Project: An investigation into the genetic basis of primary angle- closure glaucoma

Grant Recipient: Dr Sancy Low BSc (Hons) MRCOphth, UCL, Institute of Ophthalmology, London

Recruitment was completed in February 2010: we now have a total of 553 participants, 460 of whom have had genome-wide microarray genotyping performed which is a larger number than originally anticipated. This was helped immensely by our collaborators at St. George's University Hospital where the laboratory work was performed by myself and Dr Pia Ostergaard. The in-house genotyping helped to keep the laboratory costs down, allowing more participants to have genetics investigations performed.

Three main components have resulted from my research:

- I have identified a small group of families where mutations in FBN1, ADAMTSL4, and BEST1 were identified. The first two genes are associated with ectopia lentis (dislocation of the lens), and this is the likely mechanism of angle-closure, when the lens dislocates forward into the anterior chamber. The last gene BEST1, causes bestrophinopathies. This group of conditions leads to scarring at the macula, and sometimes the peripheral retina, and patients with mutations in this gene also get angle-closure glaucoma (ACG). Although the ACG here is not "primary", but a secondary form of ACG, good intraocular pressure control is difficult to achieve. The complications that can result from surgery (either to the lens or glaucoma filtration surgery) include aqueous misdirection, also known as "malignant glaucoma". These groups of patients with rare mutations highlight to us the importance of recognizing hereditary ACG.

- The second and main finding of my research into PACG comes from studying over 100 families with the condition. The majority are of White European ancestry. The largest family has more than 10 affected individuals. Genealogy expertise was also sought and we identified two distant relatives with the same condition. Theoretically, such a big family would be sufficient for identifying a single causative gene, if it is inherited in a straightforward autosomal dominant fashion. The family was recruited over two years, and a total of 74 blood samples were received. Fifty-two of the participants were fully characterized with detailed eye examinations. The mode of inheritance is most likely to

be dominant in this family, although many more females are affected than males. After three comprehensive genome linkage scans of this family, we can conclude that there is not ONE locus which causes the disease in this family, but an unknown number (probably a few, maybe many). The underlying mechanism may be due to interactions between genes, even if ONE particular locus makes the most contribution. As genetic technologies evolve and become more affordable, we will continue working on the underlying mechanism in this family, therefore the request for saving a small amount of funds from this project to kick-start any future investigations. The smaller PACG families recruited show similar findings, and support a multi-factorial aetiology for the condition.

- The third segment of my PhD relates to a pilot genome wide investigation. We are extremely grateful to the IGA for funding the UK-wide DNA collection of PACG cases. In preparation for the genome-wide association study, we genotyped 99 cases with approximately 300,000 SNP markers and compared them with 2,000 subjects from the 1958 British Birth Cohort as controls. A few regions of interest have arisen but none of genome-wide statistical significance. We are confident of the methodology and look forward to continuing the research into finding out the genetic mechanisms that play a key role in the development of PACG.

Milestones for research activities in the next 18 months:

- Submission of PhD thesis for examination
- Presenting the work at major conferences. Small sections of the project have been presented to date, as we needed to be sure of our results before presenting to an international audience.
- Future research areas I hope to be working on

The material collected over the last four years will allow more hypotheses to be tested, like novel quantitative traits on ASOCT imaging, the effect of eye colour on PACG, and confirmation or exclusion of candidate genes that may become published over this mid-term period. I will continue to pursue these during my specialty training in ophthalmology, starting in August 2010.

Sancy Low

Current IGA Funded Research

Each year the IGA Grant Committee is proud to distribute grants to a range of research projects of which the objective is to advance the knowledge of the causes of glaucoma and to develop more effective methods of diagnosis and treatment. The IGA distribute grants directly via its Grants Committee, or through other organisations which are the Royal College of Ophthalmologists and the UK & Eire Glaucoma Society. Up until very recently, grants were only made to research projects led by ophthalmologists, but we are pleased to inform you that the Grants Committee has made the decision to open applications to ophthalmic nurses which will be delivered via the Royal College of Nursing.

Below is an up-to-date table summary of all the projects that the IGA has been funding since 2006 and their status. If you have any questions about these projects, please do not hesitate to contact David Wright by telephone on 01233 64 81 64 or by e-mail at info@iga.org.uk.

Year Awarded	Recipient & Hospital	Research	Completed
2006/2007	Mr Ian Murdoch Miss Sancy Low Moorfields Eye Hospital	Beta radiation or 5 flurouracil to prevent scarring in trabeculectomy in Africa	Yes
2006/2007	Andrew Lotery, Sarah Ennis Andrew Collins Southampton University	Association Mapping of Gene(s) Predisposing to Primary Open Angle Galucoma	Ongoing
2006/2007	Dr Anne Child St George's University of London	The genetics of glaucoma Year One	Ongoing

Year Awarded	Recipient & Hospital	Research	Completed
2007/2008	Dr Anne Child St George's University of London	The genetics of glaucoma Year Two	Ongoing
2008/2009	Dr Sancy Low UCL	An investigation into the genetic basic of primary angle-closure glaucoma	Ongoing
2008/2009	Mrs A Choudhary University of Liverpool	Role of Thrombospondin 1 and 2 in open angle glaucoma	Ongoing
2008/2009	Mr PJ Foster UCL	Creation of a disease-specific DNA biobank for angle-closure glaucoma in the UK	Ongoing
2008/2009	A Viswanathan Moorfields Eye Hospital	Award to support translational research initiative BMRC 043	Ongoing
2008/2009	Professor North Team University of Cardiff - UKEGS	Three Diamentional Imaging of the ageing and Glaucomatons Optic Nearve Head: Risk factors for the development of open-angle glaucoma.	Ongoing
2009/2010	Dr Anne Child St George's University of London	IGA POAG Biobank samples as Replication Cohort in Association Studies	Ongoing
2009-2010 (UKEGS Grant)	Colm O'Brien & Deborah Wallace Dublin University	Novel Anti-Connective Tissue Growth Factor Antibody Therapy in Pseudoexfoliation Glaucoma	Ongoing
2010/2011	Mr A Shar Dublin University	Affected sibling-pair analsis for susceptibility loci in primary open angle glaucoma.	Ongoing

Year Awarded	Recipient & Hospital	Research	Completed
2010/2011	Professor J E Morgan Cardiff University	Characterisation of the perineurinal net (PNN) in the glaucomatous human retina: the identification of targets for PNN digestion therapy for the restoration of retinal ganglion cell structure in glaucoma.	Ongoing
2010/2011	Mr S Dhingra Institute of Ophthalmology	Optimising success of glaucoma surgery by determining conjunctival gene expression and risk factors.	Ongoing
2010/2011	Ms Lynn Ring Epsom and St. Helier University Hospital	A Quasi Experimental study of adherence to ocular hypotensive treatment: an educational perspective	Ongoing