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.

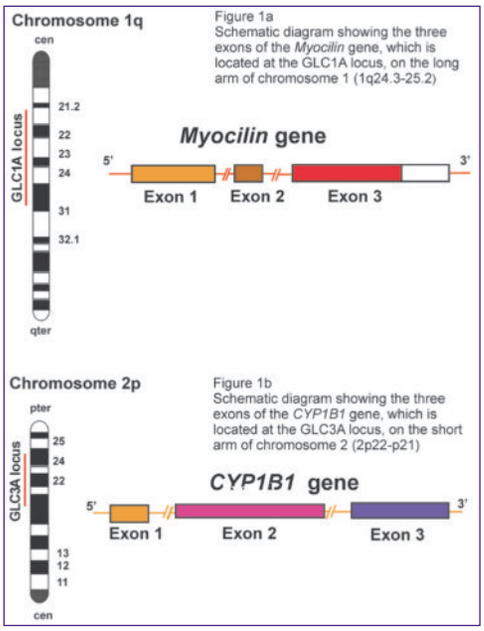

Figure 1a
Schematic diagram showing the three exons of the *Myocilin* gene, which is located at the GLC1A locus, on the long arm of chromosome 1 (1q24.3-25.2)

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.