Genetic basis of primary open-angle glaucoma

Kassandra Ali was one of the two winners of the City University/ *Optician* prize for best dissertation. Here we publish an edited extract of her winning review of the genetics of glaucoma

Glaucoma is the second leading cause of blindness worldwide and affects all age groups. Primary open-angle glaucoma (POAG) is the most prevalent type of this ocular condition, affecting 2 per cent of the general population over the age of 40. Many risk factors are associated with POAG, the major ones being high intraocular pressure, age, family history of glaucoma and ethnicity. While the actual cause of POAG is still not established, the past decade has supplied the research attention needed to fully understand its genetic basis. To date, the interaction of several environmental factors with a few implicated genes: MYOC, OPTN and WDR36 have been identified as attributable. This review will be looking into the genetics of these genes and their putative roles in the pathogenesis of POAG. As research in genetics of glaucoma is relatively new, it will also question whether these findings are significant enough to influence the prognosis of glaucoma and aid in its management.

History of genetic associations of glaucoma

The hereditary nature of glaucoma became of interest to scientists as early as 1842 when a study by Benedict questioned the existence of the familial risk of the glaucomas based on POAG occurrence in two sisters.[1] In 1869, von Gräfe reiterated the importance of inheritance in the aetiology of glaucoma and referred to families in which the disease presented in three to four generations. At this time, the method of analysing the heredity of glaucoma was primarily done by family pedigree trees (Figure 1). The first description of juvenile onset primary open-angle glaucoma (J-POAG) was done in 1932 by Bell and associates who found a large number of patients presenting with inherited glaucoma before the age of 30.[2] Up to this point, the subjects of journal articles were families where glaucoma presented in multiple members.

More than 150 years later, the work of Stone,[3] Sheffield[4] and Booth *et al*[5] identified a region on 1q that was associated with the risk of POAG. A milestone in the genetics of J-POAG was the work done by Sheffield.[4] Using linkage analysis, linkage was detected on the long arm of chromosome 1, 1q21-q31. Recombination mapping enabled the critical region to be mapped between the microsatellite markers D1S191 and D1S194 (Figure 2). Using fine mapping studies and mutation analysis, Stone *et al*[3] identified a gene and its three mutations responsible for 1q linked glaucoma as a trabecular meshwork induced glucocorticoid response protein (TIGR). Later named MYOC, this gene was discovered to be produced in response to glucocorticoids by the TM and ciliary body cells which increases resistance of the TM, restricting aqueous outflow and increasing intraocular pressure.[2]

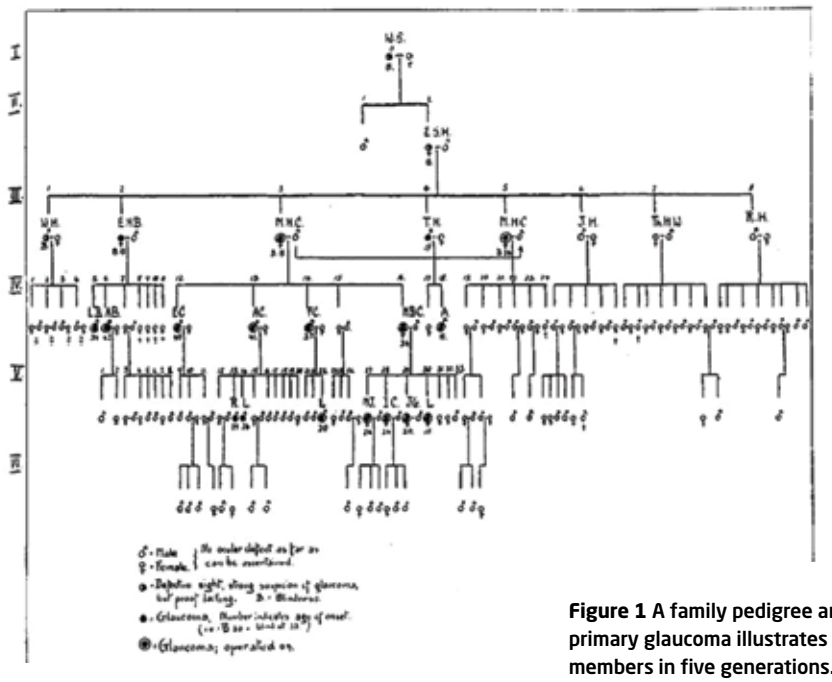

Figure 1 A family pedigree analysis for primary glaucoma illustrates 21 affected members in five generations.[9]

Our understanding of POAG's genetic basis has greatly developed from Stone's first finding of MYOC. We now know that there are Mendelian and non-Mendelian forms of OAG. The adult onset POAG, is commonly inherited as a complex trait of non-Mendelian form while the earlier onset, J-POAG, is inherited as an autosomal dominant trait.[6]

Adult-onset POAG affects approximately 2.3 per cent of the general population over 40 years of age, increasing to 4 per cent by the age of 80.[7] Its asymptomatic onset means these individuals often are treated when it is too late to recover the permanent visual field loss. To date, three causative genes (MYOC, OPTN and WDR36) have been identified and reported to account for no more than 5-10 per cent of all POAG cases.[8]

Can genotype predict glaucomatous risk and prognosis?

Considering previous studies, our understanding of the genetic basis of glaucoma is still in the developmental stage. This being said, I believe that genotyping has great value in predicting the risk and prognosis of glaucoma. If a person is genetically screened for these genes associated with glaucoma and a known mutation is found, the risk of that person presenting with a specific phenotype of glaucoma can be predicted. Depending on the age of screening and whether it is their first time being diagnosed with glaucoma, a person's prognosis can also be predicted with the use of data from research that has repeated in multiple populations.

Based on an individual with glaucoma, if genotyping is done at an approximate age of 20 years, an approximate prediction ▶

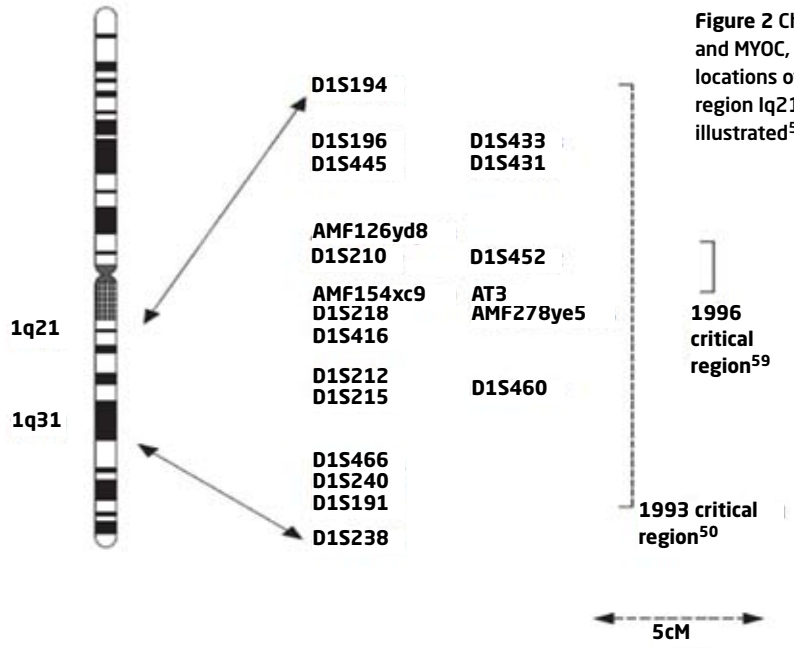

Figure 2 Chromosome 1 and MYOC, the approximate locations of DNA markers in region Iq21-q31 are illustrated[5]

of the phenotypic traits to expect of the gene mutation they are carrying can be given. Using the compilation of information gained so far, a prediction of age-of-onset, expected IOPs and severity of progression can be related to the individual's gene mutation.

Out of the four defective genes that have been researched the most, MYOC is linked to early adult to juvenile open-angle glaucoma with the different specific mutations reviewed above presenting with different traits, OPTN linked to normal tension glaucoma, WDR36 for adult-onset POAG and CYP1B1 for PCG with some cases in adult POAG.

Other contributable risk factors

Although the genes mentioned are found in patients with POAG, even the most strongly associated gene, MYOC, only accounts for 3-5 per cent of POAG cases. What contributes to the other 95 per cent of factors responsible for POAG?

Intraocular pressure

IOP consistently >21mmHG increases risk of damage to retinal ganglion axons leading to glaucomatous visual defects. High IOP exerts a force at the optic nerve head that pushes against the fenestrated lamina cribosa which the central retinal artery and retinal ganglion cells pass through, leaving the eye to form the optic nerve. When IOP is elevated above normal, the web-like structure made of collagen fibres (Figure 3) deforms and the cavities which retinal nerve fibres pass through constrict. This pinches and can even sever these fibres, leading to irreversible visual field loss.

Family ocular history

First degree relatives of an affected individual have a 22 per cent risk of developing POAG compared with only a 2.3 per cent risk of the general population. This raises the overall risk from threefold to ninefold.[10]

Studies done for WDR36 show individuals with family ocular history of glaucoma have a 50 per cent risk of inheriting the mutated WDR36 along with the gene causing the presentation of glaucoma in the affected relative. This will increase the risk to the individual logarithmically.[11]

MYOC mutations are mostly autosomal dominant, including the most severe phenotype causing mutation, Pro370Leu. OPA1 and CYP1B1 have also been found to be autosomal dominant meaning that the chances of these genes being passed on to offspring are very high.

A population of 3,391 glaucoma patients meeting criteria set out by a study were chosen from a database containing 1.5 million medical records. POAG cases and controls were analysed for familial risk of POAG. Conclusions reported 20 per cent of the risk for glaucoma being attributable to genetic factors.[12] Results are similar to previous findings but unlike previous research, it was discovered that there is an increased risk in first cousins and second cousins of an infected person. Previous studies have assessed only first-degree relatives without considering second-degree relatives.[13] The relative risk factor of 1.45 in first-degree and 1.19 in second-degree cousins whom only share 2 per cent of alleles, suggests a much stronger genetic linkage than previously believed.[14,15]

Race

POAG is more common in Afro-Caribbeans and presents at an early age. The severity and prevalence of POAG is higher in African-Caribbeans and Hispanics compared to Caucasians, which may indicate a higher genetic susceptibility to POAG in these populations. Different phenotypes of glaucoma have been shown to be prevalent in certain ethnic groups over another (Kanski, 2008).

Mutations in MYOC account for approximately 2-4.4 per cent of OAG in European, American, Canadian, Australian, Indian, African American and Japanese populations. It is found in 3.86 per cent of Caucasian patients with POAG (HTG and NTG), 3.30 per cent of patients of African descendants, and 4.44 per cent of Asian patients.[16] In Chinese OAG patients, the prevalence drops to 1.1-1.8 per cent.

The specific MYOC mutation of Gln368STOP has been identified with different prevalence among a range of populations, suggesting that it may be more common in some ethnicities compared to others. It has been found to have 5 per cent prevalence in a French study and 4.27 per cent in a Swiss OAG study and has notably not been reported in Japanese, Korean, Chinese or Indian populations.[17]

CYP1B1 mutations found in PCG patients of a small study size of the Israeli population are mainly detected in Druze (75 per cent) whom presents with a more severe phenotype when compared to Muslim Arabs (53 per cent) and Jews (22 per cent).[18] This illustrates that even within a small population, the specific ethnicity may also vary the prevalence of the mutation specific glaucoma.

Prevalence of NTG is significantly ▶

TABLE 1
Prevalence of four different genes identified as causative for OAG

GENE	MYOC	OPTN	WDR36	CYP1B1
PREVALENCE	3.9% of OAG cases	E50K= 3.5% of NTG M98K=16.9%POAG & 15.4% NTG	10-17% of glaucoma cases	80% of familial and 30% sporadic cases of PCG 3-10% of POAG

higher in Japanese than in Caucasians. Approximately 90 per cent of Japanese POAG patients suffer from the NTG phenotype.[8] Overall, previous research has found a definite difference in the prevalence between POAG-related gene mutations and race.

Environment

An individual's surroundings will expose them to various factors that may differ or alter the expression of their genes. Although our understanding of genetic associations of POAG have improved drastically, there is still a lot to learn about how these factors interact with the environment to express different phenotypes. In most of the studies reviewed, the number of individuals carrying the mutation of the gene in question presenting with glaucoma was lower than the total number of glaucoma cases. This strongly suggests that the presence of other factors, genetic and environmental, must be influencing glaucoma in these families.[19]

Age and systemic diseases

POAG is more common after the age of 40 years, with most cases occurring after the age of 65. Because health deteriorates with age, a combination of morphological changes in the body's tissues and presentation of certain health conditions will increase the risk of glaucoma. Cells in the eye change with age and tissues lose elasticity and integrity which leads to a natural increase in IOP predisposing elders to OAG. Systemic diseases, diabetes or other health conditions may require medication which will also alter the homeostasis of aqueous flow. For example, it is common to have high blood pressure at an older age in which the perfusion pressure can cause an increase in IOP leading to an increase in POAG.

Gender

Previous studies have investigated the increased risk of POAG with early menopause comparing the reduced risk of POAG with late-onset menopause. Two SNPs, in the ESR2 gene lead to increased IOPs in the Netherlands population as discovered by de Voogd.[20] This was recently investigated in a Japanese population, testing the association of oestrogen receptor beta gene polymorphisms with POAG in female patients already presenting with the disease. When comparing HTG patients to the controls, there was a significantly higher frequency of the SNPs, 30-40 per cent in the women with HTG. This provides evidence

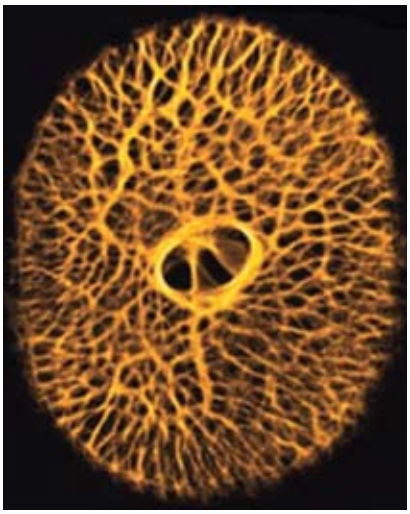

Figure 3 Lamina cribrosa

of the genetic difference of NTG and HTG and illustrates how oestrogen can reduce IOP in women proving that a reduction in its levels, such as in menopause, will then increase IOP and risk of glaucoma.[21]

Myopia

Myopia is another factor that has been linked to POAG. Myopic eyes tend to have larger discs, especially in high myopes over 6 dioptres, increasing susceptibility to damage at a lower IOP. Smaller discs maintain their integrity at higher pressures since the nerve fibres are bundled tightly the integrity of the retinal nerve fibres can be maintained at higher pressures than with larger discs. The larger the disc, the more spread out the nerve fibres are around the rim of the disc making them more vulnerable to damage.

Conclusion

Is genetics significant enough to influence glaucoma?

Since the genetic association of glaucoma was first introduced in 1842 by Benedict, further studies such as GWAS have provided evidence of glaucoma being a complex genetic eye disease with a multifactorial inheritance pattern. Recent methods of genetic research have provided unbiased results compared to earlier family genetic linkage studies and have the value of a extremely large database to compare an individual's genotype against hundreds of thousands of others for similarities.

Although only a small number of POAG patients follow the classic Mendelian inheritance pattern of this disease, genome-wide association studies and experiments looking into the association of relevant loci are promising to prove a stronger linkage in the near future. The loss of vision due to glaucoma is irreversible and therefore the ability to accurately predict the individual risk of the disease prior to symptoms is critical.[8] GWAS have proven very powerful in identifying associations between many SNPs and traits but more work is needed to determine their functional basis.[22]

How can genetics affect the treatment of POAG patients?

As the irreversible visual field loss caused by glaucoma has an enormous impact on a person's quality of life, the earlier we are able to diagnose, the less damage is done. Current treatments rely on patient compliance with frequent visits to an optometrist/ophthalmologist to monitor the progression. It has estimated that up to 35 per cent of RGC loss can occur before corresponding visual field defects are detected by perimetry and a larger percentage before the individual may recognise a problem. At this point, the eye has already lost a significant portion of vision before starting to manage and treat glaucoma.[7]

This can all be postponed if not prevented by diagnosis at an earlier stage prior to visual loss by genetic screening. If patients are found to be carrying the mutation, they will be monitored closely to enable early treatment at first presentation of glaucoma. Their first-degree relatives can get screened for the gene and only those carrying it will have to be monitored by optometrists as relatives not carrying the gene have the same risk as the general population.

Is genetic screening for POAG ultimately worth it?

In the UK, the annual cost associated with blindness because of glaucoma exceeds £100m. To add to this figure, because of supporting research, first-degree relatives of glaucoma patients which have an eightfold increase risk of POAG are encouraged to have regular eye examinations by optometrists and may never develop any form of glaucoma. Genetic screening would highlight the risk groups carrying a gene mutation associated with glaucoma and provide the necessary attention without exploiting funds on individuals who are less at risk without gene mutations.[7]

References

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