

THE GENETIC COMPONENT

Is a curative or preventive therapy on the horizon?



BY JANEY L. WIGGS, MD, PHD

Glaucoma is a leading cause of irreversible blindness, and it is estimated that, by 2020, nearly 80 million people globally will be affected by the disease.¹ Current therapies are directed toward the reduction of IOP, and, although these interventions can slow glaucomatous progression, they do not cure the disease. As the population ages and the number of patients with glaucoma increases, the need to develop curative or preventive therapies grows.

A major goal of glaucoma genetics research is to identify the genes and the biological pathways that contribute to the development of glaucoma and, therefore, could serve as therapeutic targets. This article overviews several recent research discoveries and identifies the next steps toward bridging the gap between these findings and the development of novel preventive therapies.

EARLY VERSUS ADULT ONSET

In considering glaucoma genetics, it is helpful to divide the disease into two categories: (1) *early-onset forms*, such as juvenile open-angle glaucoma (OAG), congenital glaucoma, and anterior segment development syndromes; and (2) *adult-onset forms*, such as primary open-angle glaucoma (POAG), angle-closure glaucoma, and exfoliation glaucoma.

Early onset. The early-onset forms of glaucoma are rare in the population and caused by rare mutations with large biological effects. These mutations typically disrupt protein function and generally manifest early in life. Thus, researchers often have access to multiple-generation families affected by these conditions. Implicated genes are identified using genetic linkage studies and next-generation sequencing approaches such as whole-exome and whole-genome sequencing.

Adult onset. The adult-onset forms of glaucoma are more common in the population and are associated with genetic risk factors that are relatively common. Individually, genetic risk factors associated with common disease have relatively small biological effects compared with those that cause early-onset disease. Further, adult onset-disease has complex inheritance, and multiple genetic risk factors or environmental factors can contribute to disease in any one individual.

Although family history is a risk factor for glaucoma, researchers typically do not have access to multiple-generation families for adult-onset disease as they do for early-onset disease. Therefore, to investigate adult-onset disease, we compare genetic risk factors in cases to controls through genome-wide association studies (GWAS). One challenge is that, because these genes individually have small effects, large sample sizes are necessary to achieve the statistical power required to identify associated genetic variants.

AT A GLANCE

- ▶ Although current glaucoma therapies can slow progression, they do not cure the disease.
- ▶ As the population ages and the number of patients with glaucoma increases, the need to develop curative or preventive therapies grows.
- ▶ A major goal of glaucoma genetics research is to identify the genes and the biological pathways that contribute to the development of glaucoma and that could serve as therapeutic targets.

THE NEIGHBORHOOD CONSORTIUM

In an effort to form a sample large enough to study POAG, the NEIGHBORHOOD Consortium for glaucoma genetics was founded in 2012. Supported by the National Eye Institute, this consortium comprises multiple sites and 47 ophthalmologists, geneticists, and bioinformaticists collaborating to better understand the genomic architecture of glaucoma.

Since its formation, the NEIGHBORHOOD Consortium has collected data on more than 5,000 POAG cases and conducted numerous genetic analyses, including one of the largest POAG GWAS.² To date, our work has contributed to the identification of multiple risk factors that contribute to adult-onset forms. These genes are beginning to define important pathways and biological processes that contribute to disease mechanisms and are serving to help identify potential therapeutic targets.

BIOLOGICAL PATHWAYS

Investigations have identified a wide range of biological processes implicated in glaucoma, including ocular development, cell division and death, transforming growth factor beta, membranes and lipid metabolism, vascular and lymph development, extracellular matrix, and mitochondrial function. This diversity of biological mechanisms and pathways underscores the genetic heterogeneity of glaucoma.

MYOC. *MYOC* (myocilin) was the first gene discovered to be implicated in glaucoma.³ It is now known that *MYOC* mutations are associated with familial juvenile OAG and some cases of adult-onset POAG.

In a study by Jain et al,⁴ investigators used CRISPR-Cas9-mediated genome editing to effectively remove proteins with the *MYOC* mutation and lower IOP in a mouse model of POAG. Further, CRISPR-Cas9-mediated genome editing was effective in young and older mutant mice, suggesting that the treatment could be effective for later disease stages. Preclinical studies such as this pave the way for the development of a similar treatment for humans with *MYOC* mutations, which could, in theory, be curative.

ANGPT/TEK signaling. The *TEK* gene is a cellular receptor with ligands angiopoietin-1 (*ANGPT1*) and angiopoietin-2 (*ANGPT2*). This path-

"ADDING A GENETIC COMPONENT TO ANY CLINICAL TRIAL TESTING A NEW THERAPY WILL PROVIDE IMPORTANT INFORMATION ABOUT GENETIC CONTRIBUTIONS TO THERAPEUTIC RESPONSE."

way regulates vascular homeostasis, and it is known to be important for vascular endothelial cell proliferation and survival as well as for lymphangiogenesis. Over the past few years, it has become clear that rare mutations in the gene coding for *TEK* contribute to congenital glaucoma, juvenile glaucoma, and, in some cases, young-adult glaucoma. Population studies have also shown common variants in *ANGPT1*—such as those seen in adult-onset glaucoma—to be associated with elevated IOP.

When the *ANGPT/TEK* signaling pathway is disrupted, Schlemm canal does not form properly.⁵ Therapies that restore *TEK* signaling could potentially reduce IOP, especially in patients who carry defects in this pathway.

Cholesterol. Genes linked to cholesterol metabolism have been shown to be associated with POAG and elevated IOP in population studies including *ABCA1*, *CAV1/2*, and *ARHGEF12*. These genes interact with each other in cell membranes to promote cholesterol efflux.

These genetic associations suggest that cholesterol metabolism may influence glaucoma development by elevating IOP and possibly suggest that statin therapy may be more effective in glaucoma patients who carry these glaucoma-related genetic risk factors.

Mitochondria. Mitochondria are important for energy production in the eye, and they densely populate the metabolically active unmyelinated prelaminar optic nerve. Mitochondria produce ATP through the electron

transport chain, which involves the transfer of electrons through the cytochromes. But electron transfer is not 100% efficient, and leaked electrons can cause the formation of reactive oxygen species and free radicals, which ultimately damage the mitochondria and surrounding tissues. Mitochondria, however, are prepared to address this, as they contain free radical and reactive oxygen species scavenging systems, such as the thioredoxin system.

The NEIGHBORHOOD GWAS showed a strong association between *TXNRD2* (thioredoxin reductase 2) and POAG. Interestingly, the risk variance associated with disease correlated with decreased gene expression. Decreased *TXNRD2* expression in POAG could, therefore, lead to an increase in damaging reactive oxygen species. This would suggest that restoring antioxidant function may be beneficial in these patients.

FUTURE GOALS

Studies have identified specific genes and biological pathways that are defining disease mechanisms and that could be targets of new potentially curative and preventive therapies. Future glaucoma genetics studies will identify new areas for therapy and prevention, but there are several areas of need.

No. 1: More genes to study. In collaboration with the International Glaucoma Genetics Consortium, the NEIGHBORHOOD Consortium is contributing to a multiethnic meta-analysis of more than 10,000 cases of

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POAG to identify additional genes implicated in the disease.

No. 2: Analysis of early-onset glaucoma families. Only 10 genes are known to cause early-onset glaucoma; however, these genes can only explain disease in approximately 20% of patients. Next-generation sequencing will enable researchers to more efficiently identify genes contributing to these diseases.

No. 3: Animal models. There is a need for glaucoma animal models that can be used to screen novel therapies as well as functional effects of disease-related genes.

No. 4: Information on relevant cell biology. Understanding more about

the cells that are involved in ganglion cell dysfunction and IOP elevation in glaucoma will help define the roles of novel glaucoma-related genes.

No. 5: Addition of genetics to therapeutic clinical trials.

Adding a genetic component to any clinical trial investigating a new therapy will provide important information about genetic contributions to therapeutic response. ■

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