Genes Involved in the Pathogenesis of Primary Open-Angle Glaucoma
In Search of the Holy Grail

Identification of Novel Genetic Loci for Intraocular Pressure: A Genomewide Scan of the Beaver Dam Eye Study

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Objective: To identify genetic loci that control intraocular pressure (IOP).

Methods: We performed a genomewide scan of IOP, using 486 pedigrees ascertained through a population-based cohort, the Beaver Dam Eye Study. Linkage analysis was performed using the modified Haseman-Elston regression models and variance components linkage analysis.

Results: Seven regions of interest were identified on chromosomes 2, 5, 6, 7, 12, 15, and 19. The novel linkage region on chromosome 19p had an empirical multipoint P value of $6.1 \times 10^{-5}$. Two of the regions (2 and 19) were especially interesting since each has been identified as a potential linkage region for blood pressure.

Conclusions: The results of this genomewide scan provide evidence that a quantitative trait locus may influence elevated IOP and may colocalize with blood pressure loci. These loci may control systemic pressure reflected in the eye and vascular system.

Clinical Relevance: Glaucoma is a leading cause of blindness in the world, and the identification of genes that contribute to this disease is essential. Elevated IOP is a principal risk factor for primary open-angle glaucoma and an intriguing quantitative trait that may strongly influence the development of disease.


Commentary by Louis R. Pasquale, MD

So, doctor, why is my eye pressure elevated? The answer to this seemingly innocent question posed by a patient with newly diagnosed primary open-angle glaucoma (POAG) has eluded ophthalmologists for more than a century. Examining the eyes of a patient with POAG does not provide an answer to this question. POAG is a complex disease characterized by intraocular pressure (IOP)–related, progressive optic nerve degeneration that results in irreversible blindness if untreated. This condition represents a major public health problem worldwide.

There is a considerable body of evidence that POAG has a strong genetic underpinning, yet only a minority of the genes associated with the disease have been identified.

POAG can be considered a neurodegenerative disease. Another neurodegenerative condition, Alzheimer disease, leaves a trail of neurofibrillary tangles that provide useful clues to understanding disease etiology. POAG leaves behind an excavated and atrophic optic nerve, suggesting that elevated IOP must play some role in disease etiology. Increasing IOP in a nonhuman primate model has produced a similar type of change in the optic nerve. A cross-sectional analysis of adults living in Baltimore indicates that an IOP of 35 mm Hg is associated with a 39-fold increased risk of POAG compared to an IOP of 15 mm Hg or less.

Perhaps one reason it has been difficult to discover the genes for POAG relates to the fact that POAG may consist of several endophenotypic variants, some of which produce optic nerve damage at IOPs in the statistically normal range and others that produce damage when the IOP is elevated. Rather than ask which genes might be associated with optic nerve damage from POAG, Duggal and colleagues searched for segments of DNA associated with the magnitude of IOP. In an article in the January issue of Archives of Ophthalmology, a theme issue devoted to genetics in ophthalmology, the authors provide data indicating that quantitative trait loci may contribute to variation in IOP. Specifically, just as there are genes that control qualitative traits

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such as hair color, there may be genes that control quantitative traits such as IOP. A prior study involving monozygotic and dizygotic twins supports the notion that this is indeed the case.\textsuperscript{6} Not surprisingly, Duggal et al found that several genes may control IOP, but interestingly 2 regions are also linked to loci involved in control of blood pressure.\textsuperscript{7,8}

Intraocular pressure in an individual varies with the cardiac cycle, time of day, and season of the year. In addition, a host of factors ranging from body mass index to physical activity may account for variation of IOP in a defined population. Therefore, it seems that it would be a daunting task to find genes associated with control of IOP. The authors used 486 pedigrees consisting of 1979 individuals who participated in the Beaver Dam Eye Study to find genetic regions associated with IOP. They found linkage to a region on chromosome 19p that had an empirical $P$ value of $6.1 \times 10^{-3}$. This value is well below what would be expected using a strict Bonferroni-style threshold for type I error that accounts for the multiple comparisons made when scanning the human genome with 404 tandem-repeat markers, as performed by Duggal et al.

The study performed by Duggal et al is just the beginning of a journey that could lead to the discovery of genes associated with control of IOP. Currently, these researchers report broad genomic regions in which such genes might reside. Trying to identify candidate genes in these regions may be too arduous a task. As the authors point out, it might be better to repeat genomewide scanning using a large-scale genotyping effort in another population. Commercially available products are capable of simultaneously genotyping hundreds of thousands of genetic loci either randomly chosen throughout the genome or based on linkage disequilibrium from the International HapMap Project. The costs for these products have come down considerably, making this a feasible option. The advantage of a high throughput genotyping effort is that with a multistaged study design there may be more rapid discovery of genes of interest using follow-up fine mapping, resequencing, and replication studies. The genotyping platform technologies are rapidly evolving to meet the challenge of maintaining high genotyping efficiency and accuracy using relatively small, finite quantities of DNA that, in many instances, has been archived away for many years. Furthermore, analytical methods to minimize false-positive findings as well false-negative discovery in large-scale genotyping efforts are also emerging.\textsuperscript{9}

Knowledge of genes associated with IOP and, in turn, POAG, can yield useful dividends. Currently, medical therapy aimed at lowering IOP represents the most common way to manage POAG. One randomized clinical trial has shown that lowering IOP pharmacologically slows, but does not halt, the conversion from ocular hypertension to POAG.\textsuperscript{10} Drugs to treat glaucoma have been developed based on their ability to lower IOP by any means and not necessarily because they target the cause of disease. The discovery of genetic variants associated with elevated IOP, an important risk factor for disease, may lead to alternative therapy that more effectively halts disease progression. Furthermore, knowledge of genetic variants associated with elevated IOP also may lead to early diagnosis of POAG, a disease that is insidious in onset and that does not produce significant visual symptoms until it is quite advanced. Duggal et al appear to have taken a bold new step toward discovering the reason IOP increases in patients with POAG.

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REFERENCES

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