The genetics of primary open angle glaucoma

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The advent of the discipline of molecular genetics over the past decade has led to a dramatic growth in our understanding of the genetics of a myriad of diseases. Ophthalmology has benefited greatly from this new technology, with significant advances in our knowledge about conditions as varied as aniridia and retinitis pigmentosa.1,2 Our understanding of the genetics of primary open angle glaucoma (POAG) may not be as clear as with some other ophthalmic conditions but, nevertheless, there have been great advances since the last review about the genetics of glaucoma published in the BJO in 1980.3 At that time, our knowledge was based on a number of conflicting studies attempting to link human polymorphisms, such as the ability to taste phenylthiocarbamide, with glaucoma.4 Nowadays, the positions of genes responsible for various forms of glaucoma have been localised, not just to individual chromosomes, but to specific small regions on those chromosomes. Recently, for the first time, a gene responsible for a specific form of POAG has been identified. This review aims to highlight and explain the important recent advances in our understanding of the genetics of POAG.

Inheritance of primary open angle glaucoma

Primary open angle glaucoma, for the purpose of this review, refers to those cases of glaucoma in which there is not only no evident antecedent or related ocular disease but also the angle of the anterior chamber remains open at all times.4 The possibility of a genetic predisposition to glaucoma was first realised in 1842 when Benedict reported the occurrence of glaucoma in two sisters.5 Despite the intervening 150 years, our understanding of the genetics of POAG remains unclear. Certainly, most POAG pedigrees do not show a simple Mendelian pattern of inheritance. However, relatives of patients with glaucoma do run an increased risk of developing the condition compared with the general population; estimates of the increased prevalence range from 2.8% to 13.5%.7 An oligogenic, polygenic, or multifactorial mechanism is usually proposed for POAG. This assertion is supported by a number of twin studies which have shown a degree of concordance consistent with a polygenic or multifactorial inheritance.8

A minority of POAG pedigrees do demonstrate a Mendelian pattern of inheritance. A large number of pedigrees with autosomal recessive inheritance have been described.9–15 It has been suggested that this may be the commonest type of Mendelian inheritance in POAG.16 A number of autosomal dominant pedigrees have also been described, with a degree of penetrance varying from 60% to 100%.14,15 Many of these autosomal dominant pedigrees contain members who developed glaucoma at an early age.12,13,15–20 In 1932, Bell described a large number of patients with glaucoma.21 She found that those patients with clearly inherited glaucoma tended to develop the disease before the age of 30 years. This was probably the first description of juvenile onset primary open angle glaucoma (J-POAG). J-POAG is characterised by an onset before the age of 30 (often younger), a normal cornea, high IOPs (30–50 mm Hg) with large diurnal variations, and a poor response to medical therapy, necessitating early surgical intervention.22 The appearance of the drainage angle at gonioscopy, previously thought to be normal, is in fact variable, as will be discussed.

Autosomal dominant juvenile glaucoma can occur in association with hypoplasia of the iris.23,24 Affected individuals have characteristic slate grey or chocolate brown irides, as a result of the iris pigment epithelium showing through a hypoplastic iris stroma. An unusual type of autosomal dominant glaucoma, normal pressure glaucoma, has been described. It again tends to manifest at a fairly young age.25

Extremely rare pedigrees showing possible sex linked inheritance have been reported. François discussed two pedigrees which he speculated could be compatible with a X linked inheritance.26 Studies concerning the association of sex with POAG have been contradictory. The Framingham study found that men were more than twice as likely as women to develop POAG, whereas the opposite was reported in a study from Sweden; no association between POAG and sex was found in Wales.26–28 These discrepancies may be due to small sample size.29

The adjusted prevalence rate for POAG has been shown to be at least four to five times higher in blacks than whites. It is suggested that this may reflect an underlying genetic susceptibility to the disease in both adult onset primary open angle glaucoma (A-POAG) and J-POAG.29

Traits genetically associated with primary glaucoma

Before the advent of modern genetic techniques, much effort was invested in the investigation of traits genetically associated with POAG. This was an attempt to determine whether one or more of the commonly studied human polymorphisms, as detailed below, contributed to the polygenic aetiology of glaucoma. Carefully controlled studies were conducted in the 1960s, designed to investigate the relation between the IOP response to topical steroids and glaucoma. These studies led to the proposition that not only was the observed IOP response to topical steroids inherited, but also that the gene(s) controlling this response were also closely related to the inheritance of POAG.30–32 The proposed genetic association has since been questioned owing to a low concordance of topical steroid responsiveness in monozygotic twins and poor study reproducibility.31,33

A close association between diabetes and POAG has been suggested on the basis of a number of studies.34 This relation however may well be multifactorial and so does not necessarily represent genetically associated traits.7
The ability to taste phenyl thiocarbamide within the general population is thought to be genetically determined. Thirty per cent of the normal population are unable to taste the chemical (non-tasters). In contrast, 53% of patients with POAG have been shown to be non-tasters compared with only 17% of patients with narrow angle glaucoma, a statistically significant difference. This raised the possibility of a common genetic basis or even a causal interrelation. However these studies have not been consistently reproducible.

The research investigating the possible association between the genetically determined blood groups was conflicting. No association was reported by some studies while others suggested an increased incidence of blood group A in patients with POAG. No similar association with histocompatibility antigens was shown.

Overall, studies of human polymorphisms for possible association with glaucoma have given conflicting results. The validity and full significance of these studies may only be realised when the underlying molecular genetics of glaucoma are more fully understood.

Nature versus nurture
Does the environment play a part in the development of glaucoma? Environmental influences on the pathogenesis of glaucoma have unfortunately been little studied. It has been suggested that the season of birth is a factor in the development of POAG. This was based on the observation that patients with POAG born in the British Isles since 1919 were significantly less likely to have been born in the 3 months from October to December, than during the remaining 9 months of the year. A similar result was found for patients born in South East Asia, but not for those born in the Caribbean. It was suggested that the observed seasonal variation may be due to a seasonal absence of certain crucial nutrients or the established seasonal variations in low birth weight.

An exhaustive review, concentrating on the effects of lifestyle on the relative risk of developing POAG, concluded that at present little modification of lifestyle could be advised to reduce the risk of developing POAG. It was, however, suggested that, in appropriate patients, an aerobic exercise programme might provide a small decrease in IOP. A vegan diet, in combination with an exercise programme, could be advised to reduce the risk of developing POAG.

Molecular genetics and primary open angle glaucoma
Utilisation of the new techniques of molecular genetics has dramatically altered the way in which we study the genetic basis of all conditions, including POAG, with a resultant rapid growth in our understanding of the subject. A plethora of techniques is now available to facilitate the rapid growth in our understanding of the subject. A basis of all conditions, including POAG, with a resultant reduction in IOP. A vegan diet, in combination with an exercise programme, could be advised to reduce the risk of developing POAG.

The study of chromosomal abnormalities can help pinpoint a potential region in which a disease-causing gene might lie. The discovery of patients with Rieger’s syndrome with abnormalities of chromosome 4q paved the way for the establishment of linkage of the syndrome to 4q25. This technique has not as yet, however, provided any valuable clues as to the genetic basis of POAG.

The candidate gene approach can be of value if a disease is thought to be caused by one or more of a limited number of known genes. This highly focused approach led to the discovery of a trinucleotide deletion in the peripherin RDS gene in autosomal dominant retinitis pigmentosa. Such a technique, however, is of limited value in the study of the genetics of glaucoma. This is because the number of potential causative genes is vast. A recent study looking at more than 25 candidate genes, including collagen, fibrillin, and elastin, for linkage with A-POAG found that none, in fact, were linked to the condition. Another study failed to demonstrate linkage between the potential candidate genes angiotensin and glucokinase, and A-POAG.

The technique of linkage analysis has been the most valuable tool in our attempts to unravel the genetics of POAG. The value of linkage analysis is that it can be used to localise a disease gene without any prior knowledge of the underlying pathology of the condition. Linkage analysis relies on the fact that genes which lie close to one another on a chromosome are less likely to be separated by the process of recombination during meiosis than those which lie far apart. Such genes will therefore tend to be inherited together and are described as ‘closely linked’. Recombination is the event which occurs during early meiosis, in which short lengths of chromosome are exchanged between chromosome pairs. Linkage analysis follows the co-segregation of markers of known position and the disease gene within affected pedigrees. As the position of the markers is known the relative position of the disease gene can be established. The probability of a set of observations representing true linkage is expressed as the logarithm (to the base 10) of the odds in favour of linkage. By convention, a lod score of +3.0 (equivalent to odds of 1000:1 in favour of the loci being linked) or higher is accepted as proof of linkage, while a lod score of −2.0 (equivalent to odds of 100:1 that the loci are not linked) or lower is strong evidence against linkage. Lod scores between −2.0 and +3.0 are considered inconclusive. If a crossing over takes place during meiosis between the disease gene and a DNA marker it will be observed as a recombination. The importance of a recombination event is that it allows determination of a definite proximal or distal end point to the region in which the disease-causing gene lies.

Genetics of J-POAG
An important milestone in J-POAG genetics came from the work of Sheffield et al in 1993. They studied a five generation family affected by autosomal dominant J-POAG using the technique of linkage analysis. They examined 37 members of the pedigree and found that 22 were affected. More than 90 short tandem repeat polymorphisms (a type of DNA marker) distributed over the whole human genome were investigated before linkage was detected with markers from a region of the long arm of chromosome 1, 1q21-q31, with the highest lod score at site D1S212 (a DNA marker whose relative chromosomal position is known) (see Fig 1). Recombination mapping enabled the critical region to be located between markers D1S191 and D1S194, a region of 23 cM (a centiMorgan is a unit used in linkage analysis reflecting a 1% frequency of recombination and is roughly equivalent to 1 million base pairs). Subsequent linkage studies with J-POAG pedigrees has enabled a gradual narrowing of the critical region, as detailed in Table 1.

The J-POAG disease gene on chromosome 1q was named GLC1A. A number of genes, known to lie within the critical region, were suggested as potential candidate genes. These included genes coding for the atrial natriuretic peptide receptor (ANPRA), laminin (LAMB2, LAMC1), and the ATPases (ATP1B1, ATP2B1).

Earlier this year, the gene responsible for 1q linked glaucoma was identified by Stone et al. Using a combination of fine mapping studies and mutation analysis, they identified the responsible gene as trabecular meshwork induced glucocorticoid response protein (TIGR). TIGR is produced by trabecular meshwork and ciliary body cells in response to glucocorticoids, with a timescale similar to that
observed in steroid induced glaucoma.\textsuperscript{65-67} It has previously been proposed that the TIGR protein may cause increased outflow.\textsuperscript{68} Stone \textit{et al} have reported three mutations in the \textit{TIGR} gene in chromosome 1q linked families. Two of the mutations described are missense mutations—a tyrosine to histidine change at codon 430 and a glycine to valine change at codon 357. The third is a nonsense mutation, histidine change at codon 430 and a glycine to valine change at codon 361. This change at codon 357 is followed by a stop codon.\textsuperscript{59} The third is a nonsense mutation, histidine change at codon 430 and a glycine to valine change at codon 361. This change at codon 357 is followed by a stop codon.

\textbf{Figure 1} Chromosome 1 and GLC1A. The approximate relative positions of DNA markers in the region 1q21-q31 are shown.

\begin{table}
\centering
\caption{A summary of previous studies with 1q21-q31 linked J-POAG pedigrees}
\begin{tabular}{lll}
\textbf{Author/year} & \textbf{Marker with tightest linkage} & \textbf{Recombinants} \\
Sheffield \textit{et al} 1993\textsuperscript{52} & D1S212 & D1S191-D1S194 \\
Wiggs \textit{et al} 1994\textsuperscript{51} & D1S218 & D1S196-D1S212 \\
Seghatoleslami \textit{et al} 1994\textsuperscript{54} & D1S196 & D1S452-D1S242 \\
Richards \textit{et al} 1994\textsuperscript{51} & D1S210 & D1S433-D1S431 \\
Meyer \textit{et al} 1994\textsuperscript{50} & D1S212 & D1S194-D1S218 \\
Morissette \textit{et al} 1994\textsuperscript{51} & D1S212 & D1S445-D1S416 \\
Graff \textit{et al} 1995\textsuperscript{59} & D1S210 & D1S104-D1S218 \\
Johnson \textit{et al} 1996\textsuperscript{59} & D1S433 & D1S445-D1S218 \\
Meyer \textit{et al} 1996\textsuperscript{53} & D1S452 & D1S194-AMF154c9 \\
Sheffield \textit{et al} 1996\textsuperscript{54} & AFM126y8 & AT3 \\
\end{tabular}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chromosome_1_glc1a.png}
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\end{figure}

\section*{Heterogeneity in J-POAG}

Phenotypic differences exist between J-POAG pedigrees which are linked to 1q21-q31.\textsuperscript{12} The pedigree described by Richards \textit{et al} \textsuperscript{71} had a mean age at diagnosis of 11.5 years, whereas the pedigrees analysed by Sheffield \textit{et al} \textsuperscript{50} had a mean age at diagnosis of 18 years. It has been suggested that the differences in the two phenotypes could have been caused by different mutations in the same gene.\textsuperscript{12} Recently, the question of genetic heterogeneity has been investigated in more detail and has been shown in fact to be related to phenotypic differences.\textsuperscript{72} From a total of nine J-POAG pedigrees, five pedigrees mapped to 1q21-q31 and four pedigrees did not. The five pedigrees which mapped to 1q21-q31 all showed uniform clinical features, including onset of the disease before the age of 20, a high IOP usually requiring surgical treatment, a high incidence of myopia, and typically a normal anterior segment structure. However, analysis of the clinical features of the four pedigrees that were not linked to the 1q21-q31 locus revealed several distinctive features. Although most showed an age of onset of less than 20 years old, several of the affected individuals did not demonstrate evidence of the disease until aged 35–40. In addition, many showed severe optic nerve degeneration yet did not exhibit the dramatic elevation in IOP seen in the five pedigrees showing linkage to 1q21-q31. Similar evidence of genetic heterogeneity has been shown in Hispanic pedigrees.\textsuperscript{73} This suggests that other, hitherto unknown, genes are also involved in the pathogenesis of J-POAG. Phenotypic expression of the gene has also been shown to be variable in two genetically identical twins who inherited the same copy of chromosome 1 from their affected father. One twin showed severe glaucoma at age 19, while the other only showed minimal glaucomatous change at the same age.\textsuperscript{74} It was suggested that it is possible that other genes or environmental factors may contribute to the full expression of J-POAG.

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Sheffield \textit{et al} 1996\textsuperscript{54} & AFM126y8 & AT3 \\
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\section*{Genetics of A-POAG}

Possible involvement of the 1q region in the pathogenesis of A-POAG was suggested by the discovery of a weak...
association between A-POAG and the Duffy blood group, which was later shown to be coded for by the FY gene located in the region 1q22-q23. A number of subsequent studies, however, failed to demonstrate linkage between A-POAG pedigrees and 1q21-q31.52 82-88

This apparent genotypic chasm between A-POAG and J-POAG was potentially bridged by the recent work of Morissette et al. They studied 142 members of a huge seven generation French Canadian pedigree traced back to a single affected male born in 1799. Thirty six patients were found to have J-POAG (median age at diagnosis of 27.3 years), while four individuals were found to have A-POAG (age of onset older than 40 years). Six members were diagnosed as having ocular hypertension. Linkage analysis and recombination mapping showed that not only the patients with J-POAG but also those with A-POAG and those with ocular hypertension were all tightly linked to the region 1q21-q31. The maximum lod score of 6.62 occurred with the marker AFM278ye5 (see Fig 1). The authors concluded that these results demonstrated that the same glaucoma gene is responsible for both A-POAG and J-POAG. They suggested that the J-POAG and A-POAG categories within this family may in fact be part of a clinical continuum artificially divided at 40 years. The same group have since looked at another 52 family members and report similar findings.89 The relevance of these findings to other pedigrees and affected individuals needs to be examined. The patients defined as having J-POAG in this study differed significantly from many other pedigrees: the average age of onset was at least 10 years older and IOPs at the time of diagnosis were usually in the 25–30 mm Hg range, which is about 10–15 mm Hg below that observed in other J-POAG families. Morissette et al suggested that the differences between the J-POAG phenotypes in their study and the J-POAG phenotypes described in other linkage studies may be explained by the presence of a different mutation in either the same or a closely related gene. It has since been argued that the phenotype described in their paper is an example of the variable expression of the J-POAG phenotype rather than true A-POAG.90 It is asserted that onset before age 40 years is an arbitrary distinction between two forms of the disease. In addition, the possibility exists that the four individuals classified as having A-POAG had in fact developed the disease before the age of 40 years. Despite these reservations the findings of their study are of great value to the future of glaucoma genetics and should become possible. Indeed, encouraging early studies to evaluate J-POAG screening had already been conducted before the identification of GLC1A.90 91

The future
Identification of not only the GLC1A gene, but also other glaucoma genes, has enormous potential clinical and commercial consequences. It should allow a significant advance in our understanding of the pathophysiology of POAG. It still remains to be established whether mutations in the TIGR gene result in an obstruction of aqueous humour outflow through the trabecular meshwork, as is seen in the presence of high levels of the TIGR protein.92 To this end, Stone’s and Sheffield’s groups are now trying to develop genetically engineered mice, some of which produce the mutated form of the TIGR protein, and some which do not produce any TIGR protein. With an increased understanding of the underlying pathology of glaucoma, it may be possible to develop novel treatments for glaucoma, targeted at the root cause of the condition, as opposed to the currently available rather empirical treatments. Inexpensive and accurate screening of at risk individuals, before they show any manifestations of glaucoma, should become possible. Indeed, encouraging early studies to evaluate J-POAG screening had already been conducted before the identification of GLC1A.90 91

Gene therapy is concerned with treating genetic disease at the molecular level and can involve correction, replacement, or augmentation of the functional gene. It has been suggested that treatment of glaucoma by gene therapy is a distant possibility.93 Discovery of the differing genetic causes of POAG and glaucoma in general may lead to an improved classification of the condition based on the precise causative genetic mutation rather than the current rather vague clinical classification. A similar genetic reclassification of a clinically confusing condition has already occurred to some extent with retinitis pigmentosa.94 95

Progress in the identification of other glaucoma genes, such as GLC1B and GLC1C, will depend largely on the identification of new pedigrees linked to chromosomes 2 and 3. This should enable the identification of critical recombinants, so allowing further narrowing of the regions in which GLC1B and GLC1C are known to lie. Likewise, the discovery of new loci involved in glaucoma also relies on the study of further glaucoma pedigrees. It would, therefore, be of enormous benefit if clinicians could refer potential pedigrees to an appropriate centre for further genetic investigation. Similarly, identification of POAG...
patients who demonstrate chromosomal rearrangements would be of tremendous help. It is only through this part-
nership of molecular genetics and clinical ophthalmology that these important genes will be found. The development of new polyomavirus markers within the critical regions will also
play a part in enabling localisation of these genes.

Once the location of a gene has been narrowed to a region of approximately 1 cM, physical mapping techniques can be used in an attempt to identify the gene. Once identified, putative genes can be sequenced and analysed for mutations segregating with affected individuals.

The repertoire of new techniques and ideas in molecular biology is expanding at an ever increasing rate. The impending completion of the Human Genome Mapping Project will increase the pace of advance even further. It is vital that clinical ophthalmology remain in touch with these exciting discoveries. The third millennium may then herald the arrival of radical new approaches to the diagno-
sis and management of glaucoma.

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