Guest Editorial

Visionary genomics

Over 10,000 scientists, clinicians, trainees and industry representatives gathered in Fort Lauderdale, Florida, USA, recently for the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO). In recognition of the challenges that lie ahead for the vision sciences, the theme chosen for the 2011 meeting was 'Visionary Genomics'.

We have come a very long way since the days of John Dalton and his 1794 paper on the origins of colour blindness, a condition he shared with his brother.[1] Investigators from the vision research community have worked out the major pathways of how visual information is received, processed and transmitted to the brain, and how specialised tissues such as the cornea and lens work together to focus light on the retina and filter out harmful ultraviolet light. Molecular pathways responsible for the expression and accumulation of crystallins, the specialised proteins that make up 35 per cent of the wet weight of the ocular lens, have been discovered and studied in great detail. Genes for virtually all components of the phototransduction cascade have been identified and studied to define a host of molecular defects associated with anomalous perception of the visual world.

Now that we have a comprehensive understanding of the genes responsible for the organisation and functional integration of the visual system, it is reasonable to consider the challenges posed by major heritable vision diseases that either are not treatable or for which current therapies cannot meet the global burden of disease. We can ponder whether the emergence of next-generation genome technologies will lead us closer to discovering new therapeutic strategies and achieving improved care of patients with vision disorders. Two major blinding conditions, age-related macular degeneration (AMD) and glaucoma, can serve as useful examples to highlight how far we have come, and how far we have yet to go, in our understanding of genetic influence on disease pathogenesis.

AMD is the leading cause of blindness in people aged over 60 years in North America. Many commonalities have been associated with the complex manifestation of AMD, including accumulation of excess oxidised lipoproteins in the form of drusen; atrophy of the retinal pigment epithelium; formation of new blood vessels in the choroid; and environmental influences. While the use of anti-vascular epithelial growth factor (anti-VEGF) therapies (eg bevacizumab [Avastin; Roche] and ranibizumab [Lucentis; Navartis]) has helped to slow the rate of vision loss among patients with exudative AMD, we are still in the dark about mechanisms that lead to the onset and progression of retinal degeneration, and how we may intervene to delay or halt this insidious disease.

Genome technology may help to focus the search for new therapeutic strategies against advanced AMD. Almost 30 years ago, Hyman and colleagues reported evidence for a genetic predisposition to AMD.[2] More recently, several individual gene mutations have been identified in small subsets of macular degeneration, such as Stargardt macular dystrophy,[3] Sorsby fundus dystrophy[4] and Best disease.[5] Taken together, these studies demonstrated that isolated single gene mutations were unlikely to be responsible for most of the heritability of AMD. Recent genome-wide association study (GWAS) reports have identified multiple risk

loci associated with an elevated risk for developing AMD, including several different genes associated with the complement pathway (those encoding complement factor [CF] H [*CFH*], *CFB/C2*, *C3* and *CFI*). The significance of these findings was recently reinforced by observations that *CFH* variants may modulate the treatment effect of VEGF inhibitors. Nischler and colleagues found that a specific *CFH* genotype (402H) correlated with lower visual acuity outcome after treatment with bevacizumab, suggesting that CFH plays a role in the response to the treatment of wet AMD.[6] Additional GWAS results pointed to new risk variants in the region of chromosome 10 containing the age-related maculopathy susceptibility 2 gene (*ARMS2*) and high-temperature requirement A serine peptidase 1 gene (*HTRA1*).[7] Many studies have continued to implicate this region, but the functional significance of this association is still elusive. While an exhaustive study narrowed the region to the single A69S alteration in ARMS2,[8] and further patient studies have confirmed an unstable mRNA product in the variant population,[9] the search for the function of ARMS2 is ongoing. Other studies have focused on *HTRA1* and the significance of the GWAS-associated variant in its putative promoter region. HTRA1 is a serine protease that has also been associated with cancer progression.[10] A new transgenic mouse line overexpressing the gene shows changes in Bruch's membrane that could affect the elasticity of this tissue.[11] Only time and considerable effort will tell if the clues provided by GWASs will help investigators to unravel the complex interactions between genes and the environment that underlie the development and progression of advanced AMD (reviewed by Katta *et al.*[12]).

Familial inheritance patterns for glaucoma — the second leading cause of blindness in the world — also inspired a search for genetic causes of this eye disease. Over 30 years ago, Shin and colleagues found that up to 50 per cent of patients with primary open-angle glaucoma (POAG) — the most, common form of glaucoma — had a positive family history of the disease.[13] Polansky and colleagues were among the first to identify the association between the trabecular meshwork inducible glucocorticoid response/myocilin gene (*TIGR/MYOC*) and POAG and juvenile open-angle glaucoma (JOAG)[14] that was recently confirmed in 4 per cent of POAG cases.[15] GWAS data also associate the risk for developing POAG with a variant near the caveolin 1 and caveolin 2 genes. This risk was significantly higher in Chinese populations than in Europeans, highlighting the influences of population genetics and geography on individual genetic variants identified by GWASs.[16] In a similar manner, polymorphisms in the promoter region of the lysyloxidase-like 1 gene (*LOXL1*) have been identified as major risk factors for exfoliation glaucoma. As the associated polymorphisms in this region have been population dependent and risk alleles are often present in control individuals, however, further work is necessary to elucidate the genetic and environment-dependent relationships of this disease.[17]

While the genetic influences behind the development of AMD and glaucoma have been recognised for many years, the technology available to solve the mysteries behind these diseases has simply been inadequate. Past advances in gene technology, such as the ability to clone DNA fragments and solve the nucleotide sequence of genes and their transcription products, offered the tantalising hope that solutions would be found to explain the genetic mechanisms behind these diseases. While this possibility was realised for some of the major inherited vision diseases caused by single gene mutations, such as many forms of retinitis pigmentosa and cataracts, clarification of the genetic mechanisms behind AMD and most forms of glaucoma have not yielded to this approach. With the completion of the Human Genome Project and an abundance of data already available from the 1000 Genomes Project, perhaps we are beginning to see a light at the end of the tunnel. Groups at this year's ARVO meeting highlighted the role that vision research is playing on the front line of genetic advancement, as projects were presented utilising the newest advances in exome, RNA and even whole genome sequencing. Next-generation sequencing technologies are affording opportunities

to peer deeper than ever before into the genomic landscape of these complex disorders. The search for genetic risk factors has now become a large team effort as multidisciplinary teams composed of vision specialists, statistical geneticists, engineers and biochemists — each with their unique and powerful skills and technologies — are now beginning to cast some light on the darkness of complex blinding diseases. Let us hope that their work will move us closer to making today's major blinding diseases a thing of the past.

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