“T’s a very exciting time to be in glaucoma genetics with large, interesting new studies being published almost daily,” Ananth C Viswanathan MD, PhD, National Institute for Health Research (NIHR) Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital/UCL Institute of Ophthalmology, London, UK, told a session of the ninth European Glaucoma Society Congress. In the past, traditional family linkage studies have revealed many causative genes for glaucomatous disease. However, their findings have tended to be specific to the pedigree investigated and have shed little light on glaucoma’s hereditary factors in the general population. Advances in genetic research are enabling researchers to switch to a cohort-based approach, in the form of genome-wide association studies, he reported. Genome-wide association studies provide a meticulous comparison of the genome of large cohorts of patients affected by the disease of interest with the genome of a large cohort of control patients. They can reveal the locations of subtle variations in the chromosome’s nucleotide sequences, called single nucleotide polymorphisms (SNPs). “Instead of looking at classical family-based linkage, we are now looking for the association of genetic signals involving literally millions of markers in each individual and doing that across thousands of individuals. So we are seeing the nature of this scientific endeavour change from family-based linkage to cohort-based association,” Dr Viswanathan said. 

Dr Viswanathan is the principal investigator for glaucoma in a research group funded by the Wellcome trust that has been conducting genome-wide association studies. The Wellcome Trust Case-Control Consortium 2 (WTCCC2) established in 2008 is composed of multiple research consortia across the world that are investigating the genetic basis of 15 common diseases, including glaucoma.

The WTCCC2 has identified several SNPs that may have an influence on glaucoma’s aetiology. However, those findings must be confirmed in a separate cohort of patients before they can be published, he emphasised. In the meantime, other groups conducting genome-wide studies have completed both the discovery and confirmation process with some genetic variants that could have a role in the diseases, he said.

For example, an Australian group has found associations between variations in the ATOH7 gene and variations in optic disc size (Macgregor et al, Hum. Mol. Genet. 2010; 19 (13): 2716-2724). Animal studies have shown that the gene plays a key role in retinal ganglion cell formation. The findings have been replicated by another multinational research consortium studying several population cohorts, Dr Viswanathan noted (Ramdas WD, van Koolwijk LME, Ikram MK, Jansonius NM, de Jong PTVM, et al. (2010) A Genome-Wide Association Study of Optic Disc Parameters. PLoS Genet 6(6): e1000978. doi:10.1371/journal.pgen.1000978).

Another research consortium led by an Icelandic group has identified an association between glaucoma and an SNP in close proximity to the CAV1 and CAV2 genes (Thorleifsson et al, Nature Genetics 2010; 42:906–909). Both genes are expressed in the trabecular meshwork and retinal ganglion cells. The research group’s findings were replicated in separate cohorts in Sweden, UK, Australia and China.

Another recent development has been the initiation of the European Glaucoma Society’s GlaucoGENE project. The initiative involves a consortium of experts from across Europe, including specialists in phenotyping, complex genetics and basic ophthalmic biology. The aim of the project is to create a European genetic epidemiology research network, using detailed and standardised phenotyping, to better elucidate the multifactorial nature of glaucoma’s genetics (Founti, P., Topouzis, F., van Koolwijk, L., Traverso, C. E., Pfeiffer, N. &Viswanathan, A. C. (2009). Biobanks and the importance of detailed phenotyping: a case study—the European Glaucoma Society GlaucoGENE project. Br J Ophthalmol 93(5): 577-81).

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