HOW CAN GENETIC ASSESSMENTS AFFECT GLAUCOMA SURGICAL DECISION-MAKING?

Improving care for patients whose family history is consistent with an autosomal dominant form of the disease.

BY ERIN A. BOESE, MD

A 9-year-old girl, dwarfed by the exam chair, sat in my clinic. Each of her eyes had an IOP higher than 40 mm Hg on maximum tolerated medical therapy, but fortunately, they had no measurable glaucomatous damage. Although it was the patient's first visit to the clinic, I knew her family well.

She carried the same autosomal dominant mutation in the myocilin (*MYOC*) gene as dozens of her family members. Despite the temptation to offer her a trabeculectomy (the procedure recommended to everyone else in her family), I felt confident performing gonioscopy-assisted transluminal trabeculotomy (GATT). This MIGS procedure bypasses the trabecular meshwork (TM), which is the tissue I knew to be affected in her disease. Following GATT, not only was the patient's IOP at a normal level, but she was able to discontinue all of her glaucoma medications.[1]

What is most noteworthy in this scenario is not the surgical procedure but its remarkable efficacy—an effect supported by the specific pathophysiology of the patient's disease. This case example offers a glimpse of a future in which glaucoma surgery is guided by genetic testing.

HEREDITY

With a heritability of 70% and 93% in two large population-based studies,[2,3] glaucoma is among the most heritable of human diseases. Simply having a first-degree relative with glaucoma confers a ninefold increase in a patient's lifetime risk of developing the disease.[4] The genetics underlying glaucoma, particularly primary open-angle glaucoma (POAG), remain largely complex, with the vast majority of glaucomas caused by a combination of numerous genetic and environmental factors.[5] Recent genome-wide association studies have identified 312 individual loci that collectively account for 14.1% of the familial risk.[6-9] Analyses of genome-wide association study data with new strategies, such as polygenic risk scores, have greater power to identify subsets of a population with an increased likelihood of developing glaucoma.[10,11] The clinical utility of polygenic risk score analyses for specific individuals is currently being investigated.[10]

A small proportion (5%) of glaucoma is caused by a single genetic mutation,[5] and this is where

gene-guided surgery could be the most advantageous. In Mendelian disease, the presence of the mutation alone can manifest in disease, promoting a more clear-cut understanding of the pathophysiology. There are four known single-gene or autosomal dominant (Mendelian) causes of POAG: *MYOC*, optineurin (*OPTN*), TANK-binding kinase 1 (*TBK1*), and methyltransferase-like 23 (*METTL23*).[12-15]

MYOCILIN

MYOC offers the best example to date of how genetics can influence surgical approach. Nearly 30 years following the discovery of mutations in the *MYOC* gene,[13,16] it remains the most common genetic cause of glaucoma, accounting for just 4% of adult-onset POAG cases but up to 36% of juvenile OAG (JOAG) cases.[17-19] *MYOC*-associated JOAG typically presents in young patients with markedly high IOPs that are largely resistant to medical therapy.[18] Traditionally, these patients underwent trabeculectomies and tube shunt surgery early in life. The scarring and failure rates of these procedures is elevated due to the individuals' ages.

The *MYOC* gene encodes a protein produced within the TM cells that is secreted into the aqueous humor, where the protein has no known function to date. Mutations in the *MYOC* gene cause a misfolding of this protein, leading to a toxic accumulation within the TM cells. The resulting TM apoptosis causes TM dysfunction, elevated IOP, and glaucoma.[20,21]

A defining feature of *MYOC*-associated JOAG is that the pathology has been shown to be within the TM and no other tissue. As such, TM-specific surgeries, especially GATT, are uniquely effective for the treatment of *MYOC*-associated JOAG (Figure). Studies evaluating GATT in patients with known *MYOC* variants have demonstrated the procedure's remarkable success; GATT lowered IOP by a mean of 26 mm Hg (68%) and decreased the medication burden from an average of 3.8 medication classes to zero.[1,22]

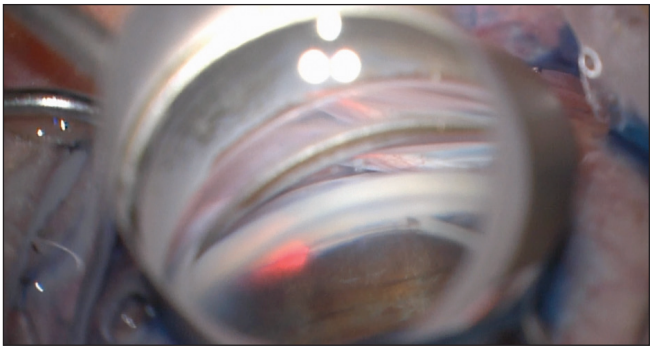

Figure. Intraoperative photograph of GATT using an iTrack Advance lighted microcatheter (Nova Eye Medical), an effective surgical approach in MYOC-associated JOAG.

TABLE. SURGICAL APPROACHES TO GLAUCOMA GUIDED BY THE UNDERLYING GENETIC MUTATION.

Genetic Mutation	Proposed Surgical Approach
MYOC	GATT
OPTN	Trabeculectomy
TBK1	Trabeculectomy
METTL23	Trabeculectomy

Abbreviations: GATT, gonioscopy-assisted transluminal trabeculotomy; *METTL23*, methyltransferase-like 23; *MYOC*, myocilin; *OPTN*, optineurin; *TBK1*, TANK-binding kinase 1.

OPTN, *TBK1*, AND *METTL23*

Mutations in *OPTN*, *TBK1*, and *METTL23* are autosomal dominant causes of normal-tension glaucoma (NTG), and each of these genetic mutations contributes to 1% to 2% of NTG cases.[23-28] Patients often present in their 30s and 40s with severe optic nerve damage despite low IOPs.[29]

The proteins that the *OPTN* and *TBK1* genes encode interact directly with each other to regulate autophagy.[15,30-32] Mutations in either *OPTN* or *TBK1* are thought to dysregulate autophagy, leading to retinal ganglion cell damage at low IOPs.[33,34] Mutations of *METTL23* may cause NTG by altering histone methylation and gene expression, ultimately compromising retinal ganglion cell health.[12]

Given the early age of onset and disease progression at low IOPs, there is a benefit to significantly lowering IOP in this patient population. In some individuals with NTG and either *OPTN* or *TBK1* mutations, glaucomatous progression was arrested after single-digit IOPs were achieved following trabeculectomy.[35,36] The presence of one of these genetic mutations may therefore warrant consideration of aggressive surgery, namely trabeculectomy, to reduce IOP into the single digits.

IMPLICATIONS

Genetic testing has the potential to provide valuable insights for glaucoma surgical decision-making. Patients whose family history is consistent with an autosomal dominant form of glaucoma may benefit from genetic testing for *MYOC*, *OPTN*, *TBK1*, and *METTL23* (Table). Although clinical acumen cannot be replaced by DNA tests, targeted genetic screening is a powerful prognostic tool with exciting therapeutic implications. ■

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