; C=86.9%

3854388	rs403439	chr19:18142075	2.60E-05	MEDU	AA=2; AG=31; GG=101	A=13.1%; G=86.9%
3854410	rs34752754	chr19:17766900	5.30E-05	MEDU	TT=24; TC=46; CC=46	T=41.8%; C=58.2%
t3854376	rs1870063	chr19:18170962	2.50E-04	OCTX	TT=12; TC=75; CC=47	T=36.9%; C=63.1%
3854378	NA	chr19:18174944:C_CTT	2.90E-04	OCTX	NA	NA
3854382	rs56984217	chr19:18327342	2.40E-04	OCTX	TT=0; TC=16; CC=118	T=6%; C=94%
3854382	rs2238646	chr19:18338101	2.40E-04	OCTX	AA=0; AG=16; GG=118	A=6%; G=94%
3854382	rs62119935	chr19:17707484	3.30E-04	OCTX	GG=4; GA=32; AA=57	G=14.9%; A=85.1%
3854398	rs17488936	chr19:16800133	1.80E-05	OCTX	TT=0; TC=22; CC=112	T=8.2%; C=91.8%
3854398	rs56003264	chr19:16670075	4.20E-05	OCTX	TT=1; TC=20; CC=112	T=8.2%; C=91.8%
3854398	rs114584410	chr19:16671545	4.20E-05	OCTX	TT=1; TC=20; CC=112	T=8.2%; C=91.8%
3854398	rs8104501	chr19:16672410	4.30E-05	OCTX	CC=1; CT=20; TT=112	C=8.2%; T=91.8%
3854398	rs55651939	chr19:16661552	4.30E-05	OCTX	TT=1; TC=20; CC=112	T=8.2%; C=91.8%
3854398	rs1559202	chr19:16674946	4.40E-05	OCTX	TT=1; TC=20; CC=112	T=8.2%; C=91.8%
3854398	rs1559201	chr19:16677289	4.50E-05	OCTX	AA=1;AC=20; CC=112	A=8.2%; C=91.8%
3854398	rs11883013	chr19:16746005	4.60E-05	OCTX	TT=1; TC=18; CC=111	T=7.5%; C=92.5%
3854398	rs56357407	chr19:16697906	4.60E-05	OCTX	AA=1;AG=20; GG=112	A=8.2%; G=91.8%
3854398	rs73023075	chr19:16656077	4.60E-05	OCTX	AA=1;AG=20; GG=112	A=8.2%; G=91.8%

3854399	rs6512146	chr19:17058813	4.50E-04	OCTX	TT=0; TC=27; CC=102	T=10.1%; C=89.9%
3854402	rs150178587	chr19:18105583	1.50E-04	OCTX	AA=0; AC=8; CC=115	A=3%; C=97%
3854403	NA	chr19:17726782:A_AAA	8.80E-05	OCTX	NA	NA
3854403	rs1316668	chr19:17730057	9.20E-05	OCTX	GG=20; GA=56; AA=47	G=35.8%; A=64.2%
3854403	rs2287851	chr19:17728502	1.20E-04	OCTX	CC=28; CT=61; TT=45	C=43.7%; T=56.3%
3854403	rs954374	chr19:17730166	1.30E-04	OCTX	CC=28; CT=61; TT=45	C=43.7%; T=56.3%
3854403	NA	chr19:17730243:TTTTC	1.30E-04	OCTX	NA	NA
3854403	NA	chr19:17730244:TTTC_	1.30E-04	OCTX	NA	NA
3854403	rs4255897	chr19:17731145	1.30E-04	OCTX	TT=27; TA=60; AA=45	T=42.5%; A=57.5%
3854403	rs56388321	chr19:17738850	1.30E-04	OCTX	TT=27; TC=61; CC=44	T=42.9%; C=57.1%
3854403	rs56359881	chr19:17730281	1.60E-04	OCTX	CC=19; CG=58; GG=56	C=35.8%; G=64.1%
3854407	rs186666936	chr19:17658320	2.60E-05	OCTX	GG=9; GC=43; CC=80	G=22.8%; C=77.2%
3854407	rs2082001	chr19:17668453	3.00E-05	OCTX	TT=9; TC=45; CC=80	T=23.5%; C=76.5%
3854407	rs34631213	chr19:17664418	3.00E-05	OCTX	AA=9; AG=45; GG=80	A=23.5%; G=76.5%
3854407	rs112012703	chr19:17658095	5.30E-05	OCTX	AA=8; AG=43; GG=7	A=22%; G=78%
3854382	rs4808069	chr19:17138985	1.10E-04	PUTM	TT=8; TC=56; CC=21	T=34.3%; C=65.7%
3854382	rs188309744	chr19:17124262	3.10E-04	PUTM	GG=0; GC=14; CC=85	G=5.2%; C=94.8%
3854402	rs11665838	chr19:17760232	4.00E-05	PUTM	TT=6; TC=36; CC=45	T=17.9%; C=82.1%

3854402	rs10409857	chr19:17694268	3.00E-04	PUTM	CC=1; CA=27; AA=81	C=10.8%; A=89.2%
3854410	rs12985340	chr19:17140541	3.00E-05	PUTM	AA=4; AG=42; GG=88	A=18.7%; G=81.3%
3854410	rs34465381	chr19:17145272	3.10E-05	PUTM	GG=3; GA=39; AA=92	G=16.8%; A=83.2%
3854410	NA	chr19:17143752:T_TTC	3.20E-05	PUTM	NA	NA
3854410	rs12982156	chr19:17144109	3.40E-05	PUTM	AA=4; AG=42; GG=88	A=18.7%; G=81.3%
3854410	rs12972373	chr19:17142617	3.40E-05	PUTM	CC=4; CG=42; GG=88	C=18.7%; G=81.3%
3854410	rs873513	chr19:17148156	4.10E-05	PUTM	AA=3; AG=41; GG=90	A=17.5%; G=82.5%
3854410	rs1079180	chr19:17149468	4.10E-05	PUTM	AA=3; AG=41; GG=90	A=17.5%; G=82.5%
3854410	rs11672734	chr19:17139700	4.40E-05	PUTM	GG=3; GC=41; CC=90	G=17.5%; C=82.5%
3854377	rs62121690	chr19:17761454	2.50E-04	SNIG	TT=24; TG=56; GG=41	T=38.8%; G=61.2%
3854377	rs11671424	chr19:17762174	3.00E-04	SNIG	AA=25; AC=57; CC=41	A=39.9%; C=60.1%
3854377	rs112914764	chr19:18299419	3.00E-04	SNIG	TT=11; TC=47; CC=43	T=25.7%; C=74.3%
3854377	NA	chr19:17762059:A_AT	3.10E-04	SNIG	NA	NA
3854377	rs11671377	chr19:17761998	3.40E-04	SNIG	AA=25; AC=57; CC=41	A=39.9%; C=60.1%
3854377	rs11672316	chr19:17762326	3.40E-04	SNIG	AA=25; AC=57; CC=41	A=39.9%; C=60.1%
3854377	rs35696404	chr19:17756094	3.90E-04	SNIG	GG=14; GA=39; AA=41	G=25%; A=75%
3854377	rs34575473	chr19:17757702	3.90E-04	SNIG	GG=16; GC=38; CC=32	G=26.1%; C=73.9%
3854377	rs35098701	chr19:17757820	3.90E-04	SNIG	AA=16AC=38; CC=32	A=26.1%; C=73.9%

3854385	rs11672428	chr19:17992385	1.20E-04	SNIG	CC=0; CT=7; TT=119	C=2.6%; T=97.4%
3854386	rs2608726	chr19:16912673	1.60E-04	SNIG	TT=14; TA=50; AA=50	T=29.1%; A=70.9%
3854386	rs113698848	chr19:18166899	2.50E-04	SNIG	TT=0; TC=10; CC=101	T=3.7%; C=96.3%
3854386	rs8101228	chr19:16842526	3.80E-04	SNIG	TT=72; TC=66; CC=40	T=41%; C=59%
3854386	rs8111063	chr19:16842565	4.40E-04	SNIG	GG=22; GA=66; AA=35	G=41%; A=59%
3854386	rs8101256	chr19:16842578	4.70E-04	SNIG	TT=22; TG=69; GG=40	T=42.2%; G=57.8%
3854386	rs8112025	chr19:16842665	4.90E-04	SNIG	CC=22; CT=69; TT=40	C=42.2%; T=57.8%
3854386	rs8112102	chr19:16842379	4.90E-04	SNIG	AA=22; AG=69; GG=40	A=42.2%; G=57.8%
3854386	rs8101218	chr19:16842500	5.10E-04	SNIG	TT=22; TC=69; CC=40	T=42.2%; C=57.8%
3854387	rs12986030	chr19:18089981	1.30E-04	SNIG	TT=1; TG=31; GG=102	T=12.3%; G=87.7%
3854387	rs11666940	chr19:18083209	1.30E-04	SNIG	CC=1; CA=31; AA=102	C=12.3%; A=87.7%
3854387	rs4808108	chr19:18083836	1.30E-04	SNIG	CC=1; CT=31; TT=102	C=12.3%; T=87.7%
3854387	rs12974434	chr19:18077413	1.40E-04	SNIG	AA=1; AC=31; CC=102	A=12.3%; C=87.7%
3854387	NA	chr19:18095838:CTG_C	1.40E-04	SNIG	NA	NA
3854400	NA	chr19:18378761:CCTGG	2.70E-04	SNIG	NA	NA
3854401	rs1812654	chr19:17345035	1.60E-04	SNIG	CC=2; CA=27; AA=85	C=11.6%; A=88.4%
3854410	NA	chr19:17554089:C_CA	3.70E-06	SNIG	NA	NA
3854378	rs28510435	chr19:17756994	1.70E-05	TCTX	AA=9; AG=30; GG=93	A=17.9%; G=82.1%

3854378	rs73009918	chr19:17757459	3.00E-05	TCTX	TT=10; TC=30; CC=93	T=18.7%; C=81.3%
3854378	rs4808089	chr19:17758554	3.70E-05	TCTX	AA=10; AT=31; TT=93	A=19%; T=81%
3854378	rs4808675	chr19:17758368	3.80E-05	TCTX	GG=10; GA=31; AA=93	G=19%; A=81%
3854379	rs12984063	chr19:17481986	2.50E-04	TCTX	AA=2; AT=40; TT=52	A=16.4%; T=83.6%
3854387	rs58025295	chr19:16755441	1.10E-04	TCTX	AA=2; AG=31; GG=101	A=13.1%; G=86.9%
3854387	rs17796739	chr19:16751240	1.30E-04	TCTX	TT=2; TC=31; CC=101	T=13.1%; C=86.9%
3854387	rs10425960	chr19:16751741	1.80E-04	TCTX	AA=3; AG=32; GG=99	A=14.2%; G=85.8%
3854399	NA	chr19:18245027:T_TA	1.60E-04	TCTX	NA	NA
3854400	rs11670033	chr19:16843687	1.30E-04	TCTX	GG=14; GC=62; CC=55	G=33.6%; C=66.4%
3854400	rs8111579	chr19:16842262	2.20E-04	TCTX	CC=23; CT=66; TT=32	C=41.8%; T=58.2%
3854400	rs8101228	chr19:16842526	2.30E-04	TCTX	TT=22; TC=66; CC=40	T=41%; C=59%
3854407	rs1870066	chr19:17105195	2.00E-04	TCTX	GG=21; GC=62; CC=52	G=38.8%; C=61.2%
3854407	rs3745337	chr19:17107825	2.00E-04	TCTX	AA=21; AG=62; GG=51	A=38.8%; G=61.2%
3854407	rs3745340	chr19:17108135	2.00E-04	TCTX	TT=21; TC=62; CC=51	T=38.8%; C=61.2%
3854407	rs60362353	chr19:17109403	2.00E-04	TCTX	AA=21; AG=62; GG=51	A=38.8%; G=61.2%
3854407	rs78077033	chr19:17141245	2.50E-04	TCTX	CC=0; CT=27; TT=83	C=10.1%; T=89.9%
3854409	rs149081991	chr19:18280096	2.30E-05	TCTX	AA=1; AG=15; GG=110	A=6.3%; G=93.7%

t3854376	NA	chr19:18435661:ATG_A	3.90E-05	THAL	NA	NA
t3854376	rs74180875	chr19:18429780	1.00E-04	THAL	TT=2; TC=24; CC=102	T=10.4%; C=89.6%
3854382	rs2303745	chr19:17420289	1.90E-04	THAL	GG=3; GT=30; TT=100	G=13.4%; T=86.6%
3854385	rs7245725	chr19:17428176	6.50E-05	THAL	CC=2; CG=22; GG=110	C=9.7%; G=90.3%
3854385	rs971694	chr19:17422833	7.20E-05	THAL	TT=2; TC=22; CC=110	T=9.7%; C=90.3%
3854399	rs113835732	chr19:17773722	3.40E-04	THAL	TT=0; TC=27; CC=102	T=10.1%; C=89.9%
3854399	rs73009964	chr19:17773246	4.20E-04	THAL	CC=1; CG=32; GG=101	C=12.7%; G=87.3%
3854399	rs16981898	chr19:17765746	4.60E-04	THAL	CC=1; CT=32; TT=101	C=12.7%; T=87.3%
3854399	rs73009941	chr19:17765408	4.60E-04	THAL	AA=1; AG=31; GG=101	A=12.3%; G=87.7%
3854399	rs73009945	chr19:17765702	4.70E-04	THAL	AA=1; AG=31; GG=101	A=12.3%; G=87.7%
3854401	rs74180875	chr19:18429780	3.40E-04	THAL	TT=2; TC=24; CC=102	T=10.4%; C=89.6%
3854401	NA	chr19:17150380:C_CG	4.60E-04	THAL	NA	NA
3854403	rs117871617	chr19:18280502	1.20E-04	THAL	AA=1; AG=8; GG=110	A=3.7%; G=96.3%
t3854376	rs55881864	chr19:18206317	2.90E-05	WHMT	TT=2; TG=39; GG=93	T=16%; G=84%
t3854376	rs12459398	chr19:17366313	5.10E-05	WHMT	TT=6; TC=50; CC=76	T=23.1%; C=76.9%
t3854376	rs9676419	chr19:17367435	1.10E-04	WHMT	CC=7; CT=49; TT=78	C=23.5%; T=76.5%
t3854376	rs112914764	chr19:18299419	1.40E-04	WHMT	TT=11; TC=47; CC=43	T=25.7%; C=74.3%

3854385	rs62126225	chr19:17356976	5.70E-05	WHMT	GG=24; GA=54; AA=52	G=38.1%; A=61.9%
3854385	rs3826729	chr19:17358133	9.70E-05	WHMT	AA=25; AG=58; GG=51	A=40.3%; G=59.7%
3854385	rs7254318	chr19:17357466	1.00E-04	WHMT	AA=25; AG=58; GG=51	A=40.3%; G=59.7%
3854385	rs11086062	chr19:17360231	1.50E-04	WHMT	GG=21; GA=62; AA=48	G=38.8%; A=61.2%
3854387	NA	chr19:17263975:G_GGT	1.70E-04	WHMT	NA	NA
3854395	rs12972955	chr19:17856138	2.70E-04	WHMT	AA=10; AG=54; GG=68	A=27.6%; G=72.4%
3854395	rs1433127	chr19:18044600	2.80E-04	WHMT	GG=18; GA=59; AA=57	G=35.4%; A=64.6%
3854395	rs12985015	chr19:17827257	2.90E-04	WHMT	AA=10; AG=55; GG=69	A=18%; G=72%
3854395	rs34119888	chr19:17839305	2.90E-04	WHMT	CC=10; CA=55; AA=69	C=28%; A=72%
3854395	rs35396652	chr19:17828600	2.90E-04	WHMT	CC=10; CA=55; AA=69	C=28%; A=72%
3854395	rs67012434	chr19:17829139	3.00E-04	WHMT	CC=10; CT=55; TT=69	C=28%; T=72%
3854395	rs34578486	chr19:17854586	3.00E-04	WHMT	TT=10; TC=55; CC=69	T=28%; C=72%
3854395	rs67586619	chr19:17849276	3.10E-04	WHMT	AA=10;AG=55; GG=69	A=28%; G=72%
3854395	rs12973232	chr19:17847768	3.10E-04	WHMT	GG=10; GT=55; TT=69	G=28%; T=72%
3854395	rs12980192	chr19:17861506	3.10E-04	WHMT	GG=10; GA=55; AA=69	G=28%; A=72%
3854397	NA	chr19:17932710:T_TTT	4.50E-05	WHMT	NA	NA
3854399	rs11881197	chr19:17498931	6.40E-05	WHMT	AA=0; AG=16; GG=115	A=6%; G=94%
3854400	NA	chr19:16442612	7.30E-05	WHMT	NA	NA

3854400	NA	chr19:16438428:G_GC	7.60E-05	WHMT	NA	NA
3854401	rs10415119	chr19:17339225	1.70E-04	WHMT	TT=21; TC=62; CC=43	T=38.8%; C=61.2%
3854401	rs2303745	chr19:17420289	2.40E-04	WHMT	GG=3; GT=30; TT=100	G=13.4%; T=86.6%
3854401	rs12710307	chr19:17395720	4.40E-04	WHMT	GG=2; GA=28; AA=103	G=11.9%; A=88.1%
3854401	rs10409801	chr19:17407415	4.60E-04	WHMT	AA=2; AG=28; GG=104+F191	A=11.9%; G=88.1%
3854402	rs12462895	chr19:18148982	2.60E-05	WHMT	AA=16; AG=45; GG=30	A=28.7%; G=71.3%
3854402	rs76744457	chr19:18268174	8.90E-05	WHMT	TT=1; TC=13; CC=120	T=5.6%; C=94.4%
3854402	rs143492548	chr19:18291082	1.70E-04	WHMT	AA=1; AG=14; GG=119	A=6%; G=94%
3854402	rs112461998	chr19:18153462	2.60E-04	WHMT	CC=10; CT=41; TT=62	C=22.8%; T=77.2%
3854407	rs111366154	chr19:17309577	1.20E-05	WHMT	TT=0; TC=13; CC=116	T=4.9%; C=95.1%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 30 Brain quantitative gene expression analyses for *HOMER3* gene variants.

Expr ID	**rsID**	**Variant**	***P*-value**	**tissue**	**Genotype_counts**	**Allele_frequency**
t3855358	rs8106607	chr19:19863340	2.10E-04	aveALL	CC=0; CG=15; GG=118	C=5.6%; G=94.4%
t3855358	rs73541375	chr19:19864991	3.30E-04	aveALL	GG=0; GA=15; AA=118	G=5.6%; A=94.4%
t3855358	rs10425230	chr19:19861682	3.40E-04	aveALL	TT=0; TC=16; CC=118	T=6%; C=94%

t3855358	rs7259104	chr19:19861402	3.40E-04	aveALL	GG=0; GA=16; AA=118	G=6%; A=94%
t3855358	rs10418343	chr19:19860846	3.40E-04	aveALL	GG=0; GC=16; CC=118	G=6%; C=94%
t3855358	rs8103257	chr19:19862970	3.70E-04	aveALL	CC=0; CG=16; GG=118	C=6%; G=94%
3855362	rs6512245	chr19:18204207	3.20E-04	aveALL	TT=2; TA=17; AA=115	T=7.8%; A=92.2%
3855362	rs62121129	chr19:18189353	4.20E-04	aveALL	CC=2; CT=18; TT=114	C=8.2%; T=91.8%
3855363	rs76744457	chr19:18268174	4.80E-04	aveALL	TT=1; TC=13; CC=120	T=5.6%; C=94.4%
3855364	rs3746184	chr19:18474587	4.00E-04	aveALL	AA=12; AT=67; TT=55	A=34%; T=66%
3855366	rs76744457	chr19:18268174	2.80E-04	aveALL	TT=1; TC=13; CC=120	T=5.6%; C=94.4%
3855373	rs1064351	chr19:19049198	2.50E-07	aveALL	AA=26; AG=65; GG=43	A=43.7%; G=56.3%
3855373	rs10407590	chr19:19047657	6.10E-07	aveALL	CC=25; CA=65; AA=37	C=42.9%; A=57.1%
3855373	rs62138076	chr19:19039908	7.40E-07	aveALL	AA=25; AG=68; GG=37	A=44%; G=56%
3855373	rs10410004	chr19:19042608	7.70E-07	aveALL	TT=25; TC=70; CC=38	T=44.8%; C=55.2%
3855373	rs62138079	chr19:19048025	8.00E-07	aveALL	CC=26; CT=66; TT=37	C=44%; T=56%
3855373	rs28714268	chr19:19041490	9.30E-07	aveALL	CC=25; CT=69; TT=38;	C=44.4%; T=55.6%
3855373	rs2301662	chr19:19037294	9.50E-07	aveALL	AA=26; AG=69; GG=38	A=45.1%; G=54.9%
3855373	rs2003449	chr19:19037685	9.50E-07	aveALL	GG=26; GC=69; CC=38	G=45.1%; C=54.9%
3855373	rs2301661	chr19:19037053	1.30E-06	aveALL	CC=27; CT=69; TT=38	C=45.9%; T=54.1%

3855373	rs7497	chr19:19039298	1.30E-06	aveALL	CC=27; CT=69; TT=38	C=45.9%; T=54.1%
3855375	rs112279424	chr19:19041023	2.20E-07	aveALL	TT=2; TC=32; CC=91	T=13.4%; C=86.6%
3855375	rs56245612	chr19:19048933	1.30E-06	aveALL	AA=2; AG=28; GG=103	A=11.9%; G=88.1%
3855375	rs117094514	chr19:19048060	1.30E-06	aveALL	TT=2; TC=29; CC=103	T=12.3%; C=87.7%
3855375	rs1064351	chr19:19049198	1.30E-06	aveALL	AA=26; AG=65; GG=43	A=43.7%; G=56.3%
3855375	rs16995785	chr19:19039698	1.50E-06	aveALL	CC=2; CG=29; GG=103	C=12.3%; G=87.7%
3855375	rs111304645	chr19:19036110	2.10E-06	aveALL	GG=2; GA=28; AA=100	G=11.9%; A=88.1%
3855375	rs111790312	chr19:19047895	4.90E-06	aveALL	AA=0; AG=6; GG=111	A=2.2%; G=97.8%
3855375	rs10407590	chr19:19047657	9.70E-06	aveALL	CC=25; CA=65; AA=37	C=42.9%; A=57.1%
3855375	rs62138079	chr19:19048025	1.10E-05	aveALL	CC=26; CT=66; TT=37	C=44%; T=56%
3855375	rs10410004	chr19:19042608	1.40E-05	aveALL	TT=25; TC=70; CC=38	T=44.8%; C=55.2%
3855380	rs1985976	chr19:18273539	4.40E-04	aveALL	TT=0; TA=17; AA=76	T=6.3%; A=93.7%
3855380	rs12974657	chr19:18237571	1.90E-04	CRBL	CC=10; CT=58; TT=62	C=29.1%; T=70.9%
3855380	rs4808749	chr19:18238473	2.40E-04	CRBL	GG=10; GA=59; AA=65	G=29.5%; A=70.5%
3855380	rs4808748	chr19:18238035	2.50E-04	CRBL	GG=10; GA=59; AA=65	G=29.5%; A=70.5%
3855380	rs1811241	chr19:18235882	2.70E-04	CRBL	AA=10; AG=58; GG=65	A=29.1%; G=70.9%
3855380	NA	chr19:18179832:TTA_T	3.90E-04	CRBL	NA	NA

3855380	rs7250425	chr19:18201757	4.00E-04	CRBL	CC=35; CT=63; TT=36	C=49.6%; T=50.4%
3855359	rs897751	chr19:18193349	8.80E-04	FCTX	GG=27; GA=70; AA=36	G=46.3%; A=53.7%
3855360	rs10418343	chr19:19860846	7.10E-06	FCTX	GG=0; GC=16; CC=118	G=6%; C=94%
3855360	rs7259104	chr19:19861402	7.10E-06	FCTX	GG=0; GA=16; AA=118	G=6%; A=94%
3855360	rs10425230	chr19:19861682	7.10E-06	FCTX	TT=0; TC=16; CC=118	T=6%; C=94%
3855360	rs8103257	chr19:19862970	7.20E-06	FCTX	CC=0; CG=16; GG=118	C=6%; G=94%
3855360	rs73541375	chr19:19864991	8.10E-06	FCTX	GG=0; GA=15; AA=118	G=5.6%; A=94.4%
3855360	rs8106607	chr19:19863340	3.10E-05	FCTX	CC=0; CG=15; GG=118	C=5.6%; G=94.4%
3855362	rs56687216	chr19:19048901	7.00E-05	FCTX	CC=5; CT=39; TT=86	C=18.3%; T=81.7%
3855362	rs2271883	chr19:18314917	7.10E-04	FCTX	GG=6; GT=61; TT=67	G=27.2%; T=72.8%
3855362	rs2280344	chr19:18315283	7.10E-04	FCTX	GG=6; GC=61; CC=67	G=27.2%; C=72.8%
3855362	rs2049051	chr19:18315831	7.10E-04	FCTX	GG=6; GA=61; AA=67	G=27.2%; A=72.8%
3855362	rs7259012	chr19:18321273	7.10E-04	FCTX	AA=6; AG=61; GG=67	A=27.2%; G=72.8%
3855362	NA	chr19:18320508:TTC_T	7.40E-04	FCTX	NA	NA
3855363	NA	chr19:19914514:AT_A	5.30E-04	FCTX	NA	NA
3855364	rs11673466	chr19:18401142	2.30E-04	FCTX	CC=0; CA=26; AA=108	C=9.7%; A=90.3%
3855364	rs11668229	chr19:18387220	2.30E-04	FCTX	AA=0; AC=25; CC=108	A=9.3%; C=90.7%

3855366	rs76744457	chr19:18268174	1.20E-04	FCTX	TT=1; TC=13; CC=120	T=5.6%; C=94.4%
3855366	rs143492548	chr19:18291082	1.30E-04	FCTX	AA=1; AG=14; GG=119	A=6%; G=94%
3855366	rs1985976	chr19:18273539	1.80E-04	FCTX	TT=0; TA=17; AA=76	T=6.3%; A=93.7%
3855366	rs16995485	chr19:18310678	2.90E-04	FCTX	CC=2; CG=16; GG=116	C=7.5%; G=92.5%
3855367	rs4808950	chr19:19518889	1.00E-04	FCTX	GG=2; GA=40; AA=91	G=16.4%; A=83.6%
3855367	rs11669516	chr19:19532682	1.00E-04	FCTX	AA=2.AG=41; GG=91	A=16.8%; G=83.2%
3855367	rs34647936	chr19:19548239	1.10E-04	FCTX	GG=2; GT=40; TT=91	G=16.4%; T=83.6%
3855367	rs12973258	chr19:19488718	1.20E-04	FCTX	CC=2; CT=40; TT=92	C=16.4%; T=83.6%
3855367	rs12983940	chr19:19516431	1.50E-04	FCTX	AA=2; AG=39; GG=91	A=16%; G=84%
3855367	rs11668386	chr19:19531910	2.50E-04	FCTX	GG=0; GA=31; AA=103	G=11.6%; A=88.4%
3855367	rs79954596	chr19:19548643	2.50E-04	FCTX	GG=0; GT=30; TT=103	G=11.2%; T=88.8%
3855367	rs10424702	chr19:19508013	2.50E-04	FCTX	GG=0; GA=30; AA=103	G=11.2%; A=88.8%
3855367	NA	chr19:19560756:TATCT	2.70E-04	FCTX	NA	NA
3855367	rs28478453	chr19:19531175	2.80E-04	FCTX	GG=1; GC=38; CC=91	G=14.9%; C=85.1%
3855380	NA	chr19:18440959:CAT_C	3.10E-04	FCTX	NA	NA
3855380	rs117780632	chr19:18464181	4.10E-04	FCTX	AA=3; AG=9; GG=117	A=5.6%; G=94.4%
3855359	rs181358521	chr19:19799184	4.10E-04	HIPP	CC=0; CT=20; TT=86	C=7.5%; T=92.5%

3855364	rs17885551	chr19:18179672	2.40E-04	HIPP	CC=3; CT=37; TT=89	C=16%; T=84%
3855364	rs17886399	chr19:18179702	2.40E-04	HIPP	AA=3; AG=37; GG=89	A=16%; G=84%
3855364	NA	chr19:18179832:TTA_T	3.00E-04	HIPP	NA	NA
3855364	rs12150884	chr19:18179973	3.60E-04	HIPP	AA=4; AG=38; GG=90	A=17.2%; G=82.8%
3855364	rs2305739	chr19:18180194	3.80E-04	HIPP	AA=4; AG=40; GG=90	A=17.9%; G=82.1%
3855364	rs2305740	chr19:18180236	3.80E-04	HIPP	GG=4; GA=40; AA=90	G=17.9%; A=82.15
3855359	rs59813731	chr19:18146068	2.80E-04	MEDU	TT=3; TC=28; CC=61	T=12.7%; C=87.3%
3855359	rs73014268	chr19:18147967	3.30E-04	MEDU	CC=4; CA=29; AA=72	C=13.8%; A =86.2%
3855359	rs56855322	chr19:18147723	3.30E-04	MEDU	CC=4; CT=29; TT=72	C=13.8%; T=86.2%
3855359	rs139293293	chr19:18150992	3.50E-04	MEDU	GG=6; GT=32; TT=72	G=16.4%; T=83.6%
3855359	rs111293286	chr19:18153031	3.50E-04	MEDU	GG=6; GA=32; AA=72	G=16.4%; A=83.6%
3855359	rs67472645	chr19:18152908	3.50E-04	MEDU	TT=6; TA=32; AA=72	T=16.4%; A=83.6%
3855359	rs897753	chr19:18154576	3.80E-04	MEDU	CC-=7; CA=32; AA=72	C=17.2%; A=82.8%
3855359	rs62121088	chr19:18152256	5.80E-04	MEDU	AA=6; AG=33; GG=71	A=16.8%; G=83.2%
t3855358	rs424608	chr19:18141950	1.80E-04	MEDU	CC=3; CT=46; TT=85	C=19.4%; T=80.6%
t3855358	rs388159	chr19:18141996	1.80E-04	MEDU	TT=3; TC=46; CC=85	T=19.4%; C=80.6%
t3855358	rs425663	chr19:18142423	1.80E-04	MEDU	CC=3; CT=46; TT=85	C=19.4%; T=80.6%

t3855358	rs374614	chr19:18142682	1.80E-04	MEDU	CC=3; CT=46; TT=85	C=19.4%; T=80.6%
3855360	rs424608	chr19:18141950	8.50E-05	MEDU	CC=3; CT=46; TT=85	C=19.4%; T=80.6%
3855360	rs388159	chr19:18141996	8.50E-05	MEDU	TT=3; TC=46; CC=85	T=19.4%; T=80.6%
3855360	rs425663	chr19:18142423	8.50E-05	MEDU	CC=3; CT=46; TT=85	C=19.4%; T=80.6%
3855360	rs374614	chr19:18142682	8.50E-05	MEDU	CC=3; CT=46; TT=85	C=19.4%; T=80.6%
3855362	rs73512431	chr19:18111864	1.00E-03	MEDU	AA=2; AG=9; GG=122	A=4.9%; G=95.1%
3855361	rs247794	chr19:19860523	4.30E-04	OCTX	AA=15; AG=51; GG=68	A=30.2%; G=69.8%
3855361	rs247793	chr19:19860922	4.30E-04	OCTX	AA=15; AG=51; GG=68	A=30.2%; G=69.8%
3855361	NA	chr19:19859181:ATGGC	4.50E-04	OCTX	NA	NA
3855361	rs247790	chr19:19862966	5.10E-04	OCTX	TT=15; TC=50; CC=68	T=29.9%; C=70.1%
3855363	rs66495698	chr19:18911151	5.50E-04	OCTX	AA=10; AT=50; TT=26	A=26.1%; T=73.9%
3855363	NA	chr19:18912141:CA_C	5.50E-04	OCTX	NA	NA
3855363	rs28555441	chr19:18912264	5.60E-04	OCTX	CC=11; CA=51; AA=27	C=27.2%; A=72.8%
3855363	NA	chr19:18912140:CCA_C	5.70E-04	OCTX	NA	NA
3855363	NA	chr19:18910393:GTGGA	5.90E-04	OCTX	NA	NA
3855366	NA	chr19:18546028:CA_C	6.30E-04	OCTX	NA	NA
3855380	NA	chr19:18174944:C_CTT	2.60E-04	PUTM	NA	NA

3855361	rs12982014	chr19:19125967	1.80E-04	SNIG	CC=8; CT=41; TT=56	C=21.3%; T=78.7%
3855361	rs143729015	chr19:19130750	2.10E-04	SNIG	AA=0; AG=14; GG=117	A=5.2%; G=94.8%
3855361	rs148321348	chr19:19092434	2.90E-04	SNIG	TT=0; TC=6; CC=117	T=2.2%; C=97.8%
3855361	rs80341032	chr19:19207229	5.10E-04	SNIG	AA=1; AG=15; GG=114	A=6.3%; G=93.7%
3855366	rs12981022	chr19:18166278	5.30E-05	SNIG	AA=0; AG=9; GG=102	A=3.4%; G=96.6%
3855366	rs12981024	chr19:18166286	5.70E-05	SNIG	AA=0; AG=9; GG=102	A=3.4%; G=96.6%
3855366	rs12983785	chr19:18166275	6.20E-05	SNIG	CC=0; CA=9; AA=102	C=3.4%; A=96.6%
3855361	rs7226	chr19:18480609	6.00E-04	TCTX	TT=8; TC=52; CC=74	T=25.4%; C=74.6%
3855361	rs2161106	chr19:18481229	6.00E-04	TCTX	CC=8; CT=52; TT=74	C=25.4%; T=74.6%
3855362	NA	chr19:18174947:TC_T	9.20E-04	TCTX	NA	NA
3855366	NA	chr19:18174947:TC_T	6.40E-04	TCTX	NA	NA
3855363	rs248948	chr19:19891154	1.40E-04	THAL	GG=16; GC=67; CC=49	G=36.9%; C=63.1%
3855363	rs248949	chr19:19891215	2.60E-04	THAL	CC=20; CA=65; AA=47	C=39.2%; A=60.8%
3855363	rs248951	chr19:19893833	2.60E-04	THAL	TT=20; TG=65;GG=47	T=39.2%; G=60.8%
3855364	rs2238661	chr19:19003219	3.20E-04	THAL	CC=0; CT=5; TT=106	C=1.9%; T=98.1%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 31: Brain quantitative gene expression analyses for *TBX18* gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
t2963142	NA	chr6:85892356:GGAAA	3.60E-04	aveALL	NA	NA
2963164	NA	chr6:84641525:T_TA	1.20E-04	CRBL	NA	NA
2963167	rs4706238	chr6:86121473	8.60E-07	CRBL	CC=37;CT=62;TT=32	C=50.7%;T=49.3%
2963167	rs12213716	chr6:86119089	1.00E-06	CRBL	CC=37;CT=63;TT=32	C=51.1%;T=48.9%
2963167	rs6454467	chr6:86147332	3.20E-06	CRBL	TT=19;TC=65;CC=50	T=38.4%;C=61.6%
2963167	rs2181187	chr6:86134059	7.40E-06	CRBL	AA=19;AG=64;GG=51	A=38.1%;G=61.9%
2963167	rs9450282	chr6:86195298	8.70E-06	CRBL	AA=17;AG=69;GG=48	A=38.4%;G=61.6%
2963167	rs9450287	chr6:86211984	8.90E-06	CRBL	AA=17;AG=69;GG=48	A=38.4%;G=61.6%
2963167	rs7739563	chr6:86156315	1.00E-05	CRBL	CC=16;CT=63;TT=52	C=35.4%;T=64.6%
2963167	rs2065114	chr6:86159143	1.10E-05	CRBL	AA=16;AG=64;GG=54	A=35.8%;G=64.2%
2963167	rs6931295	chr6:86144875	1.20E-05	CRBL	TT=16;TC=64;CC=54	T=35.8%;C=64.2%
2963145	NA	chr6:84662527:ACT_A	6.50E-04	FCTX	NA	NA
2963157	rs9342002	chr6:85534582	2.00E-04	FCTX	GG=1;GA=24;AA=108	G=9.7%;A=90.3%
2963157	rs858738	chr6:85523135	2.80E-04	FCTX	TT=1;TG=23;GG=110	T=9.3%;G=90.7%
2963157	rs858740	chr6:85527080	3.00E-04	FCTX	AA=1;AC=23;CC=110	A=9.3%;C=90.7%

2963157	rs1102485	chr6:85531615	3.20E-04	FCTX	GG=1;GA=23; AA=110	G=9.3%;A=90.7%
2963157	rs149182547	chr6:85537156	3.30E-04	FCTX	TT=1;TC=33;CC=83	T=13.1%;C=86.9%
2963157	rs6454396	chr6:85533497	3.40E-04	FCTX	CC=1;CT=23;TT=110	C=9.3%;T=90.7%
2963157	rs2224213	chr6:85534101	3.40E-04	FCTX	TT=1;TC=23;CC=110	T=9.3%;C=90.7%
t2963142	rs9362033	chr6:84948961	5.80E-04	HIPP	GG=1;GA=34; AA=93	G=13.4%,A=86.6%
2963145	rs6916255	chr6:85383871	2.00E-04	HIPP	CC=14;CT=61; TT=55	C=33.2%;T=66.8%
2963145	rs7768657	chr6:85383196	3.90E-04	HIPP	TT=15;TA=57; AA=57	T=32.5%;A=67.5%
2963145	rs9450002	chr6:85376381	5.00E-04	HIPP	CC=37;CT=65; TT=32	C=51.9%;T=48.1%
2963145	NA	chr6:85369726:A_AT	7.20E-04	HIPP	NA	NA
2963145	rs7743504	chr6:85379042	7.20E-04	HIPP	AA=14;AG=60; GG=60	A=32.8%;G=67.2%
2963161	rs12194396	chr6:85331136	3.60E-04	HIPP	TT=0;TC=7;CC=108	T=2.6%;C=97.4%
t2963142	rs4706191	chr6:84971513	2.20E-04	MEDU	GG＝0; GA=16;AA＝118	G=6％;A=94%
t2963142	rs56284038	chr6:84988406	3.40E-04	MEDU	TT=0;TC=17;CC=117	T=6.3%;C=93.7%
t2963142	rs111805135	chr6:85000471	3.40E-04	MEDU	AA=0;AG=17; GG=117	A=6.3%;G=93.7%
t2963142	rs62449339	chr6:85012150	3.80E-04	MEDU	AA=0;AG=17; GG=117	A=6.3%;G=93.7%
2963145	rs9341976	chr6:85186889	4.10E-04	MEDU	TT=24;TG=54; GG=51	T=38.1%;G=61.9%
2963145	rs144986770	chr6:85185986	4.10E-04	MEDU	TT=24;TC=54; CC=51	T=38.1%;C=61.9%

2963154	rs4706191	chr6:84971513	2.20E-04	MEDU	GG=0;GA=16; AA=118	G=6%;A=94%
2963154	rs56284038	chr6:84988406	2.60E-04	MEDU	TT=0;TC=17;CC=117	T=6.3%;C=93.7%
2963154	rs111805135	chr6:85000471	2.90E-04	MEDU	AA=0;AG=17; GG=117	A=6.3%;G=93.7%
2963154	rs62449339	chr6:85012150	3.20E-04	MEDU	AA=0;AG=17; GG=117	A=6.3%;G=93.7%
2963154	rs4429910	chr6:84950723	6.60E-04	MEDU	TT=11;TG=54; GG=65	T=28.4%;G=71.6%
2963154	NA	chr6:84949780:AG_A	6.70E-04	MEDU	NA	NA
2963154	rs6454358	chr6:84949473	6.70E-04	MEDU	GG=11;GA=54; AA=65	G=28.4%;A=71.6%
2963154	rs9353171	chr6:84965782	7.40E-04	MEDU	GG=11.GT=57; TT=65	G=29.5%;T=70.5%
2963154	rs9341973	chr6:84965947	7.40E-04	MEDU	AA=11;AG=57; GG=65	A=29.5%;G=70.5%
2963154	rs10455152	chr6:86018348	1.00E-03	MEDU	CC=2;CA=22; AA=66	C=9.7%;A=90.3%
2963155	NA	chr6:84380923	2.80E-06	MEDU	NA	NA
2963155	NA	chr6:84385616:C_CA	1.10E-05	MEDU	NA	NA
2963155	NA	chr6:84393942	1.10E-05	MEDU	NA	NA
2963155	NA	chr6:84398565	1.10E-05	MEDU	NA	NA
2963155	NA	chr6:84407466	1.10E-05	MEDU	NA	NA
2963155	NA	chr6:84387905	1.10E-05	MEDU	NA	NA
2963155	NA	chr6:84401807	1.10E-05	MEDU	NA	NA
2963155	NA	chr6:84377985	1.20E-05	MEDU	NA	NA
2963155	NA	chr6:84383958	1.20E-05	MEDU	NA	NA
2963155	NA	chr6:84377956	1.20E-05	MEDU	NA	NA

2963144	NA	chr6:86514881:CCTT_	6.40E-05	OCTX	NA	NA
2963144	rs147447729	chr6:86468512	6.70E-05	OCTX	GG=1;GA=39;AA=57	G=15.3%;A=84.7%
2963144	rs2484355	chr6:86394403	7.50E-05	OCTX	AA=24;AG=66;GG=44	A=42.5%;G=57.5%
2963144	rs1885607	chr6:86394905	7.70E-05	OCTX	AA=24;AG=66;GG=44	A=42.5%;G=57.5%
2963144	NA	chr6:86314490:T_TG	1.10E-04	OCTX	NA	NA
2963144	NA	chr6:86314493:G_GC	1.10E-04	OCTX	NA	NA
2963144	rs4707209	chr6:86229369	1.10E-04	OCTX	CC=21;CA=67;AA=42	C=40.7%;A=59.3%
2963144	rs4145082	chr6:86352016	1.20E-04	OCTX	AA=22;AG=65;GG=40	A=40.7%,G=59.3%
2963144	rs4351223	chr6:86237797	1.20E-04	OCTX	AA=21;AG=68;GG=45	A=41%;G=59%
2963144	rs9294337	chr6:86248460	1.20E-04	OCTX	TT=21;TC=68;CC=45	T=41%;C=59%
2963145	rs215971	chr6:84701763	4.70E-04	OCTX	TT=17;TC=56;CC=44	T=33.6%;C=66.4%
2963162	rs9449832	chr6:84904086	1.30E-04	OCTX	AA=1;AG=5:GG=121	A=2.6%;G=97.4%
2963162	rs9449815	chr6:84873080	2.60E-04	OCTX	TT=5;TG=5;GG=122	T=5.6%;G=94.4%
2963162	rs6910156	chr6:84881148	2.60E-04	OCTX	AA=5;AG=5;GG=124	A=5.6%;G=94.4%
2963162	rs6910586	chr6:84881634	2.60E-04	OCTX	GG=5;GA=5;AA=124	G=5.6%;A=94.4%
2963162	rs6939593	chr6:84882628	2.60E-04	OCTX	AA=5;AT=5;TT=124	A=5.6%;T=94.4%
2963162	rs6905922	chr6:84877816	2.70E-04	OCTX	TT=5;TC=5;CC=122	T=5.6%;C=94.4%

2963162	rs9283802	chr6:84879486	2.70E-04	OCTX	CC=5;CG=5;GG=122	C=5.6%;G=94.4%
2963162	rs2497153	chr6:84869361	3.00E-04	OCTX	GG=5;GC=5;CC=122	G=5.6%;C=94.4%
2963162	rs12527719	chr6:84893055	3.00E-04	OCTX	AA=2;AG=5;GG=124	A=3.4%;G=96.6%
2963162	rs2476908	chr6:84866938	3.00E-04	OCTX	AA=5;AG=6;GG=122	A=6%;G=94%
2963164	rs78800837	chr6:86344886	1.70E-05	OCTX	GG=1;GA=10;AA=120	G=4.5%;A=95.5%
2963168	NA	chr6:84391540	7.00E-05	OCTX	NA	NA
2963168	NA	chr6:84388176	7.00E-05	OCTX	NA	NA
2963168	NA	chr6:84395310	7.10E-05	OCTX	NA	NA
2963168	NA	chr6:84399635	7.30E-05	OCTX	NA	NA
2963168	NA	chr6:84402322	7.40E-05	OCTX	NA	NA
2963168	NA	chr6:84380565:CT_C	1.30E-04	OCTX	NA	NA
2963168	NA	chr6:84394091	1.50E-04	OCTX	NA	NA
2963168	NA	chr6:84380660	1.50E-04	OCTX	NA	NA
2963157	rs75490889	chr6:85817828	2.00E-04	PUTM	TT=4;TG=30;GG=100	T=14.2%;G=85.8%
2963157	rs41347044	chr6:85818978	2.00E-04	PUTM	GG=4;GA=30;AA=100	G=14.2%;A=85.8%
2963157	NA	chr6:85854902:TA_T	3.90E-04	PUTM	NA	NA
2963160	rs72896897	chr6:85121959	1.10E-04	PUTM	TT=1;TC=31;CC=75	T=12.3%;C=87.7%
2963160	rs9449897	chr6:85120013	4.80E-04	PUTM	CC=3;CT=23;TT=108	C=10.8%;T=89.2%
2963160	rs9444174	chr6:85119504	4.80E-04	PUTM	AA=3;AC=23;CC=108	A=10.8%;C=89.2%

2963160	rs9444173	chr6:85119377	4.80E-04	PUTM	CC=3;CT=23;TT=108	C=10.8%;T=89.2%
2963160	NA	chr6:85117957:CAT_C	5.30E-04	PUTM	NA	NA
2963160	rs12527156	chr6:85117770	5.50E-04	PUTM	TT=3;TC=23;CC=108	T=10.8%;C=89.2%
2963160	rs9444172	chr6:85117025	6.10E-04	PUTM	CC=3;CT=23;TT=108	C=10.8%;T=89.2%
2963160	rs72896872	chr6:85117071	9.00E-04	PUTM	CC=3;CT=23;TT=107	C=10.8%;T=89.2%
t2963142	rs1325471	chr6:84567675	7.90E-04	SNIG	GG=0;GA=10;AA=120	G=3.7%;A=96.3%
t2963142	rs9353143	chr6:84563147	7.90E-04	SNIG	AA=0;AG=10;GG=120	A=3.7%;G=96.3%
t2963142	rs2298291	chr6:84563281	7.90E-04	SNIG	GG=0;GT=10;TT=120	G=3.7%;T=96.3%
2963159	rs145750856	chr6:85318248	3.60E-04	SNIG	CC=3;CT=29;TT=52	C=13.1%;T=86.9%
2963164	rs1325471	chr6:84567675	1.20E-04	SNIG	GG=0;GA=10;AA=120	G=3.7%;A=96.3%
2963164	rs9353143	chr6:84563147	1.20E-04	SNIG	AA=0;AG=10;GG=120	A=3.7%;G=96.3%
2963164	rs2298291	chr6:84563281	1.20E-04	SNIG	GG=0;GT=10;TT=120	G=3.7%;T=96.3%
2963164	rs4706189	chr6:84557170	1.20E-04	SNIG	CC=0;CA=10;AA=120	C=3.7%,A=96.3%
2963164	rs9362012	chr6:84558314	1.20E-04	SNIG	TT=0;TA=10;AA=120	T=3.7%;A=96.3%
2963164	NA	chr6:84558947:C_CTT	1.20E-04	SNIG	NA	NA
2963164	rs12173431	chr6:84558784	1.20E-04	SNIG	GG=0;GC=10:CC=120	G=3.7%;C=96.3%
2963164	rs9294281	chr6:84534229	1.20E-04	SNIG	CC=0;CT=7;TT=120	C=2.6%;T=97.4%

t2963142	rs7453917	chr6:85295547	6.30E-04	TCTX	TT=0;TC=13;CC=114	T=4.9%;C=95.1%
2963159	rs10944016	chr6:85296237	1.30E-04	TCTX	TT=0;TC=16;CC=98	T=6%;C=94%
2963161	rs78261651	chr6:85799282	4.50E-04	TCTX	CC=0;CA=14;AA=120	C=5.2%;A=94.8%
2963161	rs78335147	chr6:85802481	5.10E-04	TCTX	AA=0;AC=14;CC=120	A=5.2%;C=94.8%
2963161	rs55897238	chr6:85804399	5.10E-04	TCTX	TT=0;TC=14;CC=120	T=5.2%;C=94.8%
2963161	rs1853906	chr6:85805347	5.10E-04	TCTX	CC=0;CG=14;GG=120	C=5.2%,G=94.8%
2963161	rs1853907	chr6:85805573	5.10E-04	TCTX	CC=0;CG=14;GG=120	C=5.2%,G=94.8%
2963161	rs76310293	chr6:85805903	5.10E-04	TCTX	TT=0;TC=14;CC=120	T=5.2%;C=94.8%
2963161	rs55983666	chr6:85810193	5.10E-04	TCTX	GG=0;GC=14;CC=120	G=5.2%;C=94.8%
2963161	rs75867809	chr6:85815695	5.10E-04	TCTX	CC=0;CT=14;TT=120	C=5.2%;T=94.8%
2963159	rs9353242	chr6:85701774	6.10E-05	THAL	TT=19;TG=45;GG=69	T=31%;G=69%
2963159	rs9353239	chr6:85700525	6.40E-05	THAL	AA=19;AG=45;GG=69	A=31%;G=69%
2963159	rs2146461	chr6:85691341	8.90E-05	THAL	CC=19;CT=46;TT=69	C=31.3%;T=68.7%
2963159	rs2324764	chr6:85690595	9.10E-05	THAL	AA=19;AG=46;GG=69	A=31.3%;G=68.7%
2963159	rs9353237	chr6:85695913	9.50E-05	THAL	TT=17;TG=42;GG=70	T=28.4%;G=71.6%
2963159	rs9362119	chr6:85679883	4.10E-04	THAL	GG=26;GA=61;AA=47	G=42.2%;A=57.8%
2963159	rs1322876	chr6:85680477	4.10E-04	THAL	TT=26;TC=61;CC=47	T=42.2%;C=57.8%

2963159	rs1322875	chr6:85682479	4.10E-04	THAL	AA=26;AG=61; GG=47	A=42.2%;G=57.8%
2963160	NA	chr6:84380492	9.50E-04	THAL	NA	NA
2963161	rs10943964	chr6:84729614	2.30E-04	THAL	TT=0;TA=25;AA=53	T=9.3%;A=90.7%
2963145	rs192891293	chr6:85382517	5.40E-04	WHMT	CC=0;CA=11; AA=114	C=4.1%;A=95.9%
2963160	rs9362048	chr6:85119727	8.90E-04	WHMT	CC=3;CT=40;TT=91	C=17.2%;T=82.8%
2963167	rs6916224	chr6:85745004	5.80E-06	WHMT	GG=3;GA=40; AA=91	G=17.2%;A=82.8%
2963168	rs16875429	chr6:85706347	5.40E-05	WHMT	TT=0;TC=19;CC=115	T=7.1%;C=92.9%
2963168	rs1322866	chr6:85708041	5.50E-05	WHMT	CC=0;CT=19;TT=115	C=7.1%;T=92.9%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 32: Brain quantitative gene expression analyses for *NT5E* gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
2915830	rs1884478	chr6:85588632	1.80E-04	aveALL	CC=30;CT=60;TT=44	C=44.8%;T=55.2%
2915830	rs7746065	chr6:86174845	2.20E-04	aveALL	AA=16;AC=64;CC=53	A=35.8%;C=64.2%
2915858	rs582600	chr6:86099058	7.50E-05	aveALL	TT=35;TC=68;CC=31	T=51.5%;C=48.5%
2915858	rs9444340	chr6:86099813	7.50E-05	aveALL	GG=35;GT=68;TT=31	G=51.5%;T=48.5%
2915858	rs313200	chr6:86110920	7.70E-05	aveALL	CC=35;CT=68;TT=31	C=51.5%;T=48.5%
2915858	rs313195	chr6:86107092	7.80E-05	aveALL	GG=35;GA=68;AA=31	G=51.5%;A=48.5%

2915858	rs493441	chr6:86094567	7.90E-05	aveALL	GG=35;GA=68;AA=31	G=51.5%;A=48.5%
2915861	rs79007188	chr6:86390675	8.50E-04	aveALL	TT=0;TA=8;AA=92	T=3%;A=97%
2915867	NA	chr6:86679979:ATATA	3.10E-05	aveALL	NA	NA
2915829	rs9450277	chr6:86157419	1.90E-05	CRBL	GG=39;GA=66;AA=29	G=53.7%;A=46.3%
2915829	NA	chr6:86158426:TGTTA	1.90E-05	CRBL	NA	NA
2915829	rs11752251	chr6:86162868	2.00E-05	CRBL	GG=39;GA=66;AA=29	G=53.7%,A=46.3%
2915829	rs9885944	chr6:86149161	2.20E-05	CRBL	CC=28;CG=65;GG=29	C=53.4%;G=46.6%
2915829	rs4706238	chr6:86121473	2.30E-05	CRBL	CC=37;CT=62;TT=32	C=50.7%;T=49.3%
2915829	rs12191637	chr6:86153378	2.30E-05	CRBL	GG=27;GT=66;TT=40	G=44.8%;T=55.2%
2915829	rs12213716	chr6:86119089	3.00E-05	CRBL	CC=37;CT=63;TT=32	C=51.1%,T=48.9%
2915829	rs4288177	chr6:86151908	3.50E-05	CRBL	GG=39;GA=65;AA=28	G=53.4%;A=46.6%
2915829	rs9450273	chr6:86137888	3.60E-05	CRBL	CC=39;CT=65;TT=30	C=53.4%;T=46.6%
2915829	rs10944128	chr6:86180732	4.60E-05	CRBL	AA=34;AC=66;CC=34	A=50%;C=50%
2915830	rs1409190	chr6:85791717	1.50E-04	CRBL	GG=1;GA=25;AA=108	G=10.1%;A=89.9%
2915830	rs4279398	chr6:85781130	1.70E-04	CRBL	GG=1;GA=22;AA=108	G=9%;'!=91%
2915830	rs7767861	chr6:85817854	2.10E-04	CRBL	TT=0;TC=22;CC=112	T=8.2%;C=91.8%
2915830	rs1325975	chr6:85818620	2.10E-04	CRBL	CC=0;CG=22;GG=112	C=8.2%;G=91.8%
2915830	rs16875673	chr6:85818874	2.10E-04	CRBL	CC=0;CT=22;TT=112	C=8.2%;T=91.8%
2915846	rs149197154	chr6:85411647	2.50E-05	CRBL	TT=9;TC=61;CC=31	T=29.5%;C=70.5%

2915846	rs146943331	chr6:85411649	3.30E-05	CRBL	AA=10;AC=61;CC=30	A=30.2%;C=69.8%
2915846	NA	chr6:85391678:AGTTT	3.60E-05	CRBL	NA	NA
2915846	rs9341990	chr6:85391568	4.60E-05	CRBL	AA=22;AG=77;GG=35	A=45.1%;G=54.9%
2915846	rs9362083	chr6:85396119	4.60E-05	CRBL	TT=22;TA=77;AA=35	T=45.1%;A=54.9%
2915846	rs761391	chr6:85448103	6.40E-05	CRBL	CC=23;CT=81;TT=28	C=47.4%;T=52.6%
2915849	rs4121274	chr6:87126155	4.20E-05	CRBL	TT=0;TG=42;GG=88	T=15.7%;G=84.3%
2915849	rs12203951	chr6:87080572	1.60E-04	CRBL	CC=2;CG=44;GG=88	C=17.9%;G=82.1%
2915849	rs12193927	chr6:87082151	1.60E-04	CRBL	TT=2;TA=44;AA=88	T=17.9%;A=82.1%
2915853	rs499144	chr6:86018542	1.80E-05	CRBL	AA=12;AG=55;GG=20	A=29.5%;G=70.5%
2915853	rs313187	chr6:86025339	2.60E-05	CRBL	AA=10;AC=63;CC=61	A=31%;C=69%
2915853	rs313184	chr6:86028265	2.60E-05	CRBL	AA=10;AG=63;GG=61	A=31%;G=69%
2915853	rs532949	chr6:86013352	3.70E-05	CRBL	GG=9;GT=64;TT=61	G=30.6%;T=69.4%
2915853	rs313217	chr6:86006733	3.90E-05	CRBL	AA=9;AC=64;CC=61	A=30.6%;C=69.4%
2915853	rs313216	chr6:86007092	3.90E-05	CRBL	AA=9;AG=64;GG=61	A=30.6%;G=69.4%
2915853	rs313210	chr6:86008956	3.90E-05	CRBL	TT=9;TC=64;CC=61	T=30.6%;C=69.4%
2915853	rs313211	chr6:86008315	4.10E-05	CRBL	CC=9;CT=64;TT=61	C=30.6%;T=69.4%
2915853	rs167508	chr6:86002326	4.10E-05	CRBL	AA=9;AG=63;GG=61	A=30.2%;G=69.8%
2915853	rs313221	chr6:86003141	4.20E-05	CRBL	TT=9;TA=64;AA=61	T=30.6%;A=69.4%

2915830	NA	chr6:86861113:G_GA	9.20E-05	FCTX	NA	NA
2915830	NA	chr6:86701235:TG_T	1.20E-04	FCTX	NA	NA
2915830	rs11756375	chr6:87140901	2.10E-04	FCTX	AA=1;AC=34;CC=98	A=13.4%;C=86.6%
2915851	rs13202806	chr6:86051820	4.50E-05	FCTX	AA=0;AG=15;GG=110	A=5.6%;G=94.4%
2915860	rs146943331	chr6:85411649	7.00E-04	FCTX	AA=10;AV=61;CC=30	A=30.2%;C=69.8%
2915861	rs55810031	chr6:85207833	9.70E-04	FCTX	GG=3;GC=46;CC=77	G=19.4%;C=80.6%
2915862	rs7745560	chr6:86288921	1.10E-04	FCTX	AA=0;AT=18;TT=106	A=6.7%;T=93.3%
2915862	rs7741914	chr6:86804775	1.30E-04	FCTX	TT=0;TC=17;CC=116	T=6.3%;C=93.7%
2915862	NA	chr6:86805090:TG_T	1.30E-04	FCTX	NA	NA
2915867	rs13202806	chr6:86051820	7.40E-05	FCTX	AA=0;AG=15;GG=110	A=5.6%;G=94.4%
2915867	rs35011769	chr6:86083209	1.40E-04	FCTX	TT=0;TC=18;CC=108	T=6.7%;C=93.3%
2915868	NA	chr6:86083372:C_CA	3.30E-04	FCTX	NA	NA
2915849	rs9444269	chr6:85683704	1.20E-04	HIPP	GG=13;GA=62;AA=59	G=32.8%;A=67.2%
2915858	rs9444291	chr6:85777885	7.90E-05	HIPP	Tt=0;TC=26;CC=105	T9.7%;C=90.3%
2915858	rs9450140	chr6:85776709	8.00E-05	HIPP	GG=0;GT=26;TT=105	G=9.7%;T=90.3%
2915858	rs9450139	chr6:85774633	8.10E-05	HIPP	AA=0;AG=27;GG=105	A=10.1%;G=89.9%
2915858	rs57664101	chr6:85773712	8.20E-05	HIPP	TT=0;TC=27;CC=105	T=10.1%;C=89.9%
2915849	NA	chr6:87102568:C_CAT	1.60E-04	OCTX	NA	NA
2915861	NA	chr6:86057584:C_CT	1.10E-03	OCTX	NA	NA
2915862	NA	chr6:87238638	7.30E-05	OCTX	NA	NA
2915866	NA	chr6:86707719:G_GA	2.20E-04	OCTX	NA	NA
2915866	NA	chr6:86707719:G_GA	2.20E-04	OCTX	NA	NA
2915868	rs4311487	chr6:86004484	5.30E-04	OCTX	TT=5;TC=52;CC=76	T=23.1%;C=76.9%

2915868	rs62422872	chr6:85691647	6.20E-04	OCTX	AA=4;AC=29;CC=96	A=13.8%;C=86.2%
2915868	NA	chr6:86030494:G_GTA	7.60E-04	OCTX	NA	NA
2915868	rs13191546	chr6:86030901	7.70E-04	OCTX	TT=5;TC=52;CC=77	T=23.1%;C=76.9%
2915868	rs10485066	chr6:85689003	8.10E-04	OCTX	CC=6;CT=33;TT=95	C=16.8%;T=83.2%
2915868	rs17521560	chr6:85690875	8.10E-04	OCTX	AA=6;AG=33;GG=95	A=16.8%;G=83.2%
2915860	rs911830	chr6:86033751	3.50E-04	PUTM	AA=20;AT=60;TT=36	A=37.3%;T=62.7%
2915860	NA	chr6:86033749:T_TTA	6.40E-04	PUTM	NA	NA
2915860	rs558132	chr6:86033750	6.40E-04	PUTM	TT=20;TG=61;GG=36	T=37.7%;G=62.3%
2915860	rs1665781	chr6:86014547	8.70E-04	PUTM	TT=13;TG=47;GG=40	T=27.2%;G=72.8%
2915860	rs1665780	chr6:86014543	8.90E-04	PUTM	TT=13;TC=47;CC=40	T=27.2%;C=72.8%
2915860	rs140538325	chr6:86021956	9.40E-04	PUTM	TT=8;TA=44;AA=42	T=22.4%;A=77.6%
2915860	rs77447586	chr6:86019983	1.20E-03	PUTM	CC=27;CT=63;TT=36	C=43.7%;T=56.3%
2915868	rs75490889	chr6:85817828	8.90E-04	PUTM	TT=4;TG=30;GG=100	T=14.2%;G=85.8%
2915868	rs7744612	chr6:85289193	7.00E-04	SNIG	GG=0;GC=11;CC=110	G=4.1%;C=95.9%
2915868	rs7764466	chr6:85289192	7.30E-04	SNIG	TT=0;TC=11;CC=110	T=4.1%;C=95.9%
t2915828	rs493641	chr6:86100241	1.20E-04	TCTX	TT=11;TC=52;CC=61	T=27.6%;C=72.4%
2915846	rs493641	chr6:86100241	2.50E-05	TCTX	TT=11;TC=52;CC=61	T=27.6%;C=72.4%
2915846	rs313201	chr6:86111201	6.60E-05	TCTX	TT=11;TC=53;CC=70	T=28%;C=72%
2915846	rs692830	chr6:86099731	6.70E-05	TCTX	CC=12;CT=52;TT=70	C=28.4%;T=71.6%
2915846	rs313196	chr6:86107232	6.80E-05	TCTX	AA=11;AG=53;GG=70	A=28%;G=72%

2915849	NA	chr6:86258694:T_TA	1.00E-04	TCTX	NA	NA
2915849	rs151191231	chr6:86540376	1.30E-04	TCTX	GG=6;GC=42;CC=55	G=20.1%;C=79.9%
2915849	rs1582127	chr6:86697204	1.70E-04	TCTX	TT=6;TC=39;CC=55	T=19%;C=81%
2915849	NA	chr6:86697203:GCC_G	1.70E-04	TCTX	NA	NA
2915849	rs1582126	chr6:86697205	1.70E-04	TCTX	AA=6;AC=39;CC=55	A=19%;C=81%
2915858	NA	chr6:86763221:TTTG_	4.10E-05	TCTX	NA	NA
2915860	NA	chr6:85833650:CT_C	5.50E-04	TCTX	NA	NA
2915862	NA	chr6:86679979:ATATA	7.60E-05	TCTX	NA	NA
2915862	rs313245	chr6:86055197	1.10E-04	TCTX	TT=3;TG=32;GG=99	T=14.2%;G=85.8%
2915862	rs313242	chr6:86057368	1.10E-04	TCTX	TT=3;TC=32;CC=98	T=14.2%;C=85.8%
2915862	rs313239	chr6:86062148	1.10E-04	TCTX	AA=3;AT=32;TT=98	A=14.2%;T=85.8%
2915862	rs313247	chr6:86053988	1.10E-04	TCTX	AA=3;AG=32;GG=99	A=14.2%;G=85.8%
2915862	rs598593	chr6:86073301	1.30E-04	TCTX	CC=3;CA=32;AA=97	C=14.2%;A=85.8%
2915867	rs9362270	chr6:86815115	9.50E-05	TCTX	CC=0;CA=17;AA=116	C=6.3%;A=93.7%
2915867	rs9450389	chr6:86820340	9.60E-05	TCTX	CC=0;CT=15;TT=116	C=5.6%;T=94.4%
2915867	NA	chr6:86805090:TG_T	9.90E-05	TCTX	NA	NA
2915867	rs112617781	chr6:86812776	9.90E-05	TCTX	TT=0;TC=17;CC=116	T=6.3%;C=93.7%
2915867	rs7741914	chr6:86804775	1.00E-04	TCTX	TT=0;TC=17;CC=116	T=6.3%;C=93.7%
2915867	rs7772723	chr6:86623698	1.30E-04	TCTX	AA=0;AT=19;TT=114	A=7.1%;T=92.9%
2915867	rs7752222	chr6:86623592	1.40E-04	TCTX	TT=0;TA=19;AA=114	T=7.1%;A=92.9%
2915869	rs493641	chr6:86100241	3.10E-05	TCTX	TT=11;TC=52;CC=61	T=27.6%;C=72.4%

2915869	rs597623	chr6:86100109	1.20E-04	TCTX	AA=11;AG=53;GG=70	A=28%;G=72%
2915869	rs577388	chr6:86100832	1.20E-04	TCTX	AA=11;AG=53;GG=70	A=28%;G=72%
2915869	rs7775853	chr6:86100916	1.20E-04	TCTX	AA=11;AG=53;GG=70	A=28%;G=72%
2915869	rs550763	chr6:86101444	1.20E-04	TCTX	AA=11;AT=53;TT=70	A=28%;T=72%
2915869	rs614124	chr6:86101535	1.20E-04	TCTX	TT=11;TC=53;CC=70	T=28%;C=72%
2915869	rs547037	chr6:86101836	1.20E-04	TCTX	GG=11;GT=53;TT=70	G=28%;T=72%
2915869	rs615848	chr6:86101894	1.20E-04	TCTX	TT=11;TG=53;GG=70	T=28%;G=72%
2915869	rs545407	chr6:86101963	1.20E-04	TCTX	GG=11;GA=53;QQ=70	G=28%;A=72%
2915851	rs1407157	chr6:85962802	6.20E-05	THAL	AA=2;AG=27;GG=104	A=11.6%;G=88.4%
2915851	rs535422	chr6:85982564	9.60E-05	THAL	GG=2;GA=27;AA=105	G=11.6%;A=88.4%
2915851	rs1958939	chr6:85985187	9.60E-05	THAL	CC=2;CT=27;TT=105	C=11.6%;T=88.4%
2915851	rs1885015	chr6:85963538	9.60E-05	THAL	GG=2;GA=27;AA=105	G=11.6%;A=88.4%
2915851	rs563095	chr6:85969754	9.60E-05	THAL	CC=2;CT=27;TT=105	C=11.6%;T=88.4%
2915851	rs520390	chr6:85974924	9.60E-05	THAL	AA=2;AC=27;CC=105	A=11.6%;C=88.4%
2915851	rs7746109	chr6:85961891	9.60E-05	THAL	AA=2;AT=27:TT=105	A=11.6%;T=88.4%
2915851	rs1535314	chr6:85959417	9.60E-05	THAL	CC=2;CT=27;TT=105	C=11.6%;T=88.4%
2915860	NA	chr6:85638564:A_AAT	7.20E-04	THAL	NA	NA
2915861	rs149840483	chr6:85548149	2.20E-04	THAL	GG=4;GC=31;CC=96	G=14.6%;C=85.4%
2915861	rs6924488	chr6:85549039	2.20E-04	THAL	CC=4;CT=31;TT=96	C=14.6%;T=85.4%
2915861	rs182871488	chr6:85540122	2.50E-04	THAL	GG=4;GA=31;AA=96	G=14.6%;A=85.4%

2915861	rs138687409	chr6:85538838	2.90E-04	THAL	GG=4;GC=32;CC=96	G=14.9%;C=85.1%
2915861	rs9359617	chr6:85688541	8.80E-04	THAL	TT=7;TG=33;GG=92	T=17.5%;G=82.5%
2915861	rs9351027	chr6:85723224	1.00E-03	THAL	TT=8;TC=33;CC=92	T=18.3%;C=81.7%
2915861	rs9359620	chr6:85723226	1.00E-03	THAL	CC=8;CG=33;GG=92	C=18.3%;G=81.7%
2915866	rs4053810	chr6:85894932	4.60E-04	THAL	AA=3;AG=31;GG=99	A=13.8%;G=86.2%
2915866	rs535422	chr6:85982564	5.50E-04	THAL	GG=2;GA=27;AA=105	G=11.6%;A=88.4%
2915866	rs1958939	chr6:85985187	5.50E-04	THAL	CC=2;CT=27;TT=105	C=11.6%;T=88.4%
2915866	rs563095	chr6:85969754	5.50E-04	THAL	CC=2;CT=27;TT=105	C=11.6%;T=88.4%
2915866	rs520390	chr6:85974924	5.50E-04	THAL	AA=2;AC=27;CC=105	A=11.6%;C=88.4%
2915866	rs1885015	chr6:85963538	5.50E-04	THAL	GG=2;GA=27;AA=105	G=11.6%;A=88.4%
2915866	rs1981016	chr6:85961443	5.50E-04	THAL	GG=2;GA=27;AA=105	G=11.6%;A=88.4%
2915866	rs7746109	chr6:85961891	5.50E-04	THAL	AA=2;AT=27:TT=105	A=11.6%;T=88.4%
2915866	rs4053810	chr6:85894932	4.60E-04	THAL	AA=3;AG=31;GG=99	A=13.8%;G=86.2%
2915866	rs535422	chr6:85982564	5.50E-04	THAL	GG=2;GA=27;AA=105	G=11.6%;A=88.4%
2915866	rs1958939	chr6:85985187	5.50E-04	THAL	CC=2;CT=27;TT=105	C=11.6%;T=88.4%
2915866	rs563095	chr6:85969754	5.50E-04	THAL	CC=2;CT=27;TT=105	C=11.6%;T=88.4%
2915866	rs520390	chr6:85974924	5.50E-04	THAL	AA=2;AC=27;CC=105	A=11.6%;C=88.4%
2915866	rs1885015	chr6:85963538	5.50E-04	THAL	GG=2;GA=27;AA=105	G=11.6%;A=88.4%
2915866	rs1981016	chr6:85961443	5.50E-04	THAL	GG=2;GA=27;AA=105	G=11.6%;A=88.4%

2915866	rs7746109	chr6:85961891	5.50E-04	THAL	AA=2;AT=27:TT=105	A=11.6%;T=88.4 %
t2915828	rs9342002	chr6:85534582	2.70E-05	WHMT	GG=1;GA=24;AA=108	G=9.7%;A=90.3%
t2915828	rs78814887	chr6:85498798	1.30E-04	WHMT	GG=1;GA=19;AA=114	G=7.8%;A=92.2%
t2915828	rs77077151	chr6:85496965	1.30E-04	WHMT	AA=1;AG=19;GG=114	A=7.8%;G=92.2%
t2915828	rs910176	chr6:85501964	1.30E-04	WHMT	TT=1;TC=19;CC=114	T=7.8%;C=92.2%
t2915828	rs77071319	chr6:85492128	1.30E-04	WHMT	AA=1;AC=19;CC=113	A=7.8%;C=92.2%
t2915828	rs16875134	chr6:85489520	1.30E-04	WHMT	TT=1;TC=19;CC=113	T=7.8%;C=92.2%
t2915828	rs858737	chr6:85512754	1.30E-04	WHMT	GG=1;GC=19;CC=114	G=7.8%,C=92.2%
t2915828	rs866505	chr6:85514485	1.30E-04	WHMT	CC=1;CT=19;TT=114	C=7.8%;T=92.2%
t2915828	rs16875178	chr6:85516100	1.30E-04	WHMT	CC=1;CT=19;TT=114	C=7.8%;T=92.2%
2915845	rs112188458	chr6:85483448	7.40E-06	WHMT	AA=1;AG=19;GG=113	A=7.8%;G=92.2%
2915845	rs76697394	chr6:85484333	7.40E-06	WHMT	CC=1;CG=19;GG=113	C=7.8%;G=92.2%
2915845	rs113674809	chr6:85484156	7.40E-06	WHMT	GG=1;GC=19;CC=113	G=7.8%,C=92.2%
2915845	rs78656156	chr6:85480843	7.40E-06	WHMT	GG=1;GA=19;AA=113	G=7.8%;A=92.2%
2915845	rs9342002	chr6:85534582	7.60E-06	WHMT	GG=1;GA=24;AA=108	G=9.7%;A=90.3%
2915845	rs16875134	chr6:85489520	7.60E-06	WHMT	TT=1;TC=19;CC=113	T=7.8%;C=92.2%
2915845	rs77071319	chr6:85492128	7.70E-06	WHMT	AA=1;AC=19;CC=113	A=7.8%;C=92.2%

2915845	rs77077151	chr6:85496965	8.00E-06	WHMT	AA=1;AG=19;GG=114	A=7.8%;G=92.2%
2915845	rs78814887	chr6:85498798	8.00E-06	WHMT	GG=1;GA=19;AA=114	G=7.8%;A=92.2%
2915845	rs910176	chr6:85501964	8.20E-06	WHMT	TT=1;TC=19;CC=114	T=7.8%;C=92.2%
2915851	rs9342002	chr6:85534582	2.40E-05	WHMT	GG=1;GA=24;AA=108	G=9.7%;A=90.3%
2915866	rs9342002	chr6:85534582	5.50E-04	WHMT	GG=1;GA=24;AA=108	G=9.7%;A=90.3%
2915866	rs9342002	chr6:85534582	5.50E-04	WHMT	GG=1;GA=24;AA=108	G=9.7%;A=90.3%
2915869	rs9767353	chr6:85414898	1.00E-04	WHMT	AA=1;AG=32;GG=101	A=12.7%;G=87.3%
2915870	rs9342002	chr6:85534582	7.60E-07	WHMT	GG=1;GA=24;AA=108	G=9.7%;A=90.3%
2915870	rs4401629	chr6:85541393	4.30E-06	WHMT	CC=1;CA=30;AA=68	C=11.9%;A=88.1%
2915870	rs145351744	chr6:85536888	5.40E-06	WHMT	TT=1;TC=23;CC=102	T=9.3%;C=90.7%
2915870	rs10944044	chr6:85536247	6.70E-06	WHMT	AA=1;AT=24;TT=108	A=9.7%;T=90.3%
2915870	rs858740	chr6:85527080	7.40E-06	WHMT	AA=1;AC=23;CC=110	A=9.3%;C=90.7%
2915870	rs858738	chr6:85523135	7.40E-06	WHMT	TT=1;TG=23;GG=110	T=9.3%;G=90.7%
2915870	rs1102485	chr6:85531615	7.40E-06	WHMT	GG=1;GA=23;AA=110	G=9.3%;A=90.7%
2915870	rs6454396	chr6:85533497	7.50E-06	WHMT	CC=1;CtT=23;TT=110	C=9.3%;T=90.7%
2915870	rs2224213	chr6:85534101	7.50E-06	WHMT	TT=1;TC=23;CC=110	T9.3%;C=90.7%
2915870	NA	chr6:85536128:A_AT	8.80E-06	WHMT	NA	NA

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 33: Brain quantitative gene expression analyses for *SNX14* gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
t2963313	rs692830	chr6:86099731	3.50E-04	aveALL	CC=12;CT=52;TT=70	C=28.4%;T=71.6%
t2963313	rs12213716	chr6:86119089	3.90E-04	aveALL	CC=37;CT=63;TT=32	C=51.1%;T=48.9%
t2963313	rs4706238	chr6:86121473	4.20E-04	aveALL	CC=37;CT=62;TT=32	C=50.7%;T=49.3%
2963314	rs215930	chr6:85506222	1.70E-04	aveALL	TT=17;TG=58;GG=59	T=34.3%;G=65.7%
2963314	rs150118533	chr6:85529517	2.50E-04	aveALL	CC=15;CA=46;AA=70	C=28.4%;A=71.6%
2963315	rs9342070	chr6:87101329	5.20E-04	aveALL	GG=23;GT=77;TT=34	G=45.9%;T=54.1%
2963330	rs12213716	chr6:86119089	1.80E-05	aveALL	CC=37;CT=63;TT=32	C=51.1%;T=48.9%
2963330	rs4706238	chr6:86121473	2.00E-05	aveALL	CC=37;CT=62;TT=32	C=50.7%;T=49.3%
2963330	rs692830	chr6:86099731	5.50E-05	aveALL	CC=12;CT=52;TT=70	C=28.4%;T=71.6%
2963331	**rs692830**	chr6:86099731	1.30E-04	aveALL	CC=12;CT=52;TT=70	C=28.4%;T=71.6%
2963331	rs12213716	chr6:86119089	1.60E-04	aveALL	CC=37;CT=63;TT=32	C=51.1%;T=48.9%
2963331	rs4706238	chr6:86121473	1.80E-04	aveALL	CC=37;CT=62;TT=32	C=50.7%;T=49.3%
2963331	NA	chr6:87108539:G_GC	2.00E-04	aveALL	NA	NA
2963331	rs313201	chr6:86111201	2.10E-04	aveALL	TT=11;TC=53;CC=70	T=28%;C=72%
2963331	rs313196	chr6:86107232	2.10E-04	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963331	rs313198	chr6:86109615	2.10E-04	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%

2963331	rs313199	chr6:86109700	2.10E-04	aveALL	CC=11;CT=53;TT=70	C=28%;T=72%
2963331	rs597623	chr6:86100109	2.10E-04	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963335	rs313201	chr6:86111201	2.40E-04	aveALL	TT=11;TC=53;CC=70	T=28%;C=72%
2963335	rs692830	chr6:86099731	2.40E-04	aveALL	CC=12;CT=52;TT=70	C=28.4%;T=71.6%
2963335	rs313196	chr6:86107232	2.40E-04	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963335	rs313198	chr6:86109615	2.40E-04	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963335	rs313199	chr6:86109700	2.40E-04	aveALL	CC=11;CT=53;TT=70	C=28%;T=72%
2963335	rs597623	chr6:86100109	2.40E-04	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963335	rs577388	chr6:86100832	2.40E-04	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963335	rs7775853	chr6:86100916	2.40E-04	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963336	rs692830	chr6:86099731	1.00E-05	aveALL	CC=12;CT=52;TT=70	C=28.4%;T=71.6%
2963336	rs313201	chr6:86111201	2.10E-05	aveALL	TT=11;TC=53;CC=70	T=28%;C=72%
2963336	rs313196	chr6:86107232	2.10E-05	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963336	rs313198	chr6:86109615	2.10E-05	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963336	rs313199	chr6:86109700	2.10E-05	aveALL	CC=11;CT=53;TT=70	C=28%;T=72%
2963336	rs597623	chr6:86100109	2.10E-05	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963336	rs577388	chr6:86100832	2.10E-05	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%

2963336	rs7775853	chr6:86100916	2.10E-05	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963336	rs550763	chr6:86101444	2.10E-05	aveALL	AA=11;AG=53;GG=70	A=28%;G=72%
2963336	rs614124	chr6:86101535	2.10E-05	aveALL	TT=11;TC=53;CC=70	T=28%;C=72%
2963351	rs12213716	chr6:86119089	1.70E-04	aveALL	CC=37;CT=63;TT=32	C=51.1%;T=48.9%
2963351	rs4706238	chr6:86121473	1.80E-04	aveALL	CC=37;CT=62;TT=32	C=50.7%;T=49.3%
2963351	rs9362315	chr6:87108366	3.00E-04	aveALL	CC=8;CG=49;GG=68	C=24.3%;G=75.7%
2963384	rs12171570	chr6:86951455	5.00E-05	aveALL	AA=6;AG=59;GG=69	A=26.5%;G=73.5%
2963384	rs7740808	chr6:86951962	5.30E-05	aveALL	AA=6;AG=59;GG=69	A=26.5%;G=73.5%
2963384	rs4270757	chr6:86951199	5.30E-05	aveALL	AA=6;AG=59;GG=69	A=26.5%;G=73.5%
2963384	rs9359691	chr6:86950457	5.70E-05	aveALL	TT=6;TC=59;CC=69	T=26.5%;C=73.5%
2963384	rs9359692	chr6:86950469	5.70E-05	aveALL	TT=6;TC=59;CC=69	T=26.5%;C=73.5%
2963384	rs13215434	chr6:86890653	5.80E-05	aveALL	TT=6;TC=59;CC=69	T=26.5%;C=73.5%
2963384	rs6933671	chr6:86950237	1.00E-04	aveALL	AA=6;AG=55;GG=69	A=25%;G=75%
2963384	rs4706238	chr6:86121473	1.30E-04	aveALL	CC=37;CT=62;TT=32	C=50.7%;T=49.3%
t2963313	rs4373337	chr6:86179406	4.10E-04	CRBL	AA=19;AG=66;GG=49	A=38.8%;G=61.2%
t2963313	rs4593336	chr6:86181931	4.10E-04	CRBL	AA=19;AG=66;GG=49	A=38.8%;G=61.2%
2963330	rs4373337	chr6:86179406	3.30E-05	CRBL	AA=19;AG=66;GG=49	A=38.8%;G=61.2%

2963330	rs4593336	chr6:86181931	3.40E-05	CRBL	AA=19;AG=66;GG=49	A=38.8%;G=61.2%
2963338	rs4373337	chr6:86179406	3.10E-04	CRBL	AA=19;AG=66;GG=49	A=38.8%;G=61.2%
2963338	rs4593336	chr6:86181931	3.20E-04	CRBL	AA=19;AG=66;GG=49	A=38.8%;G=61.2%
2963338	rs74679834	chr6:86819356	4.00E-04	CRBL	GG=15;GC=56;CC=59	G=32.1%;C=67.9%
2963338	rs34618171	chr6:86811165	4.10E-04	CRBL	TT=15;TG=57;GG=61	T=32.5%;G=67.5%
2963338	rs13197828	chr6:86805630	4.30E-04	CRBL	CC=15;CG=57;GG=61	C=32.5%;G=67.5%
2963338	rs7746065	chr6:86174845	6.10E-04	CRBL	AA=16;AC=64;CC=53	A=35.8%;C=64.2%
2963351	rs117661970	chr6:87208938	3.30E-05	CRBL	TT=0;TG=14;GG=116	T=5.2%;G=94.8%
2963357	NA	chr6:85555226:T_TGC	1.80E-04	CRBL	NA	NA
2963384	rs6916224	chr6:85745004	2.00E-05	CRBL	GG=3;GA=40;AA=91	G=17.2%;A=82.8%
2963384	NA	chr6:85790518:A_AT	6.30E-05	CRBL	NA	NA
2963385	rs313165	chr6:86038141	3.60E-04	CRBL	AA=20;AT=57;TT=36	A=36.2%;T=63.8%
2963385	rs313169	chr6:86036409	5.20E-04	CRBL	TT=12;TA=54;AA=40	T=29.1%;A=70.9%
2963385	NA	chr6:86035307:GA_G	7.70E-04	CRBL	NA	NA
2963314	rs9444336	chr6:86088969	1.10E-04	FCTX	CC=1;CG=26;GG=106	C=10.4%;G=89.6%
2963314	rs313203	chr6:86114137	1.30E-04	FCTX	CC=1;CT=31;TT=82	C=12.3%;T=87.7%
2963314	rs4707201	chr6:86084404	1.40E-04	FCTX	GG=6;GT=48;TT=68	G=22.4%;T=77.6%

2963314	rs313202	chr6:86112738	2.40E-04	FCTX	GG=1;GC=27;CC=106	G=10.8%;C=89.2%
2963314	rs172687	chr6:86112491	2.40E-04	FCTX	TT=1;TC=27;CC=106	T=10.8%;C=89.2%
2963314	rs9450261	chr6:86089120	2.60E-04	FCTX	GG=1;GC=27;CC=96	G=10.8%;C=89.2%
2963314	rs1744124	chr6:86087075	2.70E-04	FCTX	TT=1;TC=26;CC=107	T=10.4%;C=89.6%
2963314	NA	chr6:86084943:G_GC	2.70E-04	FCTX	NA	NA
2963338	rs313174	chr6:86035889	5.70E-04	FCTX	TT=0;TC=15;CC=116	T=5.6%;C=94.4%
2963339	rs9444336	chr6:86088969	1.70E-04	FCTX	CC=1;CG=26;GG=106	C=10.4%;G=89.6%
2963349	rs4296866	chr6:86279737	2.30E-04	FCTX	TT=18;TC=69;CC=47	T=39.2%;C=60.8%
2963353	rs9444336	chr6:86088969	5.60E-05	FCTX	CC=1;CG=26;GG=106	C=10.4%;G=89.6%
2963353	rs313203	chr6:86114137	6.10E-05	FCTX	CC=1;CT=31;TT=82	C=12.3%;T=87.7%
2963353	rs172687	chr6:86112491	7.40E-05	FCTX	TT=1;TC=27;CC=106	T=10.8%;C=89.2%
2963353	rs313202	chr6:86112738	7.40E-05	FCTX	GG=1;GC=27;CC=106	G=10.8%;C=89.2%
2963357	rs58800166	chr6:86047483	9.20E-05	FCTX	CC=0;CT=16;TT=116	C=6%;T=94%
2963386	rs7760395	chr6:85760635	3.40E-04	FCTX	CC=4;CT=39;TT=91	C=17.5%;T=82.5%
2963386	rs9444287	chr6:85751929	3.90E-04	FCTX	CC=4;CT=38;TT=91	C=17.2%;T=82.8%
2963323	rs191754530	chr6:87238639	6.80E-05	HIPP	TT=0;TG=12;GG=110	T=4.5%;G=95.5%
2963335	rs9353304	chr6:86080158	1.50E-04	HIPP	CC=3;CG=33;GG=97	C=14.6%;G=85.4%

2963338	rs17695108	chr6:85724717	6.20E-04	HIPP	CC=0;CT=20;TT=111	C=7.5%;T=92.5%
2963338	rs149702128	chr6:86020914	7.30E-04	HIPP	AA=0;AT=14;TT=112	A=5.2%;T=95.8%
2963338	rs75202618	chr6:86013713	7.70E-04	HIPP	GG=0;GA=14;AA=112	G=5.2%;A=94.8%
2963349	rs191754530	chr6:87238639	1.10E-04	HIPP	TT=0;TG=12;GG=110	T=4.5%;G=95.5%
2963357	rs62440692	chr6:87209701	1.70E-05	HIPP	AA=1;AG=21;GG=101	A=8.6%;G=91.4%
2963357	rs6911143	chr6:86221771	3.70E-05	HIPP	TT=21;TC=59;CC=46	T=37.7%;C=62.3%
2963357	rs2324775	chr6:86067614	1.70E-04	HIPP	GG=3;GT=34;TT=97	G=14.9%;T=85.1%
2963379	rs145351744	chr6:85536888	2.10E-06	HIPP	TT=1;TC=23;CC=102	T=9.3%;C=90.7%
2963379	rs6454398	chr6:85548671	2.40E-06	HIPP	GG=1;GC=23;CC=103	G=9.3%;C=90.7%
2963379	rs2224210	chr6:85574238	4.70E-06	HIPP	CC=1;CA=24;AA=109	C=9.7%;A=90.3%
2963379	rs2324751	chr6:85550546	4.70E-06	HIPP	CC=1;CT=24;TT=109	C=9.7%;T=90.3%
2963379	rs6454400	chr6:85568534	4.70E-06	HIPP	AA=1;AG=24;GG=109	A=9.7%;G=90.3%
2963379	rs9353228	chr6:85571747	4.70E-06	HIPP	TT=1;TA=24;AA=109	T=9.7%;A=90.3%
2963379	rs2207979	chr6:85572462	4.70E-06	HIPP	TT=1;TC=24;CC=109	T=9.7%;C=90.3%
2963379	rs2324754	chr6:85570015	4.70E-06	HIPP	GG=1;GA=24;AA=109	G=9.7%;A=90.3%
2963379	rs2024848	chr6:85563886	4.70E-06	HIPP	AA=1;AG=24;GG=109	A=9.7%;G=90.3%
2963379	rs2024847	chr6:85564139	4.70E-06	HIPP	CC=1;CT=24;TT=109	C=9.7%;T=90.3%

t2963313	**rs13207994**	chr6:86017382	1.50E-04	MEDU	TT=8;TG=33;GG=40	T=18.3%;G=81.7%
t2963313	rs7771048	chr6:86042433	2.00E-04	MEDU	TT=17;TC=55;CC=39	T=33.2%;C=66.8%
2963319	**rs143067645**	chr6:86017570	2.30E-05	MEDU	TT=27;TC=58;CC=38	T=41.8%;C=58.2%
2963319	rs9450238	chr6:86041923	4.30E-05	MEDU	CC=26;CA=62;AA=23	C=42.5%;A=57.5%
2963319	rs143403379	chr6:86017494	5.80E-05	MEDU	TT=26;TC=60;CC=38	T=41.8%;C=58.2%
2963319	rs145741770	chr6:86012902	6.00E-05	MEDU	GG=29;GA=61;AA=37	G=44.4%;A=55.6%
2963319	rs1665783	chr6:86019526	6.40E-05	MEDU	TT=9;TC=38;CC=40	T=20.9%;C=79.1%
2963319	rs144077722	chr6:86019168	8.40E-05	MEDU	CC=28;CT=57;TT=36	C=42.2%;T=57.8%
2963319	rs1665781	chr6:86014547	9.20E-05	MEDU	TT=13;TG=47;GG=40	T=27.2%;G=72.8%
2963319	rs1665780	chr6:86014543	9.70E-05	MEDU	TT=13;TC=47;CC=40	T=27.2%;C=72.8%
2963319	rs13203913	chr6:86016775	1.10E-04	MEDU	TT=26;TC=51;CC=39	T=38.4%;C=61.6%
2963331	rs13207994	chr6:86017382	1.40E-04	MEDU	TT=8;TG=33;GG=40	T=18.3%;G=81.7%
2963342	rs7771048	chr6:86042433	2.50E-04	MEDU	TT=17;TC=55;CC=39	T=33.2%;C=66.8%
2963351	rs62420138	chr6:86049151	4.80E-04	MEDU	GG=7;GA=54;AA=73	G=25.4%;A=74.6%
t2963313	rs78976971	chr6:87089801	4.20E-04	OCTX	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963329	**rs78976971**	chr6:87089801	1.00E-05	OCTX	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963329	rs74331769	chr6:87094433	1.00E-05	OCTX	GG=1;GC=17;CC=116	G=7.1%;C=92.9%

2963329	rs77084769	chr6:87086819	1.00E-05	OCTX	TT=1;TC=17;CC=116	T=7.1%;C=92.9%
2963329	rs79230424	chr6:87087883	1.00E-05	OCTX	CC=1;CT=17;TT=116	C=7.1%;T=92.9%
2963329	rs113210181	chr6:87099231	1.00E-05	OCTX	CC=1;CA=17;AA=116	C=7.1%;A=92.9%
2963329	rs113317083	chr6:87099879	1.00E-05	OCTX	AA=1;AC=17;CC=116	A=7.1%;C=92.9%
2963329	rs6900662	chr6:87100832	1.00E-05	OCTX	CC=1;CT=17;TT=116	C=7.1%;T=92.9%
2963329	rs78276710	chr6:87101879	1.00E-05	OCTX	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963329	rs76789012	chr6:87084390	1.00E-05	OCTX	TT=1;TC=17;CC=116	T=7.1%;C=92.9%
2963329	rs138156981	chr6:87102800	1.00E-05	OCTX	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963330	rs220418	chr6:86862386	4.80E-05	OCTX	TT=1;TC=16;CC=117	T=6.7%;C=93.3%
2963330	rs146217639	chr6:86946422	5.80E-05	OCTX	AA=0;AG=15;GG=119	A=5.6%;G=94.4%
2963330	rs4644015	chr6:86948133	5.80E-05	OCTX	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2963330	NA	chr6:86944544:GA_G	5.80E-05	OCTX	NA	NA
2963342	rs1853340	chr6:85609478	1.90E-04	OCTX	AA=A;AG=24;GG=106	A=9.7%;G=90.3%
2963342	rs4142005	chr6:85725755	2.80E-04	OCTX	CC=0;CG=26;GG=108	C=9.7%;G=90.3%
2963342	rs73750146	chr6:85727539	2.80E-04	OCTX	AA=0;AG=26;GG=108	A=9.7%;G=90.3%
2963342	rs1535547	chr6:85727858	2.80E-04	OCTX	TT=0;TC=26;CC=108	T=9.7%;C=90.3%
2963342	rs4707116	chr6:85730570	2.80E-04	OCTX	TT=0;TC=26;CC=108	T=9.7%;C=90.3%

2963342	rs9450114	chr6:85731357	2.80E-04	OCTX	AA=0;AG=26;GG=108	A=9.7%;G=90.3%
2963349	rs9362117	chr6:85670971	1.20E-04	OCTX	AA=24;AG=58;GG=45	A=39.6%;G=60.4%
2963349	rs9351023	chr6:85666475	2.10E-04	OCTX	AA=24;AG=54;GG=54	A=38.1%;G=61.9%
2963360	rs78976971	chr6:87089801	9.30E-05	OCTX	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963360	rs74331769	chr6:87094433	9.40E-05	OCTX	GG=1;GC=17;CC=116	G=7.1%;C=92.9%
2963360	rs113210181	chr6:87099231	9.40E-05	OCTX	CC=1;CA=17;AA=116	C=7.1%;A=92.9%
2963360	rs113317083	chr6:87099879	9.50E-05	OCTX	AA=1;AC=17;CC=116	A=7.1%;C=92.9%
2963360	rs78276710	chr6:87101879	9.50E-05	OCTX	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963360	rs6900662	chr6:87100832	9.50E-05	OCTX	CC=1;CT=17;TT=116	C=7.1%;T=92.9%
2963360	rs138156981	chr6:87102800	9.50E-05	OCTX	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963360	rs145998080	chr6:87103377	9.50E-05	OCTX	TT=1;TC=17;CC=116	T=7.1%;C=92.9%
2963360	rs75666720	chr6:87111883	9.50E-05	OCTX	CC=1;CT=17;TT=116	C=7.1%;T=92.9%
2963361	rs16876949	chr6:87095383	4.50E-06	OCTX	TT=1;TA=20;AA=113	T=8.2%;A=91.8%
2963361	rs6922726	chr6:87095937	4.50E-06	OCTX	GG=1;GC=20;CC=113	G=8.2%;C=91.8%
2963361	rs71572713	chr6:87096866	4.50E-06	OCTX	CC=1;CT=20;TT=113	C=8.2%;T=91.8%
2963361	rs35378388	chr6:87098679	4.50E-06	OCTX	TT=1;TG=20;GG=113	T=8.2%;G=91.8%
2963361	rs13220428	chr6:87099280	4.50E-06	OCTX	TT=1;TC=20;CC=113	T=8.2%;C=91.8%

2963361	rs35231450	chr6:87100369	4.50E-06	OCTX	AA=1;AG=20;GG=113	A=8.2%;G=91.8%
2963361	rs6920745	chr6:87100893	4.50E-06	OCTX	TT=1;TC=20;CC=113	T=8.2%;C=91.8%
2963361	rs4707273	chr6:87072684	4.50E-06	OCTX	AA=1;AG=20;GG=113	A=8.2%;G=91.8%
2963361	rs78334223	chr6:87092067	4.50E-06	OCTX	AA=1;AC=20;CC=113	A=8.2%;C=91.8%
2963361	rs35672166	chr6:87092348	4.50E-06	OCTX	TT=1;TC=20;CC=113	T=8.2%;C=91.8%
2963375	rs75005612	chr6:87088843	7.20E-07	OCTX	TT=1;TC=19;CC=113	T=7.8%;C=92.2%
2963375	rs77895110	chr6:87088842	7.20E-07	OCTX	GG=1;GT=19;TT=113	G=7.8%;T=92.2%
2963375	rs78976971	chr6:87089801	1.10E-06	OCTX	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963375	rs77084769	chr6:87086819	1.10E-06	OCTX	TT=1;TC=17;CC=116	T=7.1%;C=92.9%
2963375	rs79230424	chr6:87087883	1.10E-06	OCTX	CC=1;CT=17;TT=116	C=7.1%;T=92.9%
2963375	rs76789012	chr6:87084390	1.10E-06	OCTX	TT=1;TC=17;CC=116	T=7.1%;C=92.9%
2963375	rs74331769	chr6:87094433	1.10E-06	OCTX	GG=1;GC=17;CC=116	G=7.1%;C=92.9%
2963375	rs113210181	chr6:87099231	1.10E-06	OCTX	CC=1;CA=17;AA=116	C=7.1%;A=92.9%
2963375	rs113317083	chr6:87099879	1.10E-06	OCTX	AA=1;AC=17;CC=116	A=7.1%;C=92.9%
2963375	rs6900662	chr6:87100832	1.10E-06	OCTX	CC=1;CT=17;TT=116	C=7.1%;T=92.9%
2963315	NA	chr6:85442554:ATC_A	1.50E-04	PUTM	NA	NA
2963368	NA	chr6:85297228	4.20E-05	PUTM	NA	NA

2963368	NA	chr6:85294913	6.90E-05	PUTM	NA	NA
2963368	rs13204398	chr6:85314373	1.10E-04	PUTM	TT=7;TC=44;CC=77	T=21.6%;C=78.4%
2963370	NA	chr6:87108539:G_GC	5.70E-06	PUTM	NA	NA
2963370	rs78976971	chr6:87089801	7.60E-06	PUTM	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963370	rs74331769	chr6:87094433	7.60E-06	PUTM	GG=1;GC=17;CC=116	G=7.1%;C=92.9%
2963370	rs113210181	chr6:87099231	7.70E-06	PUTM	CC=1;CA=17;AA=116	C=7.1%;A=92.9%
2963370	rs113317083	chr6:87099879	7.70E-06	PUTM	AA=1;AC=17;CC=116	A=7.1%;C=92.9%
2963370	rs6900662	chr6:87100832	7.70E-06	PUTM	CC=1;CT=17;TT=116	C=7.1%;T=92.9%
2963370	rs78276710	chr6:87101879	7.70E-06	PUTM	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963370	rs79230424	chr6:87087883	7.70E-06	PUTM	CC=1;CT=17;TT=116	C=7.1%;T=92.9%
2963370	rs138156981	chr6:87102800	7.70E-06	PUTM	AA=1;AG=17;GG=116	A=7.1%;G=92.9%
2963370	rs145998080	chr6:87103377	7.70E-06	PUTM	TT=1;TC=17;CC=116	T=7.1%;C=92.9%
2963385	rs35651815	chr6:85823686	4.90E-04	PUTM	AA=7;AG=45;GG=81	A=22%;G=78%
2963385	rs1536277	chr6:85823394	8.10E-04	PUTM	GG=7;GA=46;AA=81	G=22.4%;A=77.6%
2963386	NA	chr6:85297953	6.50E-04	PUTM	NA	NA
2963386	NA	chr6:85298060	7.00E-04	PUTM	NA	NA
2963386	NA	chr6:85290098	8.60E-04	PUTM	NA	NA

t2963313	rs9342073	chr6:87116491	3.40E-04	SNIG	GG=2;GT=47;TT=70	G=19%;T=81%
2963315	rs9342073	chr6:87116491	3.20E-04	SNIG	GG=2;GT=47;TT=70	G=19%;T=81%
2963315	rs62440692	chr6:87209701	3.30E-04	SNIG	AA=1;AG=21;GG=101	A=8.6%;G=91.4%
2963315	rs9342070	chr6:87101329	4.30E-04	SNIG	GG=23;GT=77;TT=34	G=45.9%;T=54.1%
2963315	rs9362315	chr6:87108366	4.40E-04	SNIG	CC=8;CG=49;GG=68	C=24.3%;G=75.7%
2963315	rs55924843	chr6:86867342	5.90E-04	SNIG	AA=2;AG=26;GG=106	A=11.2%;G=88.8%
2963323	rs9342073	chr6:87116491	3.10E-05	SNIG	GG=2;GT=47;TT=70	G=19%;T=81%
2963323	rs9362315	chr6:87108366	1.10E-04	SNIG	CC=8;CG=49;GG=68	C=24.3%;G=75.7%
2963323	NA	chr6:87126146:C_CT	1.20E-04	SNIG	NA	NA
2963323	rs9342070	chr6:87101329	1.70E-04	SNIG	GG=23;GT=77;TT=34	G=45.9%;T=54.1%
2963323	rs9353404	chr6:87122799	2.40E-04	SNIG	GG=2;GA=44;AA=88	G=17.9%;A=82.1%
2963323	rs12193445	chr6:87124385	2.40E-04	SNIG	TT=2;TG=44;GG=88	T=17.9%;G=82.1%
2963323	rs6924170	chr6:87126662	2.40E-04	SNIG	AA=2;AG=44;GG=88	A=17.9%;G=82.1%
2963323	rs9344610	chr6:87125942	2.40E-04	SNIG	CC=2;CT=44;TT=88	C=17.9%;T=82.1%
2963323	rs12193553	chr6:87094486	2.40E-04	SNIG	TT=2;TG=43;GG=89	T=17.5%;G=82.5%
2963330	rs9342073	chr6:87116491	4.20E-05	SNIG	GG=2;GT=47;TT=70	G=19%;T=81%
2963339	NA	chr6:86857908:TTTC_	1.30E-05	SNIG	NA	NA

2963339	rs9342073	chr6:87116491	6.20E-05	SNIG	GG=2;GT=47;TT=70	G=19%;T=81%
2963339	rs2493177	chr6:86980204	9.10E-05	SNIG	TT=0;TG=7;GG=116	T=2.6%;G=97.4%
2963342	rs9342073	chr6:87116491	2.20E-04	SNIG	GG=2;GT=47;TT=70	G=19%;T=81%
2963342	rs75794114	chr6:86744944	2.30E-04	SNIG	CC=2;CA=30;AA=97	C=12.7%;A=87.3%
2963342	rs9344563	chr6:86759985	2.60E-04	SNIG	AA=2;AC=29;CC=97	A=12.3%;C=87.7%
2963351	rs9342073	chr6:87116491	3.20E-04	SNIG	GG=2;GT=47;TT=70	G=19%;T=81%
2963351	rs9342070	chr6:87101329	4.70E-04	SNIG	GG=23;GT=77;TT=34	G=45.9%;T=54.1%
2963357	rs62440692	chr6:87209701	1.60E-04	SNIG	AA=1;AG=21;GG=101	A=8.6%;G=91.4%
2963357	rs2224210	chr6:85574238	2.10E-04	SNIG	CC=1;CA=24;AA=109	C=9.7%;A=90.3%
2963358	rs9362315	chr6:87108366	7.60E-05	SNIG	CC=8;CG=49;GG=68	C=24.3%;G=75.7%
2963358	NA	chr6:87116852:CT_C	1.20E-04	SNIG	NA	NA
2963358	rs1508248	chr6:87116788	1.20E-04	SNIG	CC=2;CT=43;TT=86	C=17.5%;T=82.5%
2963358	NA	chr6:87101427:AT_A	1.60E-04	SNIG	NA	NA
2963358	rs34626960	chr6:87077935	1.60E-04	SNIG	TT=2;TG=43;GG=89	T=17.5%;G=82.5%
2963358	rs9362321	chr6:87136247	1.70E-04	SNIG	TT=2;TC=46;CC=86	T=18.7%;C=81.3%
2963358	rs4389738	chr6:87119847	1.70E-04	SNIG	TT=2;TA=44;AA=88	T=17.9%;A=82.1%
2963358	rs35801799	chr6:87083799	1.70E-04	SNIG	GG=2;GA=43;AA=89	G=17.5%;A=82.5%

2963358	rs9353404	chr6:87122799	1.70E-04	SNIG	GG=2;GA=44;AA=88	G=17.9%;A=82.1%
2963358	rs12193445	chr6:87124385	1.70E-04	SNIG	TT=2;TG=44;GG=88	T=17.9%;G=82.1%
2963373	rs17541873	chr6:87001570	4.30E-04	SNIG	AA=3;AG=33;GG=98	A=14.6%;G=85.4%
2963373	rs6903701	chr6:87017712	4.30E-04	SNIG	TT=3;TG=33;GG=98	T=14.6%;G=85.4%
2963373	rs72907184	chr6:87021347	4.30E-04	SNIG	AA=3;AG=33;GG=98	A=14.6%;G=85.4%
2963373	rs72907201	chr6:87026211	4.30E-04	SNIG	TT=3;TG=33;GG=98	T=14.6%;G=85.4%
2963373	rs72909179	chr6:87033296	4.30E-04	SNIG	CC=3;CT=33;TT=98	C=14.6%;T=85.4%
2963373	rs72909187	chr6:87036782	4.30E-04	SNIG	AA=3;AG=33;GG=98	A=14.6%;G=85.4%
2963373	rs72909197	chr6:87039406	4.30E-04	SNIG	AA=3;AG=33;GG=98	A=14.6%;G=85.4%
2963373	rs72911113	chr6:87042098	4.30E-04	SNIG	CC=3;CT=33;TT=98	C=14.6%;T=85.4%
2963373	rs2324927	chr6:87045175	4.30E-04	SNIG	GG=3;GA=33;AA=98	G=14.6%;A=85.4%
2963385	rs9362158	chr6:85919934	8.40E-04	SNIG	TT=17;TC=64;CC=30	T=36.6%;C=63.4%
2963385	rs9344480	chr6:85920060	1.10E-03	SNIG	TT=19;TC=59;CC=27	T=36.2%;C=63.8%
t2963313	rs9362315	chr6:87108366	2.10E-04	TCTX	CC=8;CG=49;GG=68	C=24.3%;G=75.7%
2963315	NA	chr6:87117571:CTTTC	4.80E-04	TCTX	NA	NA
2963315	rs113626304	chr6:87117437	6.30E-04	TCTX	AA=1;AC=23;CC=105	A=9.3%;C=90.7%
2963333	rs9362315	chr6:87108366	5.80E-05	TCTX	CC=8;CG=49;GG=68	C=24.3%;G=75.7%

2963335	**rs9362315**	chr6:87108366	5.50E-05	TCTX	CC=8;CG=49;GG=68	C=24.3%;G=75.7%
2963339	rs10944251	chr6:87304060	9.10E-06	TCTX	TT=5;TG=36;GG=93	T=17.2%;G=82.8%
2963339	rs62439011	chr6:87299378	3.70E-05	TCTX	TT=2;TG=25;GG=101	T=10.8%;G=89.2%
2963339	rs62440692	chr6:87209701	8.70E-05	TCTX	AA=1;AG=21;GG=101	A=8.6%;G=91.4%
2963339	rs9362315	chr6:87108366	9.70E-05	TCTX	CC=8;CG=49;GG=68	C=24.3%;G=75.7%
2963339	rs9342077	chr6:87219320	1.60E-04	TCTX	CC=2;CT=41;TT=91	C=16.8%;T=83.2%
2963339	NA	chr6:87222383:CTG_C	1.60E-04	TCTX	NA	NA
2963349	rs9362315	chr6:87108366	2.40E-04	TCTX	CC=8;CG=49;GG=68	C=24.3%;G=75.7%
2963349	rs9450450	chr6:87130477	2.60E-04	TCTX	CC=9;CT=62;TT=63	C=29.9%;T=70.1%
2963349	rs6920365	chr6:87138076	2.70E-04	TCTX	TT=9;TA=62;AA=63	T=29.9%;A=70.1%
2963357	rs10944251	chr6:87304060	3.60E-05	TCTX	TT=5;TG=36;GG=93	T=17.2%;G=82.8%
2963357	rs511836	chr6:86083779	8.30E-05	TCTX	CC=26;CT=67;TT=23	C=44.4%;T=55.6%
2963360	rs9362315	chr6:87108366	5.80E-05	TCTX	CC=8;CG=49;GG=68	C=24.3%;G=75.7%
2963386	NA	chr6:87117571:CTTTC	4.30E-04	TCTX	NA	NA
2963386	NA	chr6:87140638:T_TA	7.70E-04	TCTX	NA	NA
2963386	rs187565307	chr6:87140641	7.70E-04	TCTX	TT=1;TA=30;AA=103	T=11.9%;A=88.1%
2963386	rs76684814	chr6:87133748	7.90E-04	TCTX	GG=1;GT=29;TT=104	G=11.6%;T=88.4%

2963315	rs9362122	chr6:85746124	4.50E-04	THAL	AA=5;AG=31;GG=89	A=15.3%;G=84.7%
2963354	NA	chr6:85469407:AC_A	2.80E-04	THAL	NA	NA
2963368	rs692830	chr6:86099731	1.20E-04	THAL	CC=12;CT=52;TT=70	C=28.4%;T=71.6%
2963368	rs313196	chr6:86107232	1.40E-04	THAL	AA=11;AG=53;GG=70	A=28%;G=72%
2963368	rs597623	chr6:86100109	1.40E-04	THAL	AA=11;AG=53;GG=70	A=28%;G=72%
2963368	rs577388	chr6:86100832	1.40E-04	THAL	AA=11;AG=53;GG=70	A=28%;G=72%
2963368	rs7775853	chr6:86100916	1.40E-04	THAL	AA=11;AG=53;GG=70	A=28%;G=72%
2963368	rs550763	chr6:86101444	1.40E-04	THAL	AA=11;AT=53;TT=70	A=28%;T=72%
2963368	rs614124	chr6:86101535	1.40E-04	THAL	TT=11;TC=53;CC=70	T=28%;C=72%
2963319	rs75594123	chr6:85990805	8.90E-05	WHMT	CC=9;CT=63;TT=60	C=30.2%;T=69.8%
2963333	rs11962597	chr6:85777904	5.90E-05	WHMT	CC=0;CT=19;TT=115	C=7.1%;T=92.9%
2963333	rs17802995	chr6:85777759	6.10E-05	WHMT	CC=0;CT=19;TT=115	C=7.1%;T=92.9%
2963333	rs35593857	chr6:85769053	6.50E-05	WHMT	TT=0;TC=15;CC=119	T=7.1%;C=92.9%
2963333	rs17194619	chr6:85769151	6.50E-05	WHMT	CC=0;CA=19;AA=115	C=7.1%;A=92.9%
2963333	rs17802851	chr6:85770542	6.50E-05	WHMT	CC=0;CT=19;TT=115	C=7.1%;T=92.9%
2963333	rs11965782	chr6:85772144	6.50E-05	WHMT	AA=0;AG=19;GG=115	A=7.1%;G=92.9%
2963333	rs11965808	chr6:85772278	6.60E-05	WHMT	AA=0;AG=19;GG=115	A=7.1%;G=92.9%

2963333	rs66513010	chr6:85772897	6.60E-05	WHMT	GG=0;GA=19;AA=115	G=7.1%;A=92.9%
2963333	rs67785337	chr6:85775082	6.70E-05	WHMT	GG=0;GA=19;AA=115	G=7.1%;A=92.9%
2963349	rs9765933	chr6:85746176	1.40E-04	WHMT	CC=0;CT=13;TT=94	C=4.9%;T=95.1%
2963349	rs9767364	chr6:85746183	2.20E-04	WHMT	TT=0;TC=11;CC=93	T=4.1%;C=95.9%
2963349	rs16875429	chr6:85706347	2.70E-04	WHMT	TT=0;TC=19;CC=115	T=7.1%;C=92.9%
2963351	rs9362178	chr6:86002337	4.90E-04	WHMT	CC=2;CT=35;TT=90	C=14.6%;T=85.4%
2963351	rs150793602	chr6:86918479	4.90E-04	WHMT	AA=1;AT=10;TT=109	A=4.5%;T=95.5%
2963351	rs313228	chr6:85998172	5.50E-04	WHMT	AA=9;AG=59;GG=66	A=28.7%;G=71.3%
2963353	rs11962597	chr6:85777904	1.10E-04	WHMT	CC=0;CT=19;TT=115	C=7.1%;T=92.9%
2963353	rs17802995	chr6:85777759	1.10E-04	WHMT	CC=0;CT=19;TT=115	C=7.1%;T=92.9%
2963353	rs35593857	chr6:85769053	1.20E-04	WHMT	TT=0;TC=19;CC=115	T=7.1%;C=92.9%
2963353	rs17194619	chr6:85769151	1.20E-04	WHMT	CC=0;CA=19;AA=115	C=7.1%;T=92.9%
2963353	rs17802851	chr6:85770542	1.20E-04	WHMT	CC=0;CT=19;TT=115	C=7.1%;T=92.9%
2963353	rs11965782	chr6:85772144	1.20E-04	WHMT	AA=0;AG=19;GG=115	A=7.1%;G=92.9%
2963354	rs1888928	chr6:85986877	1.80E-05	WHMT	CC=11;CT=54;TT=69	C=28.4%;T=71.6%
2963354	rs9362178	chr6:86002337	3.10E-05	WHMT	CC=2;CT=35;TT=90	C=14.6%;T=85.4%
2963354	rs139913719	chr6:86020752	7.00E-05	WHMT	AA=2;AG=25;GG=83	A=10.8%;G=89.2%

2963354	rs4707174	chr6:85987918	8.60E-05	WHMT	CC=16;CA=58;AA=60	C=33.6%;A=66.4%
2963354	rs2093508	chr6:85803657	1.10E-04	WHMT	GG=17;GA=53;AA=64	G=32.5%;A=67.5%
2963354	rs6909854	chr6:85814526	1.10E-04	WHMT	AA=17;AG=53;GG=64	A=32.5%;G=67.5%
2963354	rs7750062	chr6:85797118	1.10E-04	WHMT	GG=17;GA=53;AA=64	G=32.5%;A=67.5%
2963354	rs10485301	chr6:85800575	1.10E-04	WHMT	CC=17;CT=53;TT=64	C=32.5%;T=67.5%
2963354	rs9450165	chr6:85819887	1.10E-04	WHMT	GG=17;GA=53;AA=64	G=32.5%;A=67.5%
2963357	rs78538329	chr6:86021445	1.10E-04	WHMT	AA=0;AG=2;GG=102	A=0.7%;G=99.3%
2963373	rs78538329	chr6:86021445	3.50E-04	WHMT	AA=0;AG=2;GG=102	A=0.7%;G=99.3%
2963385	NA	chr6:85293326	4.00E-04	WHMT	NA	NA
2963385	rs17587983	chr6:85507525	6.70E-04	WHMT	AA=0AG=18;GG=110	A=6.7%;G=93.3%
2963385	rs72912670	chr6:85567122	1.10E-03	WHMT	AA=0;AC=18;CC=109	A=6.7%;C=93.3%
2963386	NA	chr6:86720576:C_CT	4.70E-04	WHMT	NA	NA

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 34: Brain quantitative gene expression analyses for *SYNCRIP* gene variants.

Expr ID	**rsID**	**Variant**	***P*-value**	tissue	**Genotype_counts**	**Allele_frequency**
t2963407	rs139549658	chr6:85779709	3.00E-04	aveALL	TT=0;TA=13;AA=119	T=4.9%;A=95.1%

t2963407	rs6911077	chr6:85744440	9.90E-04	aveALL	GG=0;GA=15;AA=119	G=5.6%;A=94.4%
t2963407	rs78158049	chr6:85747990	9.90E-04	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2963411	rs9450110	chr6:85720375	8.60E-05	aveALL	CC=1;CA=18;AA=115	C=7.5%;A=92.5%
2963415	rs3000072	chr6:86967077	8.40E-04	aveALL	AA=8;AT=47;TT=59	A=23.5%;T=76.5%
2963415	rs2798530	chr6:86966457	8.50E-04	aveALL	GG=7;GA=52;AA=75	G=24.6%;A=75.4%
2963415	rs2988678	chr6:86962204	9.20E-04	aveALL	AA=7;AT=52;TT=75	A=24.6%;T=75.4%
2963415	rs72905273	chr6:86959025	9.40E-04	aveALL	AA=7;AT=52;TT=75	A=24.6%;T=75.4%
2963415	rs11753958	chr6:86956307	1.00E-03	aveALL	AA=7;AG=52;GG=75	A=24.6%;G=75.4%
2963409	rs7739563	chr6:86156315	1.30E-03	CRBL	CC=16;CT=63;TT=52	C=35.4%;T=64.6%
2963409	rs6454468	chr6:86150384	1.70E-03	CRBL	TT=16;TG=64;GG=54	T=35.8%;G=64.2%
2963409	rs2208725	chr6:86147774	1.70E-03	CRBL	TT=16;TC=64;CC=54	T=35.8%;C=64.2%
2963409	rs6931295	chr6:86144875	1.70E-03	CRBL	TT=16;TC=64;CC=54	T=35.8%;C=64.2%
2963411	rs16875178	chr6:85516100	6.80E-05	CRBL	CC=1;CT=19;TT=114	C=7.8%;T=92.2%
2963411	rs866505	chr6:85514485	6.80E-05	CRBL	CC=1;CT=19;TT=114	C=7.8%;T=92.2%
2963411	rs858737	chr6:85512754	6.90E-05	CRBL	GG=1;GC=19;CC=114	G=7.8%;C=92.2%
2963411	rs910176	chr6:85501964	7.00E-05	CRBL	TT=1;TC=19;CC=114	T=7.8%;C=92.2%
2963411	rs78814887	chr6:85498798	7.00E-05	CRBL	GG=1;GA=19;AA=114	G=7.8%;A=92.2%

2963411	rs77077151	chr6:85496965	7.10E-05	CRBL	AA=1;AG=19;GG=114	A=7.8%;G=92.2%
2963411	rs77071319	chr6:85492128	7.30E-05	CRBL	AA=1;AC=19;CC=113	A=7.8%;C=92.2%
2963411	rs16875134	chr6:85489520	7.30E-05	CRBL	TT=1;TC=19;CC=113	T=7.8%;C=92.2%
2963411	rs76697394	chr6:85484333	8.50E-05	CRBL	CC=1;CG=19;GG=113	C=7.8%;G=92.2%
2963412	rs9885944	chr6:86149161	1.10E-03	CRBL	CC=39;CG=65;GG=29	C=53.4%;G=46.6%
2963412	rs4288177	chr6:86151908	1.50E-03	CRBL	GG=39;GA=65;AA=28	G=53.4%;A=46.6%
2963412	rs11752251	chr6:86162868	1.50E-03	CRBL	GG=39;GA=66;AA=29	G=53.7%;A=46.3%
2963412	rs9450277	chr6:86157419	1.50E-03	CRBL	GG=39;GA=66;AA=29	G=53.7%;A=46.3%
2963412	NA	chr6:86158426:TGTTA	1.50E-03	CRBL	NA	NA
2963453	rs7766990	chr6:85670489	4.40E-04	CRBL	TT=24;TC=59;CC=50	T=39.9%;C=60.1%
2963453	rs7749260	chr6:85670612	4.40E-04	CRBL	CC=24;CT=59;TT=50	C=39.9%;T=60.1%
2963453	rs2144751	chr6:85673127	4.50E-04	CRBL	CC=24;CT=59;TT=50	C=39.9%;T=60.1%
2963453	rs9353236	chr6:85675930	4.50E-04	CRBL	CC=24;CT=59;TT=50	C=39.9%;T=60.1%
2963453	rs2208880	chr6:85684033	6.20E-04	CRBL	CC=23;CT=59;TT=52	C=39.2%;T=60.8%
t2963407	rs9444336	chr6:86088969	6.40E-04	FCTX	CC=1;CG=26;GG=106	C=10.4%;G=89.6%
2963412	rs4706225	chr6:85906615	1.50E-03	FCTX	AA=2;AG=18;GG=114	A=8.2%;G=91.8%
2963415	rs117204153	chr6:86771039	7.60E-04	FCTX	TT=4;TA=38;AA=92	T=17.2%;A=82.8%

2963415	rs6923394	chr6:86767686	7.60E-04	FCTX	AA=4;AG=38;GG=92	A=17.2%;G=82.8%
2963415	rs62443462	chr6:86775018	7.70E-04	FCTX	AA=4;AG=38;GG=92	A=17.2%;G=82.8%
2963425	rs9450261	chr6:86089120	5.80E-04	FCTX	GG=1;GC=27;CC=96	G=10.8%;C=89.2%
2963425	rs313203	chr6:86114137	7.80E-04	FCTX	CC=1;CT=31;TT=82	C=12.3%;T=87.7%
2963425	rs9444336	chr6:86088969	1.10E-03	FCTX	CC=1;CG=26;GG=106	C=10.4%;G=89.6%
2963425	rs7762479	chr6:86084501	1.20E-03	FCTX	TT=1;TC=26;CC=102	T=10.4%;C=89.6%
2963451	rs2104205	chr6:85805584	1.70E-03	FCTX	AA=16;AG=60;GG=52	A=34.3%;G=65.7%
t2963407	rs139549658	chr6:85779709	4.50E-04	HIPP	TT=0;TA=13;AA=119	T=4.9%;A=95.1%
2963409	rs143405116	chr6:85537381	2.60E-04	HIPP	GG=3;GA=42;AA=26	G=17.9%;A=82.1%
2963412	rs17695108	chr6:85724717	1.50E-03	HIPP	CC=0;CT=20;TT=111	C=7.5%;T=92.5%
2963415	rs139549658	chr6:85779709	9.50E-04	HIPP	TT=0;TA=13;AA=119	T=4.9%;A=95.1%
2963415	rs193100232	chr6:87310833	1.10E-03	HIPP	AA=1;AG=7;GG=113	A=3.4%;G=96.6%
2963425	NA	chr6:85924728:G_GT	7.60E-04	HIPP	NA	NA
2963425	rs74607413	chr6:86604073	1.20E-03	HIPP	GG=3;GA=31;AA=58	G=13.8%;A=86.2%
2963425	rs220418	chr6:86862386	8.40E-04	MEDU	TT=1;TC=16;CC=117	T=6.7%;C=93.3%
2963453	rs6923147	chr6:85825072	1.70E-04	MEDU	GG=12;GT=50;TT=71	G=27.6%;T=72.4%
2963453	rs6900487	chr6:85825058	5.10E-04	MEDU	TT=24;TC=58;CC=49	CT=39.6%;C=60.4%

2963453	rs4707124	chr6:85826148	7.50E-04	MEDU	GG=24;GA=58;AA=51	G=39.6%;A=60.4%
2963453	rs6901432	chr6:85825687	7.50E-04	MEDU	GG=24;GA=58;AA=51	G=39.6%;A=60.4%
2963412	rs189936733	chr6:85794298	1.50E-03	OCTX	TT=1;TA=18;AA=113	T=7.5%;A=92.5%
2963423	rs1007281	chr6:85623383	4.60E-04	OCTX	TT=19;TC=61;CC=52	T=36.9%;C=63.1%
2963451	rs7741755	chr6:87070493	2.20E-03	OCTX	TT=6;TG=39;GG=89	T=19%;G=81%
2963451	rs7741760	chr6:87070505	2.20E-03	OCTX	AA=6;AG=39;GG=89	A=19%;G=81%
2963409	rs186418041	chr6:85703419	1.40E-03	PUTM	GG=1;GT=13;TT=115	G=5.6%;T=94.4%
2963453	NA	chr6:85334331	7.10E-04	PUTM	NA	NA
2963423	NA	chr6:87126921:TTGC_	7.20E-05	SNIG	NA	NA
2963425	rs10944040	chr6:85435550	1.90E-03	SNIG	AA=24;AG=76;GG=28	A=46.3%;G=53.7%
2963425	rs146231851	chr6:85411857	2.00E-03	SNIG	GG=5;GC=80;CC=26	G=48.5%;C=51.5%
t2963407	rs62439011	chr6:87299378	8.90E-04	TCTX	TT=2;TG=25;GG=101	T=10.8%;G=89.2%
2963409	rs13195858	chr6:86877495	7.80E-04	TCTX	AA=5;AG=27;GG=101	A=13.8%;G=86.2%
2963409	rs1334645	chr6:86864255	1.60E-03	TCTX	TT=5;TG=29;GG=100	T=14.6%;G=85.4%
2963412	rs117817534	chr6:85995718	1.50E-03	TCTX	CC=1;CT=22;TT=110	C=9%;T=91%
2963422	rs62422904	chr6:85705826	1.10E-04	TCTX	AA=2;AG=34;GG=92	A=14.2%;G=85.8%
2963423	rs9362315	chr6:87108366	1.00E-04	TCTX	CC=8;CG=49;GG=68	C=24.3%;G=75.7%

2963423	rs139147946	chr6:86019707	2.90E-04	TCTX	GG=3;GA=22;AA=102	G=10.4%;A=89.6%
t2963407	rs9362146	chr6:85913059	3.40E-04	THAL	GG=12;GA=61;AA=60	G=31%;A=68.3%
2963409	NA	chr6:86079514:CA_C	1.30E-03	THAL	NA	NA
2963409	rs9353390	chr6:87070142	1.40E-03	THAL	GG=35;GA=68;AA=31	G=51.5%;A=48.5%
2963410	rs66693104	chr6:85774235	3.50E-05	THAL	CC=8;CT=41;TT=84	C=21.3%;T=78.7%
2963410	rs7768064	chr6:85773956	3.50E-05	THAL	CC=8;CT=41;TT=84	C=21.3%;T=78.7%
2963410	rs9444290	chr6:85772007	3.60E-05	THAL	CC=8;CT=41;TT=84	C=21.3%;T=78.7%
2963410	rs6901417	chr6:85767680	3.60E-05	THAL	CC=8;CG=41;GG=84	C=21.3%;G=78.7%
2963410	rs6900555	chr6:85767355	3.60E-05	THAL	TT=8;TC=41;CC=84	T=21.3%;C=78.7%
2963410	rs1923592	chr6:85761011	3.90E-05	THAL	CC=8;CT=41;TT=84	C=21.3%;T=78.7%
2963410	NA	chr6:85760952:TAGC_	3.90E-05	THAL	NA	NA
2963410	rs6901367	chr6:85760552	3.90E-05	THAL	GG=;GC=41;CC=83	G=21.3%;C=78.7%
2963410	rs6923881	chr6:85760509	4.00E-05	THAL	CC=8;CT=41;TT=83	C=21.3%;T=78.7%
2963410	rs7763333	chr6:85759786	4.00E-05	THAL	GG=8;GA=42;AA=83	G=21.6%;A=78.4%
2963412	rs9362146	chr6:85913059	1.90E-04	THAL	GG=12;GA=61;AA=60	G=31.7%;A=68.3%
2963425	rs7745560	chr6:86288921	1.90E-03	THAL	AA=0;AT=18;TT=106	A=6.7%;T=93.3%
2963451	rs9362168	chr6:85924735	4.10E-04	THAL	AA2;AT=24;TT=97	A=10.4%;T=89.6%

2963451	rs2225546	chr6:85917792	1.40E-03	THAL	GG=2;GA=27;AA=87	G=11.6%;A=88.4%
2963451	rs55795906	chr6:87196697	1.70E-03	THAL	GG=0;GC=14;CC=110	G=5.2%;C=94.8%
2963451	rs1407157	chr6:85962802	2.00E-03	THAL	AA=2;AG=27;GG=104	A=11.6%;G=88.4%
2963451	rs4053815	chr6:85921503	2.20E-03	THAL	TT=2;TA=28;AA=95	T=11.9%;A=88.1%
2963451	NA	chr6:85963897:AC_A	2.30E-03	THAL	NA	NA
t2963407	rs7760395	chr6:85760635	5.90E-04	WHMT	CC=4;CT=39;TT=91	C=17.5%;T=82.5%
t2963407	rs6916224	chr6:85745004	6.50E-04	WHMT	GG=3;GA=40;AA=91	G=17.2%;A=82.8%
t2963407	rs9444287	chr6:85751929	7.60E-04	WHMT	CC=4;CT=38;TT=91	C=17.2%;T=82.8%
2963422	rs1888928	chr6:85986877	3.00E-06	WHMT	CC=11;CT=54;TT=69	C=28.4%;T=71.6%
2963422	rs4707174	chr6:85987918	3.00E-06	WHMT	CC=16;CA=58;AA=60	C=33.6%;A=66.4%
2963422	rs6916224	chr6:85745004	4.00E-06	WHMT	GG=3;GA=40;AA=91	G=17.2%;A=82.8%
2963422	rs7760395	chr6:85760635	6.40E-06	WHMT	CC=4;CT=39;TT=91	C=17.5%;T=82.5%
2963422	rs9444287	chr6:85751929	9.20E-06	WHMT	CC=4;CT=38;TT=91	C=17.2%;T=82.8%
2963422	NA	chr6:85790518:A_AT	2.40E-04	WHMT	NA	NA
2963422	rs4053778	chr6:85988429	2.70E-04	WHMT	GG=22;GA=63;AA=47	G=39.9%;A=60.1%
2963422	rs75594123	chr6:85990805	2.70E-04	WHMT	CC=9;CT=63;TT=60	C=30.2%;T=69.8%
2963422	rs527884	chr6:85991465	3.40E-04	WHMT	CC=9;CT=61;TT=64	C=29.5%;T=70.5%

2963423	rs9362200	chr6:86076286	1.90E-04	WHMT	AA=17;AC=61;CC=55	A=35.4%;C=64.6%
2963423	rs1971185	chr6:86080872	1.90E-04	WHMT	GG=17;GA=62;AA=55	G=35.8%;A=64.2%
2963423	rs2104184	chr6:86078365	2.00E-04	WHMT	GG=17;GC=62;CC=55	G=35.8%;C=64.2%
2963423	rs6454463	chr6:86078534	2.00E-04	WHMT	TT=17;TC=62;CC=55	T=35.8%;C=64.2%
2963423	rs9765933	chr6:85746176	4.30E-04	WHMT	CC=0;CT=13;TT=94	C=4.9%;T=95.1%
2963423	rs4707198	chr6:86076677	4.70E-04	WHMT	TT=17;TC=58;CC=54	T=34.3%;C=65.7%
2963451	rs9444217	chr6:85392065	2.30E-03	WHMT	GG=3;GC=29;CC=102	G=13.1%;C=86.9%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 35: Brain quantitative gene expression analyses for *UBE2E3* gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
2518164	rs1406249	chr2:181446355	5.60E-07	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
2518164	NA	chr2:181378920:TC_T	6.40E-07	aveALL	NA	NA
2518164	rs6717744	chr2:181393742	6.80E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2518164	rs1597893	chr2:181418745	6.90E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2518164	rs13024203	chr2:181408460	6.90E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2518164	rs13031656	chr2:181368613	6.90E-07	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%

2518164	rs7561337	chr2:181352806	6.90E-07	aveALL	GG=0;GT=15;TT=119	G=5.6%;T=94.4%
2518164	rs11676228	chr2:181355237	7.00E-07	aveALL	AA=0;AT=15;TT=119	A=5.6%;T=94.4%
2518164	rs12991998	chr2:181358021	7.00E-07	aveALL	AA=0;AC=15;CC=119	A=5.6%;C=94.4%
2518164	rs59308581	chr2:181363305	7.00E-07	aveALL	AA=0;AG=15;GG=119	A=5.6%;G=94.4%
t2518155	rs7602799	chr2:182260252	4.50E-04	FCTX	TT=25;TC=61;CC=48	T=41.4%;C=58.6%
t2518155	rs7602460	chr2:182261869	4.50E-04	FCTX	AA=25;AG=61;GG=48	A=41.4%;G=58.6%
t2518155	rs12693275	chr2:182258150	4.90E-04	FCTX	CC=20;CT=56;TT=58	C=35.8%;T=64.2%
t2518155	rs13339780	chr2:182254709	5.40E-04	FCTX	GG=24;GC=62;CC=47	G=41%;C=59%
2518167	rs12693275	chr2:182258150	1.10E-04	FCTX	CC=20;CT=56;TT=58	C=35.8%;T=64.2%
2518167	rs35801397	chr2:182247623	1.80E-04	FCTX	TT=17;TC=58;CC=59	T=34.3%;C=65.7%
2518167	rs6433912	chr2:182241548	1.80E-04	FCTX	TT=17;TC=58;CC=59	T=34.3%;C=65.7%
2518167	rs959633	chr2:182241905	1.80E-04	FCTX	CC=17;CA=58;AA=59	C=34.3%;A=65.7%
2518167	rs2056042	chr2:182242768	1.80E-04	FCTX	GG=17;GA=58;AA=59	G=34.3%;A=65.7%
2518167	rs6433913	chr2:182243536	1.80E-04	FCTX	TT=17;TC=58;CC=59	T=34.3%;C=65.7%
2518167	rs13029040	chr2:182246873	1.80E-04	FCTX	TT=17;TC=58;CC=59	T=34.3%;C=65.7%
2518167	rs13029098	chr2:182246969	1.80E-04	FCTX	GG=17;GA=58;AA=59	G=34.3%;A=65.7%
2518175	rs62180166	chr2:182013497	1.20E-04	FCTX	AA=1;AG=25;GG=108	A=10.1%;G=89.9%

2518175	NA	chr2:182015189:TATA_	1.20E-04	FCTX	NA	NA
2518175	rs7577144	chr2:182016120	1.20E-04	FCTX	TT=1;TC=25;CC=108	T=10.1%;C=89.9%
2518175	rs62180168	chr2:182016234	1.20E-04	FCTX	TT=1;TG=25;GG=108	T=10.1%;G=89.9%
2518175	rs62180169	chr2:182016711	1.20E-04	FCTX	TT=1;TC=25;CC=108	T=10.1%;C=89.9%
2518175	rs11904405	chr2:182017053	1.20E-04	FCTX	AA=1;AC=25;CC=108	A=10.1%;C=89.9%
2518175	rs6758061	chr2:182019866	1.20E-04	FCTX	CC=1;CT=25;TT=108	C=10.1%;T=89.9%
2518175	rs6433896	chr2:182023555	1.20E-04	FCTX	AA=1;AG=25;GG=108	A=10.1%;G=89.9%
2518175	rs6738120	chr2:182024283	1.20E-04	FCTX	TT=1;TC=25;CC=108	T=10.1%;C=89.9%
2518175	rs79347623	chr2:182027315	1.20E-04	FCTX	CC=1;CT=25;TT=108	C=10.1%;T=89.9%
t2518155	rs3770126	chr2:182336884	2.10E-04	OCTX	GG=17;GA=59;AA=58	G=34.7%;A=65.3%
t2518155	rs7561265	chr2:181391859	8.60E-04	OCTX	TT=0;TG=15;GG=119	T=5.6%;G=94.4%
t2518155	rs149142673	chr2:181392463	8.60E-04	OCTX	AA=0;AT=15;TT=119	A=5.6%;T=94.4%
t2518155	rs13031656	chr2:181368613	8.70E-04	OCTX	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
2518167	rs73037041	chr2:181818588	8.40E-05	PUTM	GG=1;GC=12;CC=121	G=5.2%;C=94.8%
2518167	rs77634143	chr2:181819851	1.10E-04	PUTM	AA=1;AG=11;GG=121	A=4.9%;G=95.1%
t2518155	rs16867468	chr2:182551814	7.30E-04	SNIG	AA=0;AT=9;TT=116	A=3.4%;T=96.6%
t2518155	NA	chr2:182850046	6.80E-04	THAL	NA	NA

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

Table 36: Brain quantitative gene expression analyses for *CWC22* gene variants.

Expr ID	rsID	Variant	*P*-value	tissue	Genotype_counts	Allele_frequency
t2590193	rs1406249	chr2:181446355	3.50E-06	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
t2590193	rs9677541	chr2:181392911	3.80E-06	aveALL	TT=0;TA=15;AA=118	T=5.6%;A=94.4%
t2590193	rs6717744	chr2:181393742	3.80E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
t2590193	NA	chr2:181378920:TC_T	4.00E-06	aveALL	NA	NA
t2590193	rs1597893	chr2:181418745	4.10E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
t2590193	rs13031656	chr2:181368613	4.10E-06	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
t2590193	rs13024203	chr2:181408460	4.20E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
t2590193	rs7561337	chr2:181352806	4.20E-06	aveALL	GG=0;GT=15;TT=119	G=5.6%;T=94.4%
t2590193	rs12991998	chr2:181358021	4.20E-06	aveALL	AA=0;AC=15;CC=119	A=5.6%;C=94.4%
t2590193	rs11676228	chr2:181355237	4.20E-06	aveALL	AA=0;AT=15;TT=119	A=5.6%;T=94.4%
2590196	rs9677541	chr2:181392911	2.60E-06	aveALL	TT=0;TA=15;AA=118	T=5.6%;A=94.4%
2590196	rs1406249	chr2:181446355	2.80E-06	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
2590196	rs1597893	chr2:181418745	2.90E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%

2590196	rs6717744	chr2:181393742	3.00E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590196	rs13031656	chr2:181368613	3.00E-06	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
2590196	NA	chr2:181378920:TC_T	3.00E-06	aveALL	NA	NA
2590196	NA	chr2:181393221:AC_A	3.10E-06	aveALL	NA	NA
2590196	rs144689558	chr2:181395373	3.10E-06	aveALL	CC=0;CA=15;AA=119	C=5.6%;A=94.4%
2590196	rs2083248	chr2:181396985	3.10E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590196	rs12989470	chr2:181397676	3.10E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590197	rs1406249	chr2:181446355	6.90E-06	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
2590197	rs9677541	chr2:181392911	8.40E-06	aveALL	TT=0;TA=15;AA=118	T=5.6%;A=94.4%
2590197	NA	chr2:181378920:TC_T	8.70E-06	aveALL	NA	NA
2590197	rs1597893	chr2:181418745	9.60E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590197	rs13031656	chr2:181368613	9.60E-06	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
2590197	rs59308581	chr2:181363305	9.80E-06	aveALL	AA=0;AG=15;GG=119	A=5.6%;G=94.4%
2590197	rs13010875	chr2:181365923	9.80E-06	aveALL	GG=0;GA=15;AA=119	G=5.6%;A=94.4%
2590197	rs12988910	chr2:181369762	9.80E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590197	rs11682038	chr2:181373365	9.80E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590197	rs11894270	chr2:181374680	9.80E-06	aveALL	AA=0;AC=15;CC=119	A=5.6%;C=94.4%

2590205	rs1406249	chr2:181446355	3.90E-06	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
2590205	NA	chr2:181378920:TC_T	4.50E-06	aveALL	NA	NA
2590205	rs9677541	chr2:181392911	4.50E-06	aveALL	TT=0;TA=15;AA=118	T=5.6%;A=94.4%
2590205	rs1597893	chr2:181418745	4.70E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590205	rs13031656	chr2:181368613	4.70E-06	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
2590205	rs13024203	chr2:181408460	4.80E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590205	rs12991998	chr2:181358021	4.80E-06	aveALL	AA=0;AC=15;CC=119	A=5.6%;C=94.4%
2590205	rs59308581	chr2:181363305	4.80E-06	aveALL	AA=0;AG=15;GG=119	A=5.6%;G=94.4%
2590205	rs13010875	chr2:181365923	4.80E-06	aveALL	GG=0;GA=15;AA=119	G=5.6%;A=94.4%
2590205	rs12988910	chr2:181369762	4.80E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590206	rs1406249	chr2:181446355	1.60E-06	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
2590206	rs6717744	chr2:181393742	1.70E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590206	rs9677541	chr2:181392911	2.10E-06	aveALL	TT=0;TA=15;AA=118	T=5.6%;A=94.4%
2590206	rs1597893	chr2:181418745	2.50E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590206	NA	chr2:181378920:TC_T	2.50E-06	aveALL	NA	NA
2590206	rs13031656	chr2:181368613	2.60E-06	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
2590206	rs7561337	chr2:181352806	2.60E-06	aveALL	GG=0;GT=15;TT=119	G=5.6%;T=94.4%

2590206	rs13024203	chr2:181408460	2.60E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590206	rs11676228	chr2:181355237	2.60E-06	aveALL	AA=0;AT=15;TT=119	A=5.6%;T=94.4%
2590206	rs12991998	chr2:181358021	2.60E-06	aveALL	AA=0;AC=15;CC=119	A=5.6%;T=94.4%
2590207	rs1406249	chr2:181446355	1.10E-05	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
2590207	NA	chr2:181378920:TC_T	1.40E-05	aveALL	NA	NA
2590207	rs1597893	chr2:181418745	1.40E-05	aveALL	TT=0;TC=15;CC=119	T=5.6%;A=94.4%
2590207	rs12991998	chr2:181358021	1.50E-05	aveALL	AA=0;AC=15;CC=119	A=5.6%;C=94.4%
2590207	NA	chr2:181393221:AC_A	1.50E-05	aveALL	NA	NA
2590207	rs144689558	chr2:181395373	1.50E-05	aveALL	CC=0;CA=15;AA=119	C=5.6%;A=94.4%
2590207	rs2083248	chr2:181396985	1.50E-05	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590207	rs12989470	chr2:181397676	1.50E-05	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590207	rs11676110	chr2:181398855	1.50E-05	aveALL	AA=0;AG=15;GG=119	A=5.6%;G=94.4%
2590208	rs62181523	chr2:180615735	1.30E-04	aveALL	AA=7;AG=40;GG=84	A=20.1%;G=79.9%
2590217	rs1406249	chr2:181446355	1.30E-06	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
2590217	NA	chr2:181378920:TC_T	1.40E-06	aveALL	NA	NA
2590217	rs13031656	chr2:181368613	1.40E-06	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
2590217	rs1597893	chr2:181418745	1.40E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%

2590217	rs13024203	chr2:181408460	1.40E-06	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590217	rs9677541	chr2:181392911	1.50E-06	aveALL	TT=0;TA=15;AA=118	T=5.6%;A=94.4%
2590217	rs7561337	chr2:181352806	1.50E-06	aveALL	GG=0GT=15;TT=119	G=5.6%;T=94.4%
2590217	rs11676228	chr2:181355237	1.50E-06	aveALL	AA=0;AT=15;TT=119	A=5.6%;T=94.4%
2590217	rs12991998	chr2:181358021	1.50E-06	aveALL	AA=0;AC=15;CC=119	A=5.6%;C=94.4%
2590217	rs59308581	chr2:181363305	1.50E-06	aveALL	AA=0;AG=15;GG=119	A=5.6%;G=94.4%
2590219	rs1406249	chr2:181446355	6.70E-07	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
2590219	rs6717744	chr2:181393742	7.10E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590219	rs1597893	chr2:181418745	8.10E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590219	rs13024203	chr2:181408460	8.20E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590219	rs13031656	chr2:181368613	8.20E-07	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
2590219	rs7561337	chr2:181352806	8.30E-07	aveALL	GG=0;GT=15;TT=119	G=5.6%;T=94.4%
2590219	rs12991998	chr2:181358021	8.30E-07	aveALL	AA=0;AC=15;CC=119	A=5.6%;C=94.4%
2590219	rs11676228	chr2:181355237	8.30E-07	aveALL	AA=0;AT=15;TT=119	A=5.6%;T=94.4%
2590219	NA	chr2:181378920:TC_T	8.40E-07	aveALL	NA	NA
2590219	rs59308581	chr2:181363305	8.40E-07	aveALL	AA=0;AG=15;GG=119	A=5.6%;G=94.4%
2590220	rs4233782	chr2:181423589	4.90E-04	aveALL	CC=0;CA=17;AA=117	C=6.3%;A=93.7%

2590220	rs4666981	chr2:181423830	4.90E-04	aveALL	TT=0;TC=17;CC=117	T=6.3%;C=93.7%
2590220	rs1540861	chr2:181425044	4.90E-04	aveALL	AA=0;AG=17;GG=117	A=6.3%;G=93.7%
2590220	rs2887179	chr2:181425572	5.00E-04	aveALL	TT=0;TC=17;CC=117	T=6.3%;C=93.7%
2590220	rs2368169	chr2:181420615	5.10E-04	aveALL	CC=0;CG=17;GG=117	C=6.3%;G=93.7%
2590227	rs1406249	chr2:181446355	3.40E-05	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
2590227	NA	chr2:181378920:TC_T	4.10E-05	aveALL	NA	NA
2590227	rs6717744	chr2:181393742	4.10E-05	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590227	rs1597893	chr2:181418745	4.40E-05	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590227	rs13031656	chr2:181368613	4.40E-05	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
2590227	rs13024203	chr2:181408460	4.40E-05	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590227	rs12991998	chr2:181358021	4.50E-05	aveALL	AA=0;AC=15;CC=119	A=5.6%;C=94.4%
2590227	NA	chr2:181393221:AC_A	4.50E-05	aveALL	NA	NA
2590227	rs144689558	chr2:181395373	4.50E-05	aveALL	CC=0;CA=15;AA=119	C=5.6%;A=94.4%
2590227	rs2083248	chr2:181396985	4.50E-05	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590230	rs9677541	chr2:181392911	5.20E-07	aveALL	TT=0;TA=15;AA=118	T=5.6%;A=94.4%
2590230	rs13029793	chr2:181373783	5.20E-07	aveALL	AA=0;AG=15;GG=119	A=5.6%;G=94.4%
2590230	NA	chr2:181378920:TC_T	5.60E-07	aveALL	NA	NA

2590230	rs6717744	chr2:181393742	5.80E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590230	rs1597893	chr2:181418745	5.90E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590230	rs13024203	chr2:181408460	6.00E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590230	rs13031656	chr2:181368613	6.10E-07	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
2590230	rs7561337	chr2:181352806	6.20E-07	aveALL	GG=0;GT=15;TT=119	G=5.6%;T=94.4%
2590230	rs11676228	chr2:181355237	6.20E-07	aveALL	AA=0;AT=15;TT=119	A=5.6%;T=94.4%
2590230	rs12991998	chr2:181358021	6.20E-07	aveALL	AA=0;AC=15;CC=119	A=5.6%;C=94.4%
2590237	rs1406249	chr2:181446355	2.10E-07	aveALL	TT=0;TA=15;AA=119	T=5.6%;A=94.4%
2590237	NA	chr2:181378920:TC_T	2.70E-07	aveALL	NA	NA
2590237	rs9677541	chr2:181392911	2.80E-07	aveALL	TT=0;TA=15;AA=118	T=5.6%;A=94.4%
2590237	rs1597893	chr2:181418745	2.90E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590237	rs13031656	chr2:181368613	2.90E-07	aveALL	CC=0;CG=15;GG=119	C=5.6%;G=94.4%
2590237	rs13024203	chr2:181408460	3.00E-07	aveALL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590237	rs7561337	chr2:181352806	3.00E-07	aveALL	GG=0;GT=15;TT=119	G=5.6%;T=94.4%
2590237	rs11676228	chr2:181355237	3.00E-07	aveALL	AA=0;AT=15;TT=119	A=5.6%;T=94.4%
2590237	rs12991998	chr2:181358021	3.00E-07	aveALL	AA=0;AC=15;CC=119	A=5.6%;C=94.4%
2590237	rs59308581	chr2:181363305	3.00E-07	aveALL	AA=0;AG=15;GG=119	A=5.6%;G=94.4%

2590240	rs1543177	chr2:181975242	2.90E-04	aveALL	GG=16;GA=68;AA=50	G=37.3%;A=62.7%
2590240	rs6433894	chr2:181977227	2.90E-04	aveALL	GG=16;GA=68;AA=50	G=37.3%;A=62.7%
2590240	rs6731186	chr2:181977953	2.90E-04	aveALL	CC=16;CT=68;TT=50	C=37.3%;T=62.7%
2590199	rs13413058	chr2:180167065	1.40E-04	CRBL	CC=14;CA=58;AA=62	C=32.1%;A=67.9%
2590199	rs6761161	chr2:180158510	1.70E-04	CRBL	AA=13;AG=55;GG=66	A=30.2%;G=69.8%
2590199	rs11690719	chr2:180162485	1.70E-04	CRBL	GG=13;GC=55;CC=66	G=30..2%;C=69.8%
2590199	rs62179071	chr2:180144305	2.10E-04	CRBL	TT=13;TC=56;CC=65	T=30.6%;C=69.4%
2590199	rs6704926	chr2:180146515	2.20E-04	CRBL	CC=13;CA=55;AA=65	C=30.2%;A=69.8%
2590199	rs11677930	chr2:180168429	2.20E-04	CRBL	TT=16;TG=55;GG=61	T=32.5%;G=67.5%
2590199	rs4496360	chr2:180146659	2.20E-04	CRBL	AA=13;AC=55;CC=65	A=30.2%;C=69.8%
2590199	rs10198153	chr2:180147250	2.20E-04	CRBL	CC=13;CT=55;TT=65	C=30.2%;T=69.8%
2590199	rs10196058	chr2:180167652	2.20E-04	CRBL	TT=16;TA=55;AA=61	T=32.5%;A=67.5%
2590208	rs74623336	chr2:180744884	2.90E-05	CRBL	TT=0;TC=5;CC=107	T=1.9%;C=98.1%
2590232	rs113396325	chr2:180647657	5.30E-04	CRBL	AA=2;AG=17;GG=115	A=7.8%;G=92.2%
2590232	rs17773553	chr2:180609977	8.10E-04	CRBL	AA=2;AT=17;TT=114	A=7.8%;T=92.2%
2590240	rs74623336	chr2:180744884	2.40E-04	FCTX	TT=0;TC=5;CC=107	T=1.9%;C=98.1%
2590216	NA	chr2:181492520:T_TA	4.40E-04	HIPP	NA	NA

2590216	rs16867335	chr2:181458934	4.40E-04	HIPP	TT=6;TC=44;CC=84	T=20.9%;C=79.1%
2590216	rs35579320	chr2:181463612	4.40E-04	HIPP	CC=6;CT=44;TT=84	C=20.9%;T=79.1%
2590216	rs72884242	chr2:181465486	4.40E-04	HIPP	TT=6;TA=44;AA=84	T=20.9%;A=79.1%
2590216	rs6739798	chr2:181465853	4.40E-04	HIPP	CC=6;CT=44;TT=84	C=20.9%;T=79.1%
2590216	rs34842451	chr2:181480525	4.40E-04	HIPP	CC=6;CT=44;TT=84	C=20.9%;T=79.1%
2590220	rs13424082	chr2:180227865	4.20E-04	HIPP	AA=4;AG=45;GG=84	A=19.8%;G=80.2%
2590229	rs6433788	chr2:180277220	4.60E-04	MEDU	AA=3;AT=51;TT=59	A=21.3%;T=78.7%
2590232	NA	chr2:181604349:A_AAT	7.70E-04	MEDU	NA	NA
2590216	rs77720841	chr2:181935135	8.50E-05	OCTX	TT=1;TA=14;AA=119	T=6%;A=94%
2590216	rs76389760	chr2:181902065	8.50E-05	OCTX	CC=1;CT=14;TT=118	C=6%;T=94%
2590216	rs78621768	chr2:181930665	8.70E-05	OCTX	AA=1;AG=15;GG=118	A=6.3%;G=93.7%
2590216	rs78342062	chr2:181980960	1.50E-04	OCTX	CC=1;CG=16;GG=117	C=6.7%;G=93.3%
2590220	rs16866729	chr2:180295715	4.20E-04	OCTX	GG=0;GC=36;CC=97	G=13.4%;C=86.6%
2590229	rs16866729	chr2:180295715	3.30E-04	OCTX	GG=0;GC=36;CC=97	G=13.4%;C=86.6%
2590229	rs34092997	chr2:180250901	5.80E-04	OCTX	GG=0;GA=14;AA=112	G=5.2%;A=94.8%
2590232	rs12693236	chr2:181167850	8.70E-04	OCTX	CC=26;CT=58;TT=47	C=41%;T=59%
2590199	rs7581560	chr2:180573636	8.00E-05	PUTM	CC=1;CT=32;TT=101	C=12.7%;T=87.3%

2590214	NA	chr2:180262012:CAT_C	8.60E-05	PUTM	NA	NA
2590214	rs72952380	chr2:180231710	9.10E-05	PUTM	CC=2;CA=33;AA=96	C=13.8%;A=86.2%
2590214	rs13390979	chr2:180225658	9.50E-05	PUTM	GG=2;GA=33;AA=96	G=13.8%;A=86.2%
2590214	rs10187146	chr2:180223244	9.90E-05	PUTM	AA=2;AG=32;GG=96	A=13.4%;G=86.6%
2590214	NA	chr2:180262244:TAC_T	1.00E-04	PUTM	NA	NA
2590214	rs6731104	chr2:180251001	1.00E-04	PUTM	CC=4;CG=46;GG=81	C=20.1%;G=79.9%
2590229	rs16866933	chr2:180566678	6.70E-04	PUTM	AA=4;AG=17;GG=113	A=9.3%;G=90.7%
2590239	rs78621768	chr2:181930665	1.20E-05	PUTM	AA=1;AG=15;GG=118	A=6.3%;G=93.7%
2590239	rs76389760	chr2:181902065	1.80E-05	PUTM	CC=1;CT=14;TT=118	C=6%;T=94%
2590239	rs80236555	chr2:181960763	3.20E-05	PUTM	CC=2;CT=15;TT=114	C=7.1%;T=92.9%
2590239	rs77720841	chr2:181935135	5.60E-05	PUTM	TT=1;TA=14;AA=119	T=6%;A=94%
2590239	rs7568209	chr2:180202460	9.10E-05	PUTM	TT=19;TC=63;CC=50	T=37.7%;C=62.3%
2590239	rs7582128	chr2:180202305	1.50E-04	PUTM	CC=19;CT=64;TT=50	C=38.1%;T=61.9%
2590239	rs56029204	chr2:180025982	2.30E-04	PUTM	GG=0;GA=13;AA=119	G=4.9%;A=95.1%
2590239	rs78342062	chr2:181980960	2.50E-04	PUTM	CC=1;CG=16;GG=117	C=6.7%;G=93.3%
2590239	rs12105748	chr2:180179035	2.80E-04	PUTM	TT=19;TC=66;CC=49	T=38.8%;C=61.2%
2590239	rs141882830	chr2:180182763	3.90E-04	PUTM	CC=18;CT=65;TT=51	C=37.7%;T=62.3%

2590225	rs10497560	chr2:180995313	6.50E-05	SNIG	AA=1;AG=28;GG=105	A=11.2%;G=88.8%
2590225	rs72878574	chr2:180994194	6.60E-05	SNIG	TT=1;TC=28;CC=105	T=11.2%;C=88.8%
2590225	rs1518420	chr2:180997083	6.60E-05	SNIG	AA=1;AG=28;GG=105	A=11.2%;G=88.8%
2590225	rs72878595	chr2:180997773	6.70E-05	SNIG	AA=1;AG=28;GG=105	A=11.2%;G=88.8%
2590225	rs72880221	chr2:181004438	8.60E-05	SNIG	CC=2;CT=26;TT=105	C=11.2%;T=88.8%
2590225	NA	chr2:181002042:GA_G	1.50E-04	SNIG	NA	NA
2590225	rs11691364	chr2:180144763	1.60E-04	SNIG	AA=13;AG=67;GG=49	A=34.7%;G=65.3%
2590225	rs72881984	chr2:181018648	2.10E-04	SNIG	CC=2;CT=31;TT=101	C=13.1%;T=86.9%
2590201	rs6433805	chr2:180602852	1.40E-06	TCTX	AA=4;AG=20;GG=107	A=10.4%;G=89.6%
2590201	rs73048507	chr2:180631670	4.50E-06	TCTX	AA=4;AG=19;GG=110	A=10.1%;G=89.9%
2590201	rs60243803	chr2:180626823	5.50E-06	TCTX	CC=4;CT=19;TT=111	C=10.1%;T=89.9%
2590201	rs56837904	chr2:180627121	5.50E-06	TCTX	AA=4;AG=19;GG=111	A=10.1%;G=89.9%
2590201	rs73046901	chr2:180623710	5.80E-06	TCTX	CC=4;CT=19;TT=111	C=10.1%;T=89.9%
2590201	rs6433806	chr2:180602894	6.00E-06	TCTX	CC=4;CG=19;GG=111	C=10.1%;G=89.9%
2590201	rs17823821	chr2:180595745	6.10E-06	TCTX	CC=4;CT=19;TT=111	C=10.1%;T=89.9%
2590201	rs17823881	chr2:180596192	6.20E-06	TCTX	CC=4;CT=19;TT=111	C=10.1%;T=89.9%
2590201	rs7574741	chr2:180596338	6.20E-06	TCTX	CC=4;CT=19;TT=111	C=10.1%;T=89.9%

2590201	rs7574931	chr2:180596475	6.20E-06	TCTX	CC=4;CT=19;TT=111	C=10.1%;T=89.9%
2590207	NA	chr2:180667477:TAG_T	1.00E-05	TCTX	NA	NA
2590208	rs150550179	chr2:180499474	8.40E-05	TCTX	GG=3;GT=32;TT=97	G=14.2%;T=85.8%
2590208	rs77265227	chr2:180491153	1.50E-04	TCTX	TT=2;TA=31;AA=101	T=13.1%;A=86.9%
2590208	rs77475073	chr2:180493156	1.50E-04	TCTX	CC=2;CT=31;TT=101	C=13.1%;T=86.9%
2590208	rs147860683	chr2:180495681	1.50E-04	TCTX	GG=2;GA=31;AA=101	G=13.1%;A=86.9%
2590208	rs6745521	chr2:180480167	1.50E-04	TCTX	TT=3;TC=30;CC=101	T=13.4%;C=86.6%
2590208	rs55750009	chr2:181662422	2.00E-04	TCTX	GG=13;GT=58;TT=43	G=31.3%;T=68.7%
2590208	rs16866838	chr2:180459888	2.50E-04	TCTX	GG=3;GA=30;AA=101	G=13.4%;A=86.6%
2590214	rs62181523	chr2:180615735	1.50E-05	TCTX	AA=7;AG=40;GG=84	A=20.1%;G=79.9%
2590214	rs356410	chr2:180618174	2.30E-05	TCTX	GG=0;GT=12;TT=110	G=4.5%;T=95.5%
2590214	rs188707219	chr2:180619480	2.30E-05	TCTX	CC=0;CT=12;TT=110	C=4.5%;T=95.5%
2590214	rs6731078	chr2:180582073	4.40E-05	TCTX	TT=18;TC=59;CC=52	T=35.4%;C=64.6%
2590220	rs356414	chr2:180620757	5.90E-05	TCTX	GG=5;GA=37;AA=79	G=17.5%;A=82.5%
2590220	rs62181526	chr2:180616128	3.60E-04	TCTX	AA=4;AG=37;GG=93	A=16.8%;G=83.2%
2590220	rs62181524	chr2:180615897	3.60E-04	TCTX	TT=4;TC=37;CC=93	T=16.8%;C=83.2%
2590232	NA	chr2:180535223:A_AAC	1.50E-04	TCTX	NA	NA

2590232	rs77596983	chr2:180522768	9.60E-04	TCTX	GG=0;GA=16;AA=118	G=6%;A=94%
2590232	NA	chr2:180528912:ATTGT	9.60E-04	TCTX	NA	NA
2590232	rs80249501	chr2:180515298	9.60E-04	TCTX	AA=0;AG=16;GG=118	A=6%;G=94%
2590240	rs3112939	chr2:180504672	4.90E-04	TCTX	CC=1;CG=21;GG=112	C=8.6%;G=91.4%
2590240	rs13391446	chr2:180496791	5.00E-04	TCTX	TT=1;TA=21;AA=112	T=8.6%;A=91.4%
2590212	rs1406249	chr2:181446355	2.50E-05	THAL	TT=0TA=15;AA=119	T=5.6%;A=94.4%
2590212	rs12693248	chr2:181446212	3.00E-05	THAL	AA=0;A=15;TT=119	A=5.6%;T=94.4%
2590212	rs138980480	chr2:181445732	3.00E-05	THAL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590212	rs6717744	chr2:181393742	3.00E-05	THAL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590212	rs7561337	chr2:181352806	3.00E-05	THAL	GG=0;GT=15;TT=119	G=5.6%;T=94.4%
2590212	rs11676228	chr2:181355237	3.00E-05	THAL	AA=0;AT=15;TT=119	A=5.6%;T=94.4%
2590212	rs13028526	chr2:181386500	3.00E-05	THAL	TT=0;TC=15;CC=119	T=5.6%;C=94.4%
2590212	rs13010533	chr2:181386683	3.00E-05	THAL	GG=0;GT=15;TT=119	G=5.6%;T=94.4%
2590212	rs59308581	chr2:181363305	3.00E-05	THAL	AA=0;AG=15;GG=119	A=5.6%;G=94.4%
2590212	rs13010875	chr2:181365923	3.00E-05	THAL	GG=0;GA=15;AA=119	G=5.6%;A=94.4%
2590229	rs6433890	chr2:181969380	2.50E-04	THAL	TT=27;TA=55;AA=37	T=40.7%;A=59.3%
2590229	NA	chr2:181947088:AT_A	4.70E-04	THAL	NA	NA

2590229	rs6433891	chr2:181969709	6.70E-04	THAL	GG=14;GA=59;AA=60	G=32.5%;A=67.5%
2590229	rs10204666	chr2:181974699	6.80E-04	THAL	CC=14;CA=59;AA=61	C=32.5%;A=67.5%
2590229	rs6433893	chr2:181976881	6.80E-04	THAL	CC=14;CG=59;GG=61	C=32.5%;G=67.5%
2590229	rs1040228	chr2:181980885	6.80E-04	THAL	AA=14;AG=59;GG=61	A=32.5%;G=67.5%
2590232	NA	chr2:180402478:A_AAC	6.30E-04	THAL	NA	NA
2590240	rs2887174	chr2:181079920	3.40E-04	THAL	CC=5;CT=38;TT=91	C=17.9%;T=82.1%
2590240	rs16867228	chr2:181048805	3.40E-04	THAL	TT=5;TG=42;GG=87	T=19.4%;G=80.6%
2590240	rs16867229	chr2:181049144	3.40E-04	THAL	GG=5;GA=42;AA=87	G=19.4%;A=80.6%
2590208	rs55750009	chr2:181662422	1.70E-05	WHMT	GG=13;GT=58;TT=43	G=31.3%;T=68.7%
2590225	rs12151759	chr2:181643204	8.00E-05	WHMT	CC=3;CA=9;AA=122	C=5.6%;A=94.4%
2590225	rs62179778	chr2:181628960	2.10E-04	WHMT	GG=1;GC=5;CC=120	G=2.6%;C=97.4%
2590232	rs35163172	chr2:180281591	3.10E-05	WHMT	TT=25;TA=60;AA=29	T=41%;A=59%
2590240	rs1515310	chr2:180446786	1.50E-04	WHMT	TT=28;TG=63;GG=43	T=44.4%;G=55.6%

Abbreviations: ID, identification; Expr, expression; NA, not available; chr, chromosome; aveALL, average all; CRBL, cerebellum; FCTX, frontal cortex; HIPP, hippocampus; MEDU, medulla; OCTX, occipital cortex; PUTM, putamen; SNIG, substantia nigra; TCTX, temporal cortex; THAL, thalamus; WHTM, central white matter. [data was extracted from http://www.braineac.org; UK Brain Expression Consortium UKBEC].

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