



Progressive Optic Disc Cupping Over 20 Years in a Patient with *TBK1*-Associated Glaucoma

Primary open-angle glaucoma is a leading cause of visual impairment that is characterized by cupping of the optic disc and stereotypical patterns of visual field loss. Although high intraocular pressure (IOP) is a risk factor for developing disease, glaucoma can occur at any pressure. Glaucoma that occurs with maximum IOPs of less than 21 mmHg has been termed “normal-tension glaucoma” (NTG). Glaucoma is highly heritable, and many genes that contribute to the pathogenesis of NTG have been discovered. Mutations in optineurin (*OPTN*),¹ TANK-binding kinase 1 (*TBK1*),² or myocilin (*MYOC*)³ are each capable of causing glaucoma with little influence from other genetic or environmental factors. Mutations in these genes are responsible for approximately 3% of NTG.¹⁻³

TBK1-associated NTG is caused by duplication or triplication of the normal *TBK1* gene sequence. These *TBK1* gene-dosage mutations have been detected in African American,² white,^{2,4,5} and Asian^{6,7} patients with NTG and have not been identified in the genomes of more than 10 000 individuals in a large public database (gnomAD.broadinstitute.org). *TBK1* gene duplication and triplication mutations are associated with early-onset glaucoma that frequently presents with large cup-to-disc ratios and maximum IOPs of <21 mmHg.² Prior studies of *TBK1*-associated NTG have reported a mean age at diagnosis of 29 to 36 years, mean cup-to-disc ratio of 0.85 to 0.93 at first examination, and mean maximum IOP of 18 to 19 mmHg.² Some patients with NTG with *TBK1* mutations have

thin central corneas; however, a broad range of corneal thickness has been observed in this patient population.^{2,5} Typical glaucomatous visual fields have been detected in patients with *TBK1*-associated glaucoma, including arcuate defects, nasal steps, central defects, and generalized constriction.² Although many key features of the clinical phenotype of *TBK1*-associated glaucoma have been described, studies of disease progression for this molecularly defined type of NTG have not been reported.

In this case report, we present genetic testing results for a woman with familial NTG and a retrospective 20-year review of her clinical course. Written informed consent was obtained from study participants, and research was conducted with the approval and ethical review by the University of Iowa’s Internal Review Board and adhered to the tenets of the Declaration of Helsinki.

The patient, her mother, and her maternal aunt all have been diagnosed with NTG. Given our patient’s strong family history of NTG, we tested her DNA for the most commonly observed NTG mutations: Glu50Lys in *OPTN*, a gene duplication of *TBK1*, and Gln368Ter in *MYOC* using real-time polymerase chain reaction assays as previously described.^{2,3} Although the *OPTN* and *MYOC* tests showed negative results, we did detect a *TBK1* gene duplication. We subsequently confirmed the *TBK1* gene duplication and determined the precise location of its borders on chromosome 12q14 (64 681 095–65 187 566) using chromosome microarray analysis. This *TBK1* gene duplication has novel borders when compared with prior reports.^{2,5}

The patient is a Hispanic white woman with a complex ophthalmic history. She was initially evaluated by an

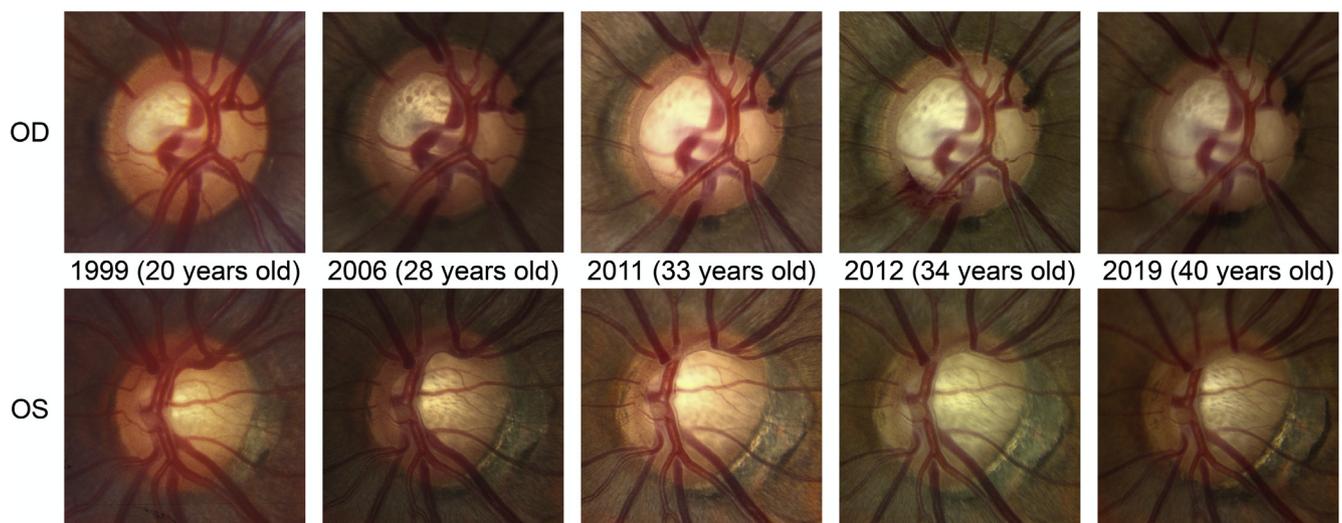


Figure 1. Serial optic disc photographs in a patient with preperimetric normal-tension glaucoma (NTG) caused by a *TBK1* gene duplication. Optic disc photographs obtained over 20 years demonstrate progressive cupping and progressive peripapillary atrophy in both eyes. In 2012, a disc hemorrhage was detected in the right eye at 7–8 o’clock. In 2019, increased cupping was detected in the right eye in the same location (7–8 o’clock). The configuration of retinal vessels at the optic disc was also noted to shift during the course of progressive cupping. OD = right eye; OS = left eye.

ophthalmologist at age 3 years for anisocoria. At age 10 years, she developed esotropia. She was determined to have a slowly progressive right third nerve palsy that spared her levator. Multiple magnetic resonance imaging scans and angiography failed to determine an etiology, and a diagnosis of a schwannoma was considered. She has myopia with anisometropia ($-1.50 +1.50 \times 090$ right eye and -5.75 sphere left eye) and has required 3 strabismus surgeries.

At age 17 years, during one of her many neuro-ophthalmology examinations, she was noted to have cup-to-disc asymmetry. By age 33 years, she had documented increased cupping (Fig 1) with thinning of the retinal nerve fiber layer on OCT (Fig S1, available at www.ophthalmologyglaucoma.org). Her IOPs were 12 mmHg in both eyes. Central corneal thickness was 546 μm in both eyes. Her Humphrey visual fields were normal (Fig S2, available at www.ophthalmologyglaucoma.org). Diurnal measurements of IOP were 9 to 14 mmHg in the right eye and 9 to 13 mmHg in the left eye. She was diagnosed with preperimetric NTG. The patient had symptoms of orthostatic hypotension and typically maintained a blood pressure (BP) in the range of 90/55 mmHg. A 24-hour BP study revealed a minimum nocturnal BP of 80/46 mmHg. She was treated with a high salt diet. At age 34 years, a disc hemorrhage was detected in the right eye (Fig 1) when her IOP was 12 mmHg. OCT at this time demonstrated thinning of the retinal nerve fiber layer and marked ganglion cell loss (Fig S1, available at www.ophthalmologyglaucoma.org). Latanoprost was begun with no significant change in her IOP. With or without treatment, her IOP was between 10 and 12 mmHg in both eyes. It was determined that no medication would lower her IOP from this range and that the next step in treatment would be a trabeculectomy.

Over the course of the next 6 years of follow-up examinations, the patient's IOP remained at <12 mmHg in both eyes and no obvious glaucomatous visual field changes were observed. Mild, nonspecific reductions in visual field sensitivity were detected (left eye $>$ right eye) that might represent early functional damage from glaucoma (Fig S2, available at www.ophthalmologyglaucoma.org).

We present a patient with a duplication in *TBK1* who demonstrates progressive optic nerve cupping with low IOP at a young age that is consistent with preperimetric NTG. Her right third nerve palsy is most likely unrelated to the bilateral cupping and glaucoma. To our knowledge, *TBK1* gene duplications have not been detected in other patients with third nerve palsy. Her complex ophthalmic history brought her to the attention of ophthalmologists who could document her progressive cupping at low-normal IOPs. One should consider testing for mutations in *TBK1* in young patients with progressive optic nerve cupping at normal IOPs, and those patients with NTG with *TBK1* mutations may require very low target IOP to limit progression (i.e., <10 – 12 mmHg).

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No animal subjects were used in this study.

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