GENETIC INVESTIGATIONS OF CENTRAL CORNEAL THICKNESS IN RELATION TO OPEN-ANGLE GLAUCOMA

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SUMMARY

Open-angle glaucoma (OAG) is a leading cause of permanent blindness in Australia, affecting 2-3% of the population over 40. Death of neurons in the retina causes a progressive loss of vision that can lead to total blindness if left untreated. OAG has a strong genetic component, yet the genetic architecture of this condition is poorly characterised.

The cornea is the transparent tissue located at the front of the eye and lower central corneal thickness (CCT) values are a major risk-factor for OAG. CCT varies between individuals, exhibiting a normal distribution in the population. Differences in CCT are evident between ethnic groups and there is evidence suggesting that skin pigmentation may also influence this trait. Several studies have indicated that CCT is highly heritable, yet the genes that account for normal CCT variation are unknown.

Given the strong correlation between a reduced CCT and OAG and the fact that both of these traits are highly heritable, this thesis was undertaken to investigate the hypothesis that genes involved in the determination of normal CCT variation are also susceptibility loci for OAG. In order to test this hypothesis, the initial goal was to identify genes associated with CCT, followed by investigation of these genes in an OAG cohort. The role of mammalian pigmentation in influencing CCT was also assessed. The aims of the work described in this thesis were:

i. To investigate the association between pigmentation and CCT.

ii. To identify novel genetic determinants of CCT.

iii. To determine if any identified CCT genes are associated with OAG.

Both human and rodent studies were used to assess if pigmentation is associated with CCT. A meta-analysis of published CCT data in different human ethnic groups was conducted, along with measurement of CCT in 13 different inbred strains of mice with various pigmentation phenotypes. Findings from the meta-analysis ($p < 0.001$) and mouse studies ($p = 0.008$) indicated that pigmentation does influence CCT, thus recognising pigment-related genes as candidates for influencing CCT.

In order to identify novel genetic determinants of CCT, two approaches were employed, a candidate gene study and a genome-wide association study. The candidate gene study involved selecting 17 genes that were hypothesised to be involved in CCT determination based on their functional properties. Two of these genes, *COL1A1* and *COL1A2*, were found to have a significant association with CCT. A genome-wide association study is a technique that interrogates the entire genome in order to find genetic loci associated with a particular trait, which in this case is CCT. The results of the genome-wide association study identified *FOXO1* and *ZNF469* as novel CCT genes. The four identified CCT genes were then screened in an OAG cohort, with *FOXO1* found to increase susceptibility to the development of OAG.

Data from this thesis has significantly improved knowledge of the factors involved in CCT variation. Along with confirmation that pigmentation influences CCT, *COL1A1*, *COL1A2, FOXO1* and *ZNF469* provided the first evidence of any genes involved in the determination of this trait. The identification of *FOXO1* as a potential OAG gene is also a finding of significance which may have implications for future research into the disease.

DECLARATION BY STUDENT

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.

David P Dimasi

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