The Genetic Study of Diabetic Retinopathy

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Date of Submission: 28/01/2010

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Summary

Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus (DM). It is the fifth most common causes of blindness in the world, accounting for approximately 4.8% of global blindness and is also the leading cause of blindness in working age adults. The pathogenesis of DR is complex and multifactorial, but at a biochemical level is related to altered glucose metabolism. Established risk factors in the development of DR include prolonged hyperglycemia, increased duration of DM, uncontrolled hypertension and hyperlipidemia. It has become evident through familial aggregation studies that susceptibility to DR also has a heritable component, independent of other established risk factors. The aim of this thesis was to further explore genetic risk factors in the development of DR in type 1 DM and type 2 DM. A meta-analysis of all of the published candidate gene studies for DR has been undertaken and a total of 34 variants in 20 genes have been analysed, with 5 genes found to be significantly associated with DR. Six candidate gene studies have been undertaken, including replication studies of two of the genes associated with DR in the meta-analysis. In particular, variation in the *vascular endothelial growth factor* and *erythropoietin* gene were found to be significantly associated with DR, especially sight-threatening DR. A serum protein study investigating the nitric oxide pathway was undertaken and found asymmetric and symmetric dimethylarginines and L-arginine to be significantly associated with sight-threatening DR. Finally, a genome-wide association study was undertaken and identified several novel susceptibility genes for sight-threatening DR. This study advances understanding of DR pathogenesis, and may assist in refinement of genetic screening programs to identify individuals at particularly high risk of DR. Data from this study may also assist in the identification of novel therapeutic targets for DR.

Signed Declaration

I certify that this thesis does not incorporate without acknowledgment 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.

Acknowledgements

This thesis is dedicated to all Persian lives lost or politically detained in the fight for human rights and democracy for their country. Although pervading with intelligence and talents, due to circumstances faced by the country they have not been as privileged as I have to live out their dreams. As descendents of world renowned academics including Avicenna, Zakariya Razi, historical greats including Cyrus the Great, Ferdowsi, Rumi and Hafez , I hope this work inspires others to live out their dreams in a free Iran.

I have had great privilege to have undertaken this thesis under the primary supervision of Assoc/Prof Jamie Craig and the extent of my gratitude to him simply cannot be conveyed. He has taught me what is entailed in undertaking world leading ophthalmic genetic research successfully by being an amazingly humble leader, mentor, teacher, scientist and clinician. But above all, he has shown me what is involved in being a genuine, indiscriminately caring human being to all those around him. A tremendous amount of gratitude is expressed to my co-supervisor Dr Kathryn Burdon, to whom I owe my genetic knowledge. She has been my female role model and academic backbone for the last three years and has provided me with immense academic support. The outcomes of this project and its successes would not have been possible without her. Together they have ensured every possible necessary resource to be available for this project, helped me to perform to the best of my abilities and have shared the enthusiasm for this project and the excitement of its results. Prof Nikolai Petrovsky is sincerely thanked for his support over the lifespan of this project and for supporting the recruitment of the majority of participants with

type 1 diabetes. His academic expertise and input, particularly for numerous publications, has been vastly appreciated.

This research could not have been undertaken without the approval of Prof Douglas Coster, who has kindly allowed the undertaking of this project in the Department of Ophthalmology, Flinders Medical Centre with his support. The Department of Ophthalmology Centre for Clinical Research Excellence of Flinders Medical Centre, the National Health and Medical Research Council and Ophthalmic Research Institute of Australia are acknowledged for their funding support.

A great amount of gratitude is owed for participating patients, ophthalmologists, nursing and clerical staff of Flinders Medical Centre Ophthalmology and Endocrine clinics, Royal Adelaide Hospital and Queen Elizabeth Hospital Ophthalmology clinics, who have made this research possible. Particular acknowledgements to Prof Dinesh Selva and Dr Michael Goggin are made for their support in recruitment from their hospitals. The assistance of all private ophthalmologists, especially Dr George Wong, for data collection of their patients is much appreciated.

Special acknowledgements go to Ms Anna Peterson and Ms Stacey Thorpe, who have been integral to this project by devoting their research nursing expertise, assisting with the recruitment of patients and data collection and entry. Their assistance has led to the ability to recruit a large number of participants for this project. The efforts of Flinders Medical Centre laboratory assistants Ms Amy McMellon, Mr Abraham Kuot and Ms Kate Laurie, who have been fundamental to this project, are vastly appreciated. Assistance for the recruitment of participants by

Drs Aanchal Gupta and Lucy Goold from the Royal Adelaide Hospital has been much appreciated. Mr Malcolm Whiting is also individually acknowledged for his incredible generosity and support, enabling the proteomic aspects of this thesis in chapter 8 to be carried out. A personal acknowledgement for Dr Stuart MacGregor at the Queensland Institute of Medical Research is made for analysing the genome-wide pooling data in chapter 9. I am also grateful for the statistical advice given by Dr Richard Woodman, Ms Miriam Keane, Ms Lan Kelly and Mr Thomas Wright. Dr Alex Hewitt is sincerely thanked for being integral to the meta-analysis, its conception, design and analyses in Chapter 2. Dr Nicholas Kasmeridis has also been integral to the conception of the ADMA proteomic analyses in Chapter 8. The general support from other members of the Departmental of Ophthalmology, Flinders Medical Centre, particularly Mr David Dimasi, Ms Tania Straga, Dr Shiwani Sharma, Ms Deb Sullivan, and Prof Keryn Williams has been also been vastly appreciated.

I could not have undertaken this project without the support of my husband Saeed, whom for over half of my existence has been the light of my life! His emotional and financial support has enabled me to comfortably dedicate myself to my passion for research and he has given me the honour of sharing the joys of this journey with me. My parents are also thanked for instilling the value of education in me and encouraging me to make the decision to undertake a PhD. They have provided utmost emotional encouragement and support for the last three years and also shared the joys of outcomes and successes of this project.

Abbreviations

ACE	Angiotensin converting enzyme
ADMA	Asymmetric dimethylarginine
AKR1B1	Aldose reductase
BMI	Body mass index
CA1	Carbonic anhydrase 1
CI	Confidence interval
CSME	Clinically significant macular edema
DDAH	Dimethylarginine dimethylaminohydrolase
DM	Diabetes mellitus
DR	Diabetic retinopathy
EPO	Erythropoietin
GWAS	Genome-wide association study
HbA1c	Hemoglobin A1c
HWE	Hardy-Weinberg Equilibrium
NO	Nitric oxide
eNOS	Endothelial nitric oxide synthase
NOS	Nitric oxide synthase
NPDR	Non-proliferative diabetic retinopathy
PKA	Protein kinase A
PKC	Protein kinase C
OR	Odds ratio
PDR	Proliferative diabetic retinopathy
SDMA	Symmetric dimethylarginine
SE	Standard error

SNP	Single nucleotide polymorphism
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
VEGF	Vascular endothelial growth factor
VEGFA	Vascular endothelial growth factor A