The Genetic Basis of Glaucoma
Part One of Three

The following article is the first in a series of three articles focusing on genes and genetic research in relationship to glaucoma.

Many characteristics such as height or hair colour are inherited down through the family line via genetic information contained in every cell in your body. In the same way there is also a chance that you may have inherited glaucoma. Research around the world is now clearly establishing the relationship between mutations in certain genes, and the glaucomas.

Every cell in our body contains DNA, which is a bit like a blueprint, or a plan, for every component of our physical appearance and our functioning. It contains over 3 billion "letters", each of which is one of four types (called A, C, G and T) organised in an incredibly complex manner. Every time a cell divides all this information is copied with such exactness that errors are seldom made. Occasionally however, mistakes in this copying process do occur (the equivalent of a "typo") and these mistakes are called mutations.

Glaucoma has a strong hereditary component, with approximately 40% of all individuals reporting a positive family history. We all carry two copies of every gene and in some cases if one copy of the gene has a mistake in it, this is enough to cause the disease. This mechanism is called autosomal dominant inheritance. As we inherit one copy of a gene from each parent, there is therefore a fifty percent chance that an individual could develop glaucoma, if one of their parents has glaucoma. However new mutations can occur spontaneously.

To date three genes have been identified, accounting for less than 12% of Primary Open Angle Glaucoma (POAG), but research suggests at least six other genes contribute. Identification of glaucoma disease genes will contribute to greater understanding of disease development, and therefore prevention.

So how do we know if we have a mistake in our genes that causes eye disease? The first thing is to understand your family history. If you have a relative (parent, grandparent, aunt or uncle, sibling) who is affected with eye disease it is imperative that you have regular eye checks with an optometrist or an ophthalmologist to detect the disease. At present gene testing is only being done on a research basis here in NZ.

The genes and research will be discussed in further issues of *Eyelights*.

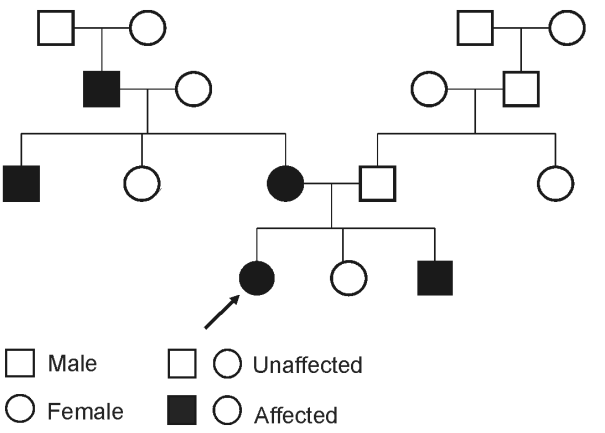

Figure 1: An example of a pedigree (family tree) with Autosomal Dominant Primary Open Angle Glaucoma

The Genetic Basis of Glaucoma
Part Two of Three

This is the second in a series of three articles written for our readers by Dr Andrea Vincent, recipient of a research grant from Glaucoma NZ in 2007 for research into the genetics of glaucoma in New Zealand.

Genes in Glaucoma

Research worldwide over the last 15 years has considerably expanded our understanding of the genetic basis for glaucoma. Finding a gene or genes that appear to cause glaucoma is crucial to further understanding the aberrant processes that cause raised pressure or nerve damage. Ideally this information may allow us to conjure up new treatment strategies. More importantly, genetic screening can identify family members of affected individuals who carry a mutation but have not yet developed the disease. This allows these at-risk individuals to be screened regularly, and treatment instigated before there is irreversible glaucomatous damage and vision loss.

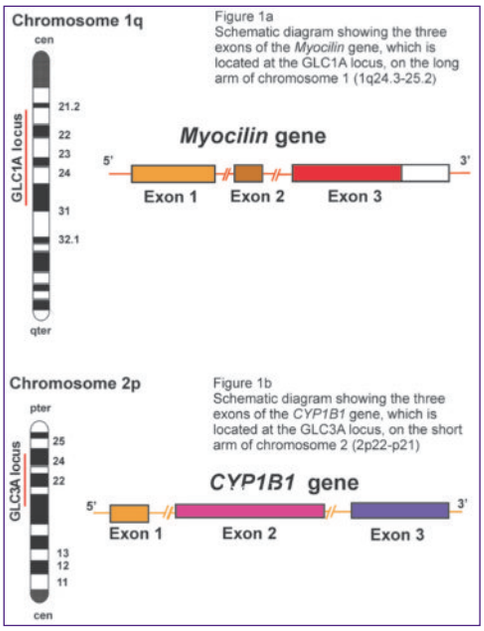

Figure 1a
Schematic diagram showing the three exons of the *Myocilin* gene, which is located at the GLC1A locus, on the long arm of chromosome 1 (1q24.3-25.2)

Figure 1b
Schematic diagram showing the three exons of the *CYP1B1* gene, which is located at the GLC3A locus, on the short arm of chromosome 2 (2p22-p21)

Myocilin was the first gene known to cause glaucoma to be discovered in 1995. This gene on chromosome 1 (Figure 1), makes a protein that is secreted in the trabecular meshwork (drainage angle) of the eye. It is most likely that mutant Myocilin protein causes glaucoma by damaging the trabecular meshwork, thereby impairing outflow of aqueous fluid from the eye.

Mistakes in Myocilin account for 4% of individuals affected with glaucoma worldwide, but given the prevalence of glaucoma, this is still a large number. Myocilin mutations account for 10% of disease in families known to have Juvenile open angle glaucoma (onset before 40 years). Certain mutations are known to cause early onset of disease with very high pressures, and it is demonstrated these patients respond better to early surgery than to medical treatment. Other mutations, including the most common (Q168X), cause a later-onset glaucoma with mild pressure elevation.

Several groups have shown that some individuals carry two mutations; one in Myocilin, and one in CYP1B1, a gene known to cause congenital glaucoma. Congenital glaucoma is caused by 2 mutations in CYP1B1. The glaucoma associated with Myocilin AND CYP1B1 is more aggressive, with an earlier onset than Myocilin alone.

Another gene described is Optineurin (OPTN). This gene located on chromosome 10 appears to play a role in protecting the optic nerve head against pressure and other insults. Mutations are known to occur in individuals with Normal tension glaucoma, and may render the optic nerve more susceptible to insult. Mutations in this gene probably account for 2% of all glaucoma.

Similarly WDR36 may cause 1% of glaucoma, but the mechanism of action is still unclear.

Extensive research has pinpointed the chromosomal positions of at least another 8 genes involved in glaucoma, but ongoing worldwide research is necessary to further identify these genes, and how they cause glaucoma.

The next instalment will discuss how New Zealand research is contributing to this knowledge.

The Genetic Basis of Glaucoma
Part Three of Three

This is the final in a series of three articles written for our readers by Dr Andrea Vincent, recipient of a research grant from Glaucoma NZ in 2007.

New Zealand Research In Glaucoma Genetics.

The current knowledge for the genetic basis for glaucoma is being slowly elicited in research laboratories around the world. Since the first gene known to cause glaucoma, Myocilin, was characterised in 1995, further research has elucidated the nature of 3 other genes, Optineurin, WDR36 and CYP1B1, with evidence that at least 8 other genes exist.

With the assistance of funding from a Glaucoma NZ research grant, we are attempting to characterise the genetic nature of glaucoma in New Zealand. Overseas research centres have been involved for years, with vast libraries of DNA (and lots of money!), but it is still worthwhile to carry out such research in New Zealand.

Firstly we have identified a number of affected individuals with a positive family history of glaucoma, i.e. at least one first degree relative affected. After informed consent we take a blood sample, a cheek swab, or a saliva specimen for DNA extraction.

Staff of the Genetic Eye Disease Investigation (GEDI) Unit in The University of Auckland Department of Ophthalmology, L to R: Lucia Tang, Dr Andrea Vincent, Janet Rhodes, Betina de Karolyi

Our screening strategy is firstly to sequence the Myocilin gene. The frequency of Myocilin mutations is about 4% in the populations already characterised, so in a group of 100 patients we would expect to only find 3 or 4 with a disease-causing sequence change, or mutation. In those with a mutation, we then recruit their family members, both affected and unaffected, to make sure the mutation occurred only in conjunction with the disease, and not in the unaffected individuals.

As Myocilin is very well characterised we could then check with databases and research publications to ascertain whether our mutations have been characterised before. Our research can add to the pool of knowledge helping to confirm the status of a sequence change, or maybe even finding new mutations.

After screening the Myocilin gene, we would then screen OPTN, WRD36 and CYP1B1. It is likely after this process that at least 85-90% of patients would not have a genetic diagnosis, and it is this group of patients and their families which provide us with a powerful tool to identify new genes. Certainly when a very large, multiple generational family is discovered, with no mutations identified in known genes, a genetic method known as Linkage, can be employed to try and determine if the disease “links” to a certain area of a chromosome. Then we would look for genes within that area of a chromosome.

Although this work is very time-consuming and expensive, screening a New Zealand Glaucoma population for genetic causes can contribute to the world-wide knowledge, and has the potential to identify new genes.