Finding genes associated with glaucoma may lead to new diagnostic tools and therapeutic options

When it comes to genetics, eye diseases are complex. Finding a single gene with a single mutation that causes an ocular pathology is more the exception than the rule. For the most part, many diseases of the eye may result from the combined effect of several mutations in two or more genes coupled with the interaction of environmental factors. Consequently, powerful research tools are required to gain insight into the molecular choreography that leads from a primary genetic error to a set of clinical symptoms.

A good illustration of such complexity is primary open-angle glaucoma (POAG), which affects 70 million people worldwide. For instance, a person with a first-degree relative who has POAG is seven to 10 times more likely to develop POAG than someone without such a connection. Of course, genetics aren’t the only reason people develop POAG, given such known risk factors as hypertension, diabetes and cigarette smoking.

At the last count approximately 20 genetic loci were linked to POAG, about three quarters of which have been assigned to a specific gene, as summarised in Table 1.

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While the progress as summarised in the table represents an encouraging advance, only three genes to date have been identified as causative of POAG – myocilin (MYOC), optineurin (OPTN) and WD repeat domain 36 (WDR36).

Together these three genes account for fewer than 10% of the glaucoma cases around the world and so a significant amount of work remains if a comprehensive picture of glaucoma genetics is to be achieved.

MYOC mutations are estimated to cause approximately 2% to 4% of POAG in Caucasians with a slightly lower prevalence of 1.1% to 1.8% among Chinese patients.

Mutations in optineurin (OPTN) were found in 16.7% of families in the original study that uncovered OPTN but, according to some reports, subsequent studies on separate Caucasian and Japanese POAG patients found no specific glaucoma-causing mutation in OPTN.

The final POAG gene, WDR36, when originally reported suggested that four mutations were associated with more than 5% of all sporadic POAG. Compounding the challenge of chasing down the genes is the observation that approximately one third of all POAG patients have an IOP within the normal range of less than 22 mmHg, referred to as either normal tension glaucoma (NTG) or low tension glaucoma.

Despite this, optic nerve loss leading to blindness occurs in these patients and the exact mechanism of what causes the cell death is still unknown. Consequently, finding the genes responsible will represent only a part of the overall picture in which non-genetic or environmental factors may dictate a significant element of the actual occurrence and progression of the disease.

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Microarray expression analysis is a relatively recent research tool in which the technology allows the researcher to study several thousand genes simultaneously rather than just one at a time. This allows a reasonably funded lab to cover far more “genetic space” than would have been previously possible, while additionally permitting the researcher to observe relative contributions from different genes to a given pathology.

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Finally, candidate gene studies have benefited from both the Human Genome Sequencing Project and the commercial development of gene sequencing technologies in which the cost and speed of DNA sequencing has dropped dramatically. Direct sequencing of a candidate gene, picked on the basis of a biological hypothesis, may now be achieved in a relatively short order of time.

Strategically planned studies are now well under way that employ one or more of the above approaches to secure the greatest amount of data at the lowest cost in the quickest time. The result is a significant expansion in the volume of genetic data now openly accessible in a range of internet accessible databases, a sample of which are highlighted in Table 2.

Beyond diagnostic applications, the Holy Grail of these cumulative research efforts is to discover new therapeutic opportunities. Historically, medical treatment of POAG has concentrated on lowering the IOP with a focus on aqueous humour production and on targets that promote aqueous humour outflow. A relatively recent approach in glaucoma treatment has focused on the trabecular meshwork and Schlemm’s canal through which the aqueous humour leaves the anterior chamber of the eye. This pathway is thought to be controlled by a rheostat-like mechanism that balances a family of matrix metalloproteinases (MMPs) against tissue inhibitors of MMPs (TIMPs). The interaction of MMPs and TIMPs is understood to function in the remodelling of the trabecular meshwork’s extracellular matrix. An imbalance in the ratio of MMP:TIMP may account for observed differences in outflow between normal and glaucomatous eyes. Stimulating MMP expression can increase aqueous humour outflow and thereby reduce IOP. The prostaglandin class of drugs function in this manner by increasing MMP activity in ciliary smooth muscle cells and lowering the IOP by facilitating aqueous fluid outflow via the uveoscleral pathway.

An increasingly popular target for therapeutic intervention is an attempt to slow down the loss of retinal ganglion cells which degenerate over time by a process of apoptosis. As glaucoma is increasingly thought of as a neurodegenerative disease, the provision of neurotrophic factors to slow or halt cell death represents a rational approach aimed at maintaining visual function. Several categories of drugs are being developed as neuro-protective agents including caspase inhibitors, calcium channel blockers, nitric oxide synthase inhibitors and neurotrophins such as brain derived neurotrophic factor, ciliary neurotrophic factor and glial cell line derived neurotrophic factor.

Even with the currently available drug options all treatments are focused on the symptoms of glaucoma rather than the root causes. Given that the mechanisms leading from genetic error to disease are still to be elucidated, this is entirely practical. However, the objective of the genetic approach is to devise a strategy that addresses the underlying genetic component once clear targets become available.

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Table 2. Eye genetics-related databases available over the internet:

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<th>Database</th>
<th>Website</th>
<th>Maintained by</th>
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<td>KMEYEDB</td>
<td><a href="http://neibank.nei.nih.gov/">http://neibank.nei.nih.gov/</a></td>
<td>Keio University School of Medicine, Japan</td>
</tr>
<tr>
<td>RetNet</td>
<td><a href="http://www.sph.uth.tmc.edu/Retnet/">http://www.sph.uth.tmc.edu/Retnet/</a></td>
<td>University of Texas, Houston, US</td>
</tr>
<tr>
<td>Lens GDDB</td>
<td><a href="http://ken.mitton.com/ern/lensbase.html">http://ken.mitton.com/ern/lensbase.html</a></td>
<td>Eye Research Institute, Oakland University</td>
</tr>
<tr>
<td>Human PAX 6 allelic variant database</td>
<td><a href="http://pax6.hgu.mrc.ac.uk">http://pax6.hgu.mrc.ac.uk</a></td>
<td>MRC Human Genetics Unit, Edinburgh, UK</td>
</tr>
<tr>
<td>Retinoschisis DB</td>
<td><a href="http://www.dmd.nl/rs/">http://www.dmd.nl/rs/</a></td>
<td>Leiden University Medical Centre</td>
</tr>
</tbody>
</table>

Glossary

**Apoptosis:** A mechanism of cell death in which cellular demise is orchestrated in a “silent” manner without inflammation or cell lysis. The process is co-ordinated by a family of proteases known as the “caspsases”. In a disease context, too much apoptosis may arise in neurodegenerative disorders such as retinitis pigmentosa, while too little apoptosis may permit the progression of various forms of cancer.

**Loci:** Or “locus” refers to the physical location on a given chromosome where a particular gene may be found.

**Uveoscleral pathway:** refers to the route of aqueous humour between the ciliary muscle bundles into the supraciliary and suprachoroidal spaces from where it is drained through the sclera.