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Mendelian Genes in Primary Open Angle Glaucoma

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Abstract

Mutations in each of three genes, myocilin (*MYOC*), optineurin (*OPTN*), and TANK binding kinase 1 (*TBK1*), may cause primary open-angle glaucoma (POAG) that is inherited as a Mendelian trait. *MYOC* mutations cause 3–4% of POAG cases with IOP > 21 mmHg, while mutations in *OPTN*, *TBK1*, and *MYOC* each cause ~1% of POAG with IOP ≤ 21 mmHg, i.e. normal tension glaucoma. Identification of these disease-causing genes has provided insights into glaucoma pathogenesis. Mutations in *MYOC* cause a cascade of abnormalities in the trabecular meshwork including intracellular retention of MYOC protein, decreased aqueous outflow, higher intraocular pressure, and glaucoma. Investigation of *MYOC* mutations demonstrated that abnormal retention of intracellular MYOC and stimulation of endoplasmic reticular (ER) stress may be important steps in the development of MYOC-associated glaucoma. Mutations in *OPTN* and *TBK1* cause a dysregulation of autophagy which may directly cause retinal ganglion cell damage and normal tension glaucoma. Discovery of these Mendelian causes of glaucoma has also provided a new set of potential therapeutic targets that may ultimately lead to novel, gene-directed glaucoma treatments

1. Introduction

Glaucoma is one of the most common cause of irreversible blindness worldwide (Leske and Podgor, 1983; Quigley and Broman, 2006). Glaucoma is comprised of a group of diseases resulting in progressive optic nerve cupping with corresponding and characteristic visual field loss. Primary open-angle glaucoma (POAG) is defined as glaucoma in the absence of secondary findings (i.e. anatomically normal), and is the most common type of glaucoma worldwide. In the United States, 1.6% of subjects over the age of 40 are affected by POAG (Kahn and Milton, 1980).

Studies of the heredity of glaucoma date back to Von Graefe, who reported multigeneration families with glaucoma in 1869 (Graefe, 1869). Since then many more large pedigrees with inherited glaucoma have been described (François, 1966; Stokes, 1940). Population-based studies have also shown familial clustering of POAG cases that suggest a genetic basis

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Declaration of interests

Nil.

(Becker et al., 1960). First degree relatives have a 9-fold increased risk, carrying a lifetime glaucoma risk of 22% (Wolfs et al., 1998). While early twins studies reported the heritability of POAG to be approximately 13% (Teikari, 1987), more recent and much larger studies have estimated POAG heritability to be 70% (Wang et al., 2017) and 93% (Polubriaginof et al., 2018). Another clue into the heritability of POAG lies with the significant variation of POAG between different races and ethnicities. POAG is five-fold more common in African Americans and in Hispanic Americans than in Caucasians (Tielsch et al., 1991; Varma et al., 2004).

The genetics of most cases of POAG are complex. As many as 95% of POAG cases are caused in part by the combined action of dozens of genetic, and possibly environmental, risk factors. (Fingert, 2011) More than 25 of these POAG risk factor genes have been discovered to date and more remain to be identified (Choquet et al., 2017; Gharahkhani et al., 2018; Shiga et al., 2018; Wiggs and Pasquale, 2017). The discovery and characterization of these genetic risk factor genes is the topic of an accompanying review article in this issue of Experiment Eye Research (Reference to other relevant article in this issue to be added by editors)

At least 5% of POAG cases are caused primarily by a mutation in one of three genes: myocilin (*MYOC*), optineurin (*OPTN*), or TANK binding kinase 1 (*TBK1*) (Fingert, 2011). A mutation in any one of these genes causes glaucoma with clear autosomal dominant (Mendelian) inheritance. This article aims to review the genetics of Mendelian (single gene) causes of glaucoma and will focus on the *MYOC*, *OPTN*, or *TBK1* genes.

2. Myocilin (*MYOC*)

Perhaps the most notable genetic defects to be associated with the development of glaucoma occur within the Myocilin (*MYOC*) gene. *MYOC* was the first gene to be associated with glaucoma and remains the most common, known-cause of POAG. *MYOC*-associated glaucoma is inherited in an autosomal dominant pattern. One set of mutations in this gene has been associated with juvenile open angle glaucoma (JOAG) with an onset of disease before 35 years of age and markedly elevated IOP. A different set of *MYOC* mutations has been detected in POAG patients with an onset of disease after 40 years of age. Most cases of POAG associated with *MYOC* mutations have occurred with high IOP (>21 mmHg). However, *MYOC* mutations have also been detected in POAG patients with IOP ≤21 mmHg (i.e. normal tension glaucoma) (Alward et al., 2019; Michels-Rautenstrauss et al., 2002). The frequency of *MYOC* mutations in POAG patients appears to be higher with increased IOP.

In 1997, *MYOC* was discovered to be a glaucoma-causing gene via positional cloning studies of large JOAG pedigrees (Sheffield et al., 1993; Stone et al., 1997); studies of human trabecular meshwork cells (Polansky et al., 1997); and studies of gene expression in human retina (Kubota et al., 1997). These different research studies were conducted in parallel and referred to the same gene as *GLC1A*, *TIGR*, and *MYOC*. Myocilin and the gene symbol *MYOC* were designated as the official name for this gene by the nomenclature committee of the Human Genome Organization (HUGO).

2.1. Epidemiology of *MYOC*-associated glaucoma

Over 100 genetic *MYOC* mutations have been reported in patients with either JOAG or POAG (H.-W. Wang et al., 2018). The prevalence of *MYOC* mutations is much higher in cohorts of JOAG patients than in cohorts of POAG patients (described below) and myocilin mutations are rare in unexamined large general population studies (Han et al., 2018; Nag et al., 2016). The population allele frequencies of the *MYOC* mutations described below are catalogued in Supplemental Table 1.

MYOC and JOAG.—*MYOC* mutations have been detected in several studies of individual JOAG pedigrees (Kennan et al., 1998; Mansergh et al., 1998; Stoilova et al., 1997). Additionally, case-control studies have estimated that 8 to 63% of unrelated JOAG patients have *MYOC* mutations (Adam et al., 1997; Wiggs et al., 1998) The variability in the detected frequency of *MYOC* mutations is like due in part to the small cohorts of this rare form of glaucoma that have been studied.

MYOC and POAG.—The overall prevalence of *MYOC* mutations among POAG patients is 3 to 4% among Caucasian, Asian, and African populations worldwide (Fingert et al., 1999; 2002; Gong et al., 2004). The majority of *MYOC* mutations are unique to POAG patients from populations of either Caucasian, Asian, or African ancestry. However, the most commonly detected *MYOC* mutation overall, Gln368Stop, has been identified in POAG populations of all racial ancestries, though much more frequently among Caucasian patients. A few instances of the Gln368Stop mutation have been detected in African American POAG patients and Indian POAG patients (Bhattacharjee et al., 2007; Fingert et al., 1999). The Gln368Stop mutation has been detected in 1.6% of patients with POAG in Caucasian populations. As such, Gln368Stop is the most frequent, molecularly-defined mutation that is known to be associated with POAG (Fingert, 2011).

2.2. Genotype-phenotype correlations for MYOC-associated glaucoma

One group of *MYOC* mutations has been associated with early-onset disease (JOAG), while a different group of MYOC mutations has been associated with adult-onset disease (POAG).

JOAG phenotype and MYOC mutations.—Several *MYOC* mutations have been identified in multiple JOAG pedigrees that share key features including: high penetrance (most mutation carriers develop disease); early-onset of disease; strong family history with autosomal dominant inheritance; and markedly elevated IOP. Some examples of MYOC mutations associated with JOAG are Pro370Leu, Thr377Met, Tyr437His, and Ile477Asn (Table 1). Patients with JOAG caused by these mutations typically require surgery for adequate IOP control (Johnson et al., 1993).(Stoilova et al., 1998)

POAG phenotype and MYOC mutations.—Some *MYOC* mutations are associated with POAG that has clinical features more typical for adult-onset POAG (Table 1). The Gln368Stop mutation, for example has a mean age at diagnosis of that ranges between 36 and 59 years (Allingham et al., 1998; Alward et al., 1998; Angius et al., 2000; Shimizu et al., 2000). Mean maximum IOP for patients with the Gln368Stop has been reported as 29 to 30 mmHg with a range of 21 mmHg to 56 mmHg (Allingham et al., 1998; Alward et

al., 1998; Angius et al., 2000; Shimizu et al., 2000). Patients with a Gln368Stop mutation respond to medical therapy and require glaucoma surgeries at a rate that is no different than patients without known mutations (Graul et al., 2002).

Age is major risk factor for glaucoma, even for highly heritable forms of glaucoma, such as *MYOC*-associated disease. The proportion of patients with a *MYOC* mutation that have developed glaucoma is termed the penetrance. Pedigree studies have shown that the penetrance of *MYOC* mutations is highly age-dependent and becomes larger with increasing age (Allingham et al., 1998; Craig et al., 2001; Hewitt et al., 2008). Two *MYOC* mutations that are associated with the earliest age of onset of JOAG, Ile477Asn and Pro370Leu, have >80% penetrance at 25 years of age, while the Gln368Stop mutation which has the latest onset of glaucoma (POAG) had 0% penetrance at 25 years of age. However, by 75 years of age the penetrance of all three mutations approached 100% (Hewitt et al., 2008; Mackey et al., 2003).

Although the penetrance of the Gln368Stop mutation in pedigree-based studies has been reported to be 80–100% by the seventh decade of life (Allingham et al., 1998; Hewitt et al., 2008), different results have emerged from population-based studies. More recently, huge studies of essentially unselected citizens of the United Kingdom (TwinsUK and the UKBiobank) and the Netherlands (Rotterdam Study) reported a much lower penetrance for the Gln368Stop allele, ranging from 33 to 48% by the end of the 7th decade of life. (Han et al., 2018; Nag et al., 2016). Some potential explanations for the higher penetrance of the Gln368Stop mutation observed in pedigree studies are differences in genetic background and environmental exposures, ascertainment bias, and diagnostic methods. These investigations suggest that the predictive value of detecting a Gln368Stop mutation may be substantially influenced by how subjects were enrolled for testing (Fingert, 2019).

2.3. Ocular expression pattern of *MYOC*

MYOC encodes a secreted glycoprotein of unknown function (Fingert et al., 1998; Polansky et al., 1997). *MYOC* is broadly expressed at the RNA level in non-ocular and ocular tissues (Fingert et al., 1998; Swiderski et al., 2000). Production of MYOC protein, however, is more restricted and has been primarily identified within tissues of the eye (Clark et al., 2001; Karali et al., 2000; Lütjen-Drecoll et al., 1998; Polansky et al., 1997). MYOC protein has been identified in the trabecular meshwork, sclera, ciliary body, choroid, cornea, iris, lamina cribosa, retina, and optic nerve (Adam et al., 1997; Clark et al., 2001a). MYOC protein is secreted from ocular tissues into the aqueous humor where it is also detectable (Jacobson et al., 2001)

MYOC protein was first detected in primary cultures of human trabecular meshwork with studies to identify steroid-induced proteins (Nguyen et al., 1998; Polansky et al., 1997). Glucocorticoid steroids were discovered to induce MYOC protein production by approximately 47-fold in cultured trabecular meshwork cells (Clark et al., 2001b; Polansky et al., 1997). Moreover, studies of the trabecular meshwork with cell culture, organ culture, and human donor eyes have shown that glaucoma-causing *MYOC* mutations prevent secretion and lead to intracellular retention of MYOC protein (Jacobson et al., 2001; van der Heide et al., 2018).

2.4. Structure and function of *MYOC*

The *MYOC* gene is composed of three exons that encode a 504 amino acid polypeptide (Figure 1) that includes a signal sequence for secretion, a leucine zipper domain, and an olfactomedin domain (Adam et al., 1997; Fingert et al., 1998; Polansky et al., 1997). The structure of the olfactomedin domain has been of high interest because the majority of the disease-causing variations have been detected in this segment of MYOC. The crystal structure of the olfactomedin domain has been solved (H. Han and Kursula, 2015; Pronker et al., 2015) and demonstrated to form a five-bladed β-propeller structure that promotes protein–protein interactions and oligomerization of MYOC (Donegan et al., 2015). The leucine zipper domain of MYOC also promotes protein-protein interactions (Nguyen et al., 1998). The *MYOC* gene encodes a 55–57 kDa secreted protein, however, analyses of cell lysates have identified immunoreactive protein complexes with molecular weights that are 2X or 4X multiples of MYOC. These data suggest that wild-type MYOC may form homodimers or homotetramers via interactions between the leucine zipper and/or olfactomedin domains (Nguyen et al., 1998).

2.5. Pathophysiology of *MYOC*-associated glaucoma and gene-directed therapy

The normal function of MYOC is not well characterized. In fact, there are data to suggest that MYOC may not be essential for normal ocular function. Mice with inactivated genes ($Myoc^{-/-}$) have no evidence of glaucoma or any other ocular abnormalities (Kim et al., 2001). Similarly, one patient with a hemizygous deletion spanning the *MYOC* gene did not have glaucoma (Wiggs and Vollrath, 2001). A presumably null *MYOC* mutation, Arg46Stop, is not associated with glaucoma or ophthalmic disease in humans when present as either a heterozygous or homozygous mutation (Lam et al., 2000; Pang et al., 2002). Together these observations suggest that *MYOC* mutations cause disease via a *gain-of-function* rather than a *loss-of-function* mechanism.

An abundance of data suggests that glaucoma-causing mutations prevent normal secretion and cause intracellular accumulation of MYOC protein in trabecular meshwork cells (Kwon et al., 2009). Several *MYOC* mutations have been shown to cause reduced secretion of MYOC protein in human cultured trabecular meshwork cells and/or in human organ culture systems (Jacobson et al., 2001). Similarly, *MYOC* mutations prevent secretion of MYOC protein in transgenic mice (Zhou et al., 2008; Zode et al., 2011). Intracellular MYOC protein aggregates accumulate within the endoplasmic reticulum (ER) and increase production of ER stress molecules (Joe et al., 2003; Zode et al., 2011). These observations have led to the development of new gene-directed therapies for *MYOC*-associated glaucoma that are designed to eliminate intracellular MYOC protein.

Gene-directed glaucoma therapy.—A class of drugs known as chemical chaperones (Ozcan et al., 2006), such as 4-phenylbutyrate, have been evaluated for their ability to stabilize mutant MYOC protein *in vitro* (Burns et al., 2010) and to help prevent or disperse MYOC aggregates and ultimately promote secretion in a transgenic mouse model of *MYOC* glaucoma. Both oral and topical administration of 4-phenylbutyrate to transgenic *MYOC* mice prevented accumulation of intracellular MYOC protein; prevented elevation of IOP; and prevented glaucoma (Zode et al., 2011; 2012). These preliminary animal studies suggest

therapies that promote clearance of intracellular MYOC aggregates may be an effective treatment for *MYOC*-associated glaucoma.

Genome-editing glaucoma therapy.—Given that loss of MYOC function does not appear to have adverse effects on the eye (Kim et al., 2001; Lam et al., 2000; Pang et al., 2002), genome editing has been investigated as a possible therapy of *MYOC*-associated glaucoma. The CRISPR/Cas9 endonuclease system has been used to inactivate (knock-down) expression of mutant *MYOC* genes in cultured trabecular meshwork cells, human organ culture (perfused anterior segments of human eyes), and in transgenic mice. Genome editing successfully reduced the abnormal intracellular accumulation of MYOC, reduced ER stress markers, and reduced IOP (Jain et al., 2017). These experiments indicate that genome editing may have utility as a gene-directed therapy for *MYOC*-associated glaucoma.

MYOC protein is expressed in the astrocytes and neurons of optic nerve as well as in the trabecular meshwork (Clark et al., 2001a; Karali et al., 2000; Swiderski et al., 2000). At least one study of transgenic mice has suggested that optic nerve damage may occur with *MYOC* mutations without high intraocular pressures (Chou et al., 2014). Consequently, *MYOC* mutations may also have a more direct influence on glaucoma pathophysiology at the optic head as well as via dysregulating trabecular meshwork function and IOP.

2.6. Genetic testing for *MYOC* mutations

When directed towards high-risk patients, genetic testing may be able to identify individuals who carry known disease-causing mutations, enabling physicians to plan closer monitoring and/or more aggressive treatment regimens to prevent or minimize vision loss.

General guidelines for genetic testing in ophthalmology have been provided by the American Academy of Ophthalmology. These guidelines suggest that testing may be appropriate if: 1) test results will impact treatment or disease surveillance; 2) tests are performed by Clinical Labs Information Act (CLIA)-certified labs; and 3) tests are conducted by experienced ophthalmic geneticists and/or genetic counselors to ensure proper interpretation of results (Stone et al., 2012). A registry of CLIA certified labs is available at www.ncbi.nlm.gov/gtr.

Because only 3–4% of unselected POAG patients will have a *MYOC* mutation, indiscriminate testing may have a low yield. However, testing of high-risk patients can be helpful. For example, relatives of those known to have *MYOC*-associated glaucoma may have up to a 50% risk of carrying a *MYOC* mutation. Also, testing patients who have early onset of disease, markedly high IOP, and strong family history of disease (i.e. JOAG) may have clinical utility as these patients have a higher likelihood of glaucoma caused by a *MYOC* mutation (8–63%) (Adam et al., 1997; Wiggs et al., 1998).

3. Optineurin (*OPTN*)

In 2002, a second gene associated with autosomal dominant inheritance of glaucoma was discovered. Rezaie and coworkers identified mutations in the gene optineurin (*OPTN*), that were co-inherited with normal tension glaucoma (NTG) in a large pedigree (Rezaie et al.,

2002). *OPTN* mutations were subsequently detected in several case-control studies of NTG patients (Alward et al., 2003; Aung et al., 2003; Hauser et al., 2006; Rezaie et al., 2002). However, no association was detected between *OPTN* and POAG with elevated IOP (Alward et al., 2003; Aung et al., 2003; Wiggs et al., 2003).

3.1. Epidemiology of *OPTN*-associated glaucoma

Initially a large proportion of NTG cases were attributed to mutations in *OPTN*, including Glu50Lys, Asp128Argfs22Ter, Arg545Gln (Rezaie et al., 2002). However, analyses of larger cohorts subsequently indicated that *OPTN* mutations likely cause 1 to 2% of NTG cases (Alward et al., 2003; Aung et al., 2003; Hauser et al., 2006). Two *OPTN* mutations, Glu50Lys and Arg545Gln, have been detected in several studies of NTG patients. The Arg545Gln mutation has been detected in some control populations at nearly the same frequency as in NTG populations, arguing against a role in NTG pathogenesis. (Alward et al., 2003; Funayama et al., 2004; Tang et al., 2003; Toda et al., 2004) In contrast, the data linking the Glu50Lys mutation with NTG is strong. The Glu50Lys mutation has been detected in both large NTG pedigrees and in NTG cohorts, but has not been identified in control populations (Alward et al., 2003; Aung et al., 2003; Hauser et al., 2006; Rezaie et al., 2002). Consequently, studies of the Glu50Lys mutation have been the focus of *OPTN* glaucoma research.

One additional variant in the *OPTN* gene, Met98Lys, was commonly observed in both NTG patients and in controls. Met98Lys has been detected in as many as 16.5% of control subjects (Funayama et al., 2004). In some populations, generally Caucasian cohorts, the frequency of this mutation is similar among NTG patients and controls (Alward et al., 2003; Aung et al., 2003; Hauser et al., 2006; Weisschuh et al., 2005). However, in other populations, generally Asian cohorts, the Met98Lys mutations has been detected more frequently in NTG patients than in controls (Alward et al., 2003; Funayama et al., 2004; Fuse et al., 2004; Tang et al., 2003; Toda et al., 2004). These data have suggested that although the Met98Lys mutation doesn't cause NTG, it may confer increased risk for developing glaucoma in some populations. The population allele frequencies of Met98Lys and the *OPTN* mutations described above are catalogued in Supplemental Table 1.

OPTN mutations have also been associated with amyotrophic lateral sclerosis (ALS) (Maruyama et al., 2010) and are responsible for up to 5% of familial ALS (Toth and Atkin, 2018). Of note, two *OPTN* mutations first detected in glaucoma patients, Asp128Argfs22Ter and Arg545Gln, have also been associated with autosomal dominant amyotrophic lateral sclerosis (ALS) (Weishaupt et al., 2013). While only limited information is available about the presence or absence of glaucoma in these patients, at least one ALS patient with an Arg545Gln mutation was noted to also have glaucoma (Weishaupt et al., 2013).

3.2. Genotype-phenotype correlations for *OPTN*-associated glaucoma

Glaucoma patients with a Glu50Lys mutation have been described as having an early-onset of severe optic nerve damage that occurs at low IOP (Table 2). Twelve members of the first glaucoma pedigree found to have a Glu50Lys mutation never had an IOP greater than 22 mmHg (Sarfarazi et al., 1998). The mean age at diagnosis of NTG patients with the

Glu50Lys mutation was 40 years. A retrospective case-control study showed that NTG patients with the Gln50Lys mutation had a lower peak IOP, larger cup to disc ratio, more visual field loss, and a higher rate of surgery than matched NTG patients with no known mutation (Aung et al., 2005). Most Glu50Lys mutation reports have come from studies of Caucasian populations and this mutation is less commonly detected among non-Caucasian populations (Hauser et al., 2006). In Japan, where NTG is very common, the Glu50Lys mutation in *OPTN* has been rarely identified in NTG pedigrees (Minegishi et al., 2016) and did not account for any of the cases of NTG in some case-control studies (Tang et al., 2003; Toda et al., 2004).

3.3. Ocular expression pattern of *OPTN*

OPTN is expressed early in the development of the eye, and thought to play an integral role in the formation of the optic vesicle in embryogenesis (De Marco et al., 2006; Rezaie and Sarfarazi, 2005; Ying and Yue, 2012). *OPTN* is also expressed in the adult eye and systemically in many tissues, including heart, liver, testes, kidney, brain, and skeletal muscle (Rezaie and Sarfarazi, 2005). In the eye, *OPTN* is expressed in the non-pigmented ciliary epithelium, trabecular meshwork, and most highly, in the retinal ganglion cells (Rezaie and Sarfarazi, 2005). *OPTN* has been further localized within the cytoplasm, perinuclear region, golgi apparatus, and trans-golgi network (De Marco et al., 2006).

3.4. Structure and function of *OPTN*

The *OPTN* gene is located at chromosome 10p13 spanning a 37kb genomic region. The gene has 16 exons: three non-coding exons and 13 coding exons (Figure 1) (Rezaie et al., 2002; Ying and Yue, 2012). Alternative splicing results in at least 3 different isoforms (Kumar et al., 2016). The resulting OPTN protein is composed of 577 amino acids and contains numerous domains, including 1) a microtubule associated protein 1 light chain 3 alpha (LC3) binding domain; 2) a ubiquitin binding domain; 3) a zinc finger domain; and 4) a leucine zipper domain (Sahlender et al., 2005; Wild et al., 2011; Ying and Yue, 2012). These domains allow the *OPTN* protein to be involved in multiple cellular functions, including vesicle trafficking, maintenance of the Golgi apparatus, and autophagy (Ying and Yue, 2016).

Several disparate biological functions have been attributed to OPTN. Some investigations have suggested that OPTN may influence apoptosis. In cells challenged with peroxide (oxidative stress), OPTN translocates from the Golgi apparatus to the nucleus where it may participate in a protective response to this apoptotic stimulus (De Marco et al., 2006). Moreover, OPTN is also thought to regulate intrinsic apoptosis by delaying cytochrome C release from the mitochondria. Cells that overexpress wild-type OPTN were protected against environmental stresses. By contrast, this protective effect was eliminated in cells producing OPTN with the Glu50Lys mutation, which experienced significantly higher rates of apoptosis (De Marco et al., 2006).

OPTN also has a vital role in autophagy and functions as an autophagy receptor (Wild et al., 2011). Autophagy is a process by which cells tag and selectively degrade debris and cellular components and is an important part of cellular homeostasis and cellular repair. This

process prevents the accumulation of harmful cellular biproducts and is especially important in neural tissue without the capacity for cell turnover. Targets for degradation by autophagy are captured inside an endosome, also known as an autophagosome, and are delivered to the lysosome where they are eliminated. Cells mark targets for clearance via autophagy by tagging them with ubiquitin. Next, activated OPTN draws ubiquitin-tagged targets into an autphagosome via its binding domains. OPTN's ubiquitin-binding domain attaches to targets while its LC3-binding domain attaches to the LC3 that is incorporated in the membranes of the autophagosome. Ultimately, their contents are degraded when autophagosomes fuse with lysosomes (Ying and Yue, 2016).

3.5. Pathophysiology of *OPTN*-associated glaucoma

Several hypotheses about the pathogenesis of *OPTN*-associated glaucoma have been investigated. *In vivo* and *in vitro* studies have both shown that OPTN likely is neuroprotective and that mutations may lead to disease through a downregulation or dysfunction of this protein. One effect of *OPTN* mutations appears to be dysregulation of oxidative stress-induced apoptosis of retinal ganglion cells (Wild et al., 2011; Ying and Yue, 2016). Due to the relatively high expression of *OPTN* in the retina, mutations in *OPTN* may preferentially damage retinal ganglion cells leading to optic nerve vulnerability and NTG. Overexpression of the Glu50Lys *OPTN* mutation in mice caused massive apoptosis of retinal ganglion cells (Chi et al., 2010).

Mutations within *OPTN* may also cause an inappropriate and abnormal activation of autophagy leading to irreparable damage to these cells (De Marco et al., 2006; Ying and Yue, 2016). Another glaucoma-causing gene, TANK binding kinase (*TBK1*) (Fingert et al., 2011), stimulates autophagy by phosphorylating and activating OPTN (Wild et al., 2011). Moreover, the glaucoma-causing Glu50Lys mutation increases OPTN's affinity for TBK1 (Morton et al., 2008), which may similarly promote phosphorylation and abnormal activation of OPTN. Alternatively, *OPTN* mutations may cause the autophagy process to be interrupted resulting in partially digested biproducts and the *OPTN* protein to harmfully build up in the Golgi apparatus (Park et al., 2006). These data suggest that dysregulation of autophagy may have an important role in both *OPTN*-related and *TBK1*-related glaucomas.

Another theory suggests that an imbalance in the expression of the three isoforms of *OPTN* may contribute to glaucoma pathogenesis. A study in 2007 demonstrated that an overexpression of *OPTN* results in upregulation of myocilin in trabecular meshwork cells, suggesting that one of the isoforms of *OPTN* may have a role in stabilizing *MYOC* mRNA. Disruption of this tightly regulated process may result in myocilin build up and subsequent cellular damage (Park et al., 2007).

3.6. Genetic testing for *OPTN* mutations

Testing unselected patients with open angle glaucoma for *OPTN* mutations may have low yield. The prevalence of *OPTN* mutations is estimated to be only 1–2% among NTG patients and even lower among POAG overall (Alward et al., 2003). However, higher risk patients may benefit from testing. Family members of NTG patients with a known Glu50Lys mutation may be at up to 50% risk for inheriting this *OPTN* mutation and a high likelihood

of developing glaucoma. Similarly, NTG patients with early-onset of disease and a strong family history of NTG may also be at higher risk of carrying an *OPTN* mutation. Testing such higher risk patients may facilitate earlier diagnosis, more accurate prognoses, and earlier institution of therapy which may ultimately help prevent vision loss (Fingert, 2011). Genetic testing may provide useful information to patients and their physicians, but should only be conducted by experienced ophthalmic geneticists and/or with genetic counselors to ensure appropriate tests are selected and that results are properly interpreted and explained to patients. General recommendations (Stone et al., 2012) are more completely described above in section 2.6.

3.7. Gene-targeted therapies for *OPTN*-associated glaucoma.

Gene-targeted therapies are not yet available for *OPTN*-associated glaucoma. However, the Glu50Lys mutation is associated a severe form of NTG that has an early onset of disease. Consequently, an early diagnosis may help guide clinicians to more rapidly escalate topical and surgical therapies to improve control of disease.

The efficacy of treating *OPTN*-associated glaucoma with gene-targeted agents has been investigated with cell culture and animal models of glaucoma. Timolol was shown to reduce aggregation of potentially toxic OPTN protein within stem cell-derived retinal ganglion cells, suggesting that timolol might have clinical utility in addition to pressure reduction in *OPTN*-associated glaucoma (Inagaki et al., 2018). Another drug, rapamycin, has been studied for its effects on autophagy in a rat model of *OPTN* glaucoma. Induction of autophagy in this rat model promoted clearance of mutant (Glu50Lys) OPTN protein (Ying et al., 2015) and might suggest future therapeutic avenues for *OPTN*-associated glaucoma. Finally, a TBK1 inhibitor, amlexanox has been studied in a mouse model of *OPTN*-associated glaucoma (Minegishi et al., 2016). These preliminary investigations may ultimately lead to new treatment paradigms for patients with glaucoma caused by the *OPTN* gene.

4. TANK-binding kinase 1 (*TBK1*)

4.1. Epidemiology of *TBK1*-associated glaucoma

In 2011, TANK-binding kinase 1 (*TBK1)* was associated with NTG via linkage analysis studies of a large pedigree with autosomal dominant inheritance of glaucoma (Fingert et al., 2011), making this gene the third and most recent to be identified as a Mendelian cause of POAG. Large duplications of a segment of chromosome 12q14 spanning the *TBK1* gene were detected in all members of the NTG pedigree (Fingert et al., 2011). Subsequent reports on cohorts of unrelated NTG patients from around the world found that patients with *TBK1* copy number variation (CNV) mutations account for 0.4–1.3% of NTG cases in Caucasian, Japanese, and Indian populations (Awadalla et al., 2015; Fingert et al., 2011; Kaurani et al., 2016; Kawase et al., 2012; Ritch et al., 2014). *TBK1* mutations appear to be specifically associated with NTG and mutations have not been linked with additional forms of open angle glaucoma. CNVs spanning the *TBK1* gene have not been identified in control subjects, POAG patients with IOP >21 mm Hg (Awadalla et al., 2015; Fingert et al., 2011; Kaurani et al., 2016; Liu et al., 2014), JOAG patients, or individuals with secondary open

angle glaucoma including pigmentary glaucoma and steroid-induced glaucoma (Fingert et al., 2016). Only one out of 225 (0.44%) patients with exfoliation glaucoma was found to have a *TBK1* duplication (Fingert et al., 2016), which may represent a chance co-occurrence of exfoliation syndrome and NTG. This finding is currently the only example of a *TBK1* mutation detected in a patient diagnosed with a form of glaucoma other than NTG, though very rare instances of *TBK1* duplications have been reported in large population databases of unexamined individuals (Supplemental Table 1).

4.2. Genotype-phenotype correlations for *TBK1*-associated glaucoma

The clinical phenotype of NTG patients with a *TBK1* gene duplication or triplication has been described (Table 3). The association between *TBK1* CNVs and NTG was discovered by genetic analyses of two pedigrees with autosomal dominant inheritance of glaucoma (Fingert et al., 2011). In a large African-American family, ten members were diagnosed with NTG, six of which had extensive medical records that demonstrated an early onset disease (mean age of diagnosis 36 ± 8.2 years). All affected members had normal IOP (mean maximum IOP 18.2 ± 4.1 mmHg, right eye; 16.7 ± 3.6 mmHg, left eye) and were noted at the time of initial examination to have profound optic nerve cupping (mean cup-to-disc ratio 0.95 ± 0.083, right eye; 0.93 ± 0.10, left eye). A duplication of the *TBK1* gene was detected in members of this pedigree with NTG. The second pedigree was a Caucasian family in whom eight members were affected by NTG with autosomal dominant inheritance, six of which had extensive medical records documenting their glaucoma phenotype (Awadalla et al., 2015; Bennett et al., 1989; Fingert et al., 2011). Like the African-American pedigree, these family members showed early onset disease with a mean age of diagnosis of 29 ± 6.7 years, normal IOP (mean maximum IOP 19.0 ± 4.3 mmHg, right eye; 18.8 ± 3.8, left eye), and significant though less severe optic nerve cupping at diagnosis (mean cup-to-disc ratios of 0.85 ± 0.071). A triplication of the *TBK1* gene was detected in those members of this Caucasian pedigree that were diagnosed with NTG. In both pedigrees, the glaucoma phenotype of *TBK1* duplications was characterized by severe, early onset optic nerve damage occurring at normal IOP.

4.3. Ocular expression pattern of *TBK1*

While TBK1 has broad expression throughout the human body and the eye, immunohistochemical analyses of human donor eyes demonstrated that TBK1 protein was most abundant in the ganglion cell layer of the retina (Fingert et al., 2011). A similar pattern of TBK1 production was observed in mouse eyes (Fingert et al., 2017).

4.4. Structure and function of *TBK1*

The *TBK1* gene is composed of 24 exons and encodes a 729 amino acid kinase protein (Figure 1) with an estimated molecular weight of 84 kDa (Tojima et al., 2000). Four functional domains of the human *TBK1* gene have been described: the kinase domain, the ubiquitin-like domain, the α-helical scaffold dimerization domain, and a carboxy-terminal domain. The crystal structure of human TBK1 has been solved and suggests that TBK1 forms dimers and is activated by phosphorylation of Ser172 and ubiquitination of the dimer (Larabi et al., 2013; Li et al., 2012; Tu et al., 2013)

TBK1 is a serine-threonine kinase best characterized for its role in antiviral responses of the innate immune system as well as its regulatory roles in humoral immunity and autophagy (Louis et al., 2018). TBK1 is ubiquitously expressed (Tojima et al., 2000) and essential for life as homozygous deletion of the gene has been shown to be lethal during embryogenesis in mice due to liver degeneration and apoptosis (Bonnard et al., 2000). TBK1 plays a key role in regulating immune responses by activating expression of factors involved in inflammation and host defense, including factors stimulated by NF-KB, IRF3, and IRF7 (Pomerantz and Baltimore, 1999; Sharma et al., 2003). Furthermore, TBK1 plays an important role in autophagy, a process essential for eukaryotic cell survival and maintenance that is responsible for the degradation and recycling of cytoplasmic damaged organelles (Heo et al., 2015; Lazarou et al., 2015), proteins (Korac et al., 2013), macromolecutes, and breakdown products. TBK1 activates autophagy proteins OPTN (Wild et al., 2011) and p62 (Pilli et al., 2012) to control autophagosome maturation into lytic bactericidal organelles. Specifically, TBK1 phosphorylates Ser177 of OPTN which activates it as an autophagy receptor. Phospho-OPTN brings cellular targets such as damaged mitochondria into autophagosomes for degradation (Wild et al., 2011).

Studies of transgenic mice have investigated the effects of *TBK1* duplications *in vivo* (Fingert et al., 2017). Transgenic mice were engineered to have one wild-type copy of human *TBK1* and its native promoter added to their genomes, resulting in a total of three copies of the gene (one human *TBK1* transgene and two native mouse *Tbk1* genes). Like the human *TBK1* phenotype, IOP of these mice was found to be no different than measured in wild-type littermates at a range of ages (5 weeks to 18 months). Immunohistochemical assays performed on retinas of transgenic *TBK1* mice demonstrated that an extra copy of the *TBK1* gene increased expression of the TBK1 protein in retinal ganglion cells (Fingert et al., 2017). Moreover, transgenic TBK1 mice developed progressive loss of retinal ganglion cells as they aged. Mice with two copies of the *TBK1* transgene in their genomes had even more RGC loss, suggesting a dose response between the number of *TBK1* transgenes and glaucomatous damage. These data provide compelling evidence that *TBK1* gene duplications or triplications are pathogenic to retinal ganglion cells in both humans and mice with normal intraocular pressure (Fingert et al., 2017).

4.5. Pathophysiology of *TBK1*-associated glaucoma

The key roles of *TBK1* and *OPTN* in autophagy and specifically mitophagy (degradation of mitochondria by autophagy) have been proposed as an important pathophysiologic mechanism in NTG as well as other neurodegenerative diseases. Amyotrophic lateral sclerosis (ALS) has been linked to different mutations in these same genes. Damaged mitochondria were shown to accumulate when TBK1 is either chemically inhibited or its expression is knocked down with siRNA, indicating impairment of mitophagy in ALS-associated mutations in *OPTN* and *TBK1* (Moore and Holzbaur, 2016).

Other *TBK1* mutations that are associated with NTG, e.g. *TBK1* gene duplications and triplications, have been shown to increase expression of the TBK1 protein and may also cause dysregulated autophagy. Immunohistochemical studies of human retina have shown that TBK1 protein is localized to retinal ganglion cells and the retinal nerve fiber layer,

the cells affected by glaucoma (Fingert et al., 2011; 2014). Studies of patient-derived cells have also suggested that *TBK1* gene duplications may alter the function of autophagy in retinal ganglion cell-like neurons. Tucker et al. has produced retinal ganglion cell-like neurons from skin biopsies of patients with NTG caused by a *TBK1* gene duplication using induced pluripotent stem cell methods (Tucker et al., 2014). Compared with controls, retinal ganglion cell-like neurons with a *TBK1* gene duplication have increased levels of lipidated LC3 (a component of autophagosome membranes and marker of autophagy activity). This finding suggests that *TBK1* duplications may abnormally stimulate autophagy in retinal ganglion cells and subsequently contribute to their demise. However, the precise mechanism by which aberrant autophagy or mitophagy may promote retinal ganglion cell death remains unclear. Though caused by different sets of mutations and phenotypically distinct, the complex pathophysiology underlying ALS and NTG may share some common mechanisms involving *TBK1* and *OPTN.*

4.6. Genetic testing for *TBK1* mutations

Testing for *TBK1* mutations associated with glaucoma is not currently available for clinical use.

4.7. Gene-targeted therapies for *TBK1*-associated glaucoma.

The discovery that *TBK1* (or *OPTN)* mutations may cause glaucoma via dysregulation of autophagy has suggested new modes of therapy. Inhibition of TBK1 kinase to block phosphorylation/activation of OPTN and subsequent stimulation of autophagy has been explored as a possible therapy for glaucoma associated with *TBK1* or *OPTN* mutations. Minegishi et al. investigated the impact of amlexanox, a TBK1 kinase inhibitor, on retinal ganglion cell loss in transgenic *knock-in* mice engineered to have an *Optn* mutation, Glu50Lys (Minegishi et al., 2016). Amlexanox was shown to prevent retinal ganglion cell loss associated with the Glu50Lys mutation, possibly via its effects on autophagy. Amlexanox or other TBK1 kinase inhibitors may have utility for treating *OPTN* and *TBK1*-associated glaucoma. While additional studies are needed to make such drugs available for clinical use, these findings serve as compelling evidence that personalized therapies for at least a subset of inherited open angle glaucoma is a possibility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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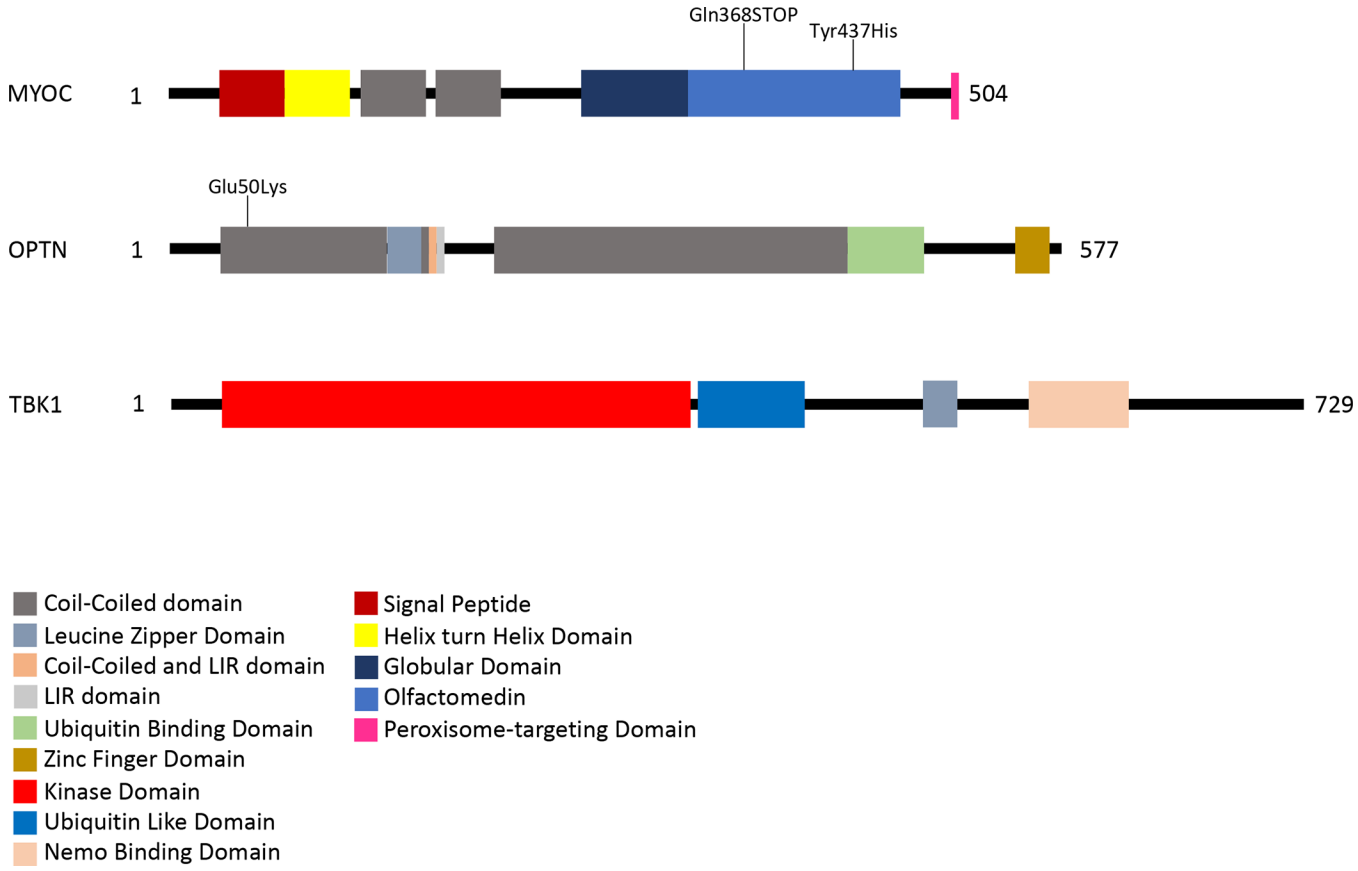

Figure 1. Protein Structure of MYOC, OPTN, and TBK1.

Each protein is represented by a linear diagram proportional to its length in amino acids (AA), 504 AA for MYOC, 577 AA for OPTN, and 729 AA for TBK1. Functional domains and sequence motifs are indicated by colored boxes. The location of some of the more commonly detected glaucoma-causing mutations are indicated on these diagrams.

Table 1.

Features associated with *MYOC* mutations.

	JOAG			
	Pro370Leu	**Thr377Met**	**Tyr437His**	**Ile477Asn**
Inheritance pattern	AD	AD	AD	AD
Penetrance	>75% by 25 years	88% by 30 years	100% by 40 years	>75% by 25 years
Mean age at diagnosis (range) in years	12–30 (5–35)	37–38 (20–60)	20 (8–41)	21 (12–41)
Maximum IOP (range) in mm Hg	45 (25–66)	31 (20–50)	44 (14–77)	40 (20–52)
References	(Adam, 1997)	(Stone et al, 1997)	(Stone et al, 1997)	(Alward et al, 1998)
	(Stoilova, 1998)	(Alward et al, 1998)	(Alward et al, 1998)	(Richards, 1998)
	(Shimizu, 2000)	(Fingert et al, 1999)	(Fingert et al, 1999)	(Fingert et al, 1999)
		(Shimizu, 2000)		(Shimizu, 2000)
		(Mackey et al, 2003		

AD: autosomal dominant.

Table 2.

Features associated with the *OPTN* Glu50Lys mutation.

	***OPTN* Glu50Lys Mutations in 4 cohorts**			
Instances of Glu50Lys per cohort	7/52	1/105	2/132	1/67
Inheritance pattern	AD	NA	NA	NA
Penetrance	70.40%	NA	NA	NA
IOP data (mm Hg)	81.6% had IOP < 21	NA	NA	Mean Max IOP = 16
References	Rezaie et al, 2002	Alward et al, 2003	Aung et al, 2003	Hauser et al 2006

AD: autosomal dominant, NA: Not available.

Table 3.

Features associated with *TBK1* mutations.

	Original pedigree with a *TBK1* duplication	***TBK1* Copy Number Variations in 5 cohorts**				
Instances of CNVs	NA	2/152	4/334	2/158	1/96	1/252
Ancestry	African American	Caucasian (USA)	Caucaisian (Austrailia)	Asian (India)	Caucasian (U.S.A.)	Asian (Japan)
Inheritance pattern	AD	AD	AD	NA	NA	NA
Prevalence	NA	1.3% of NTG	1.2% of NTG	1.3% of NTG	1% of NTG	0.4% of NTG
CNV type	Duplication	Duplication (1/2) Triplication (1/2)	Duplication (3/4) Triplication (1/4)	Duplication	Duplication	Duplication
Mean age at diagnosis in years	36	29	45	63	47	42
Mean Maximum IOP in mm Hg	18	19	14	16	16	18
References	Fingert et al., 2011	Fingert et al., 2011	Awadalla et al., 2015	Kaurani, 2016	Ritch, 2014	Kawase, 2011

AD: autosomal dominant, NA: Not applicable or not available.