A novel mutation in a case of dominant optic atrophy?

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A 39-year-old healthy woman presented for decreased vision at distance and near for 4 years. She also noted a decrease in her color vision. Her best-corrected visual acuities were 20/70 in each eye. Her visual fields were abnormal, and she had bilateral sluggish pupils, impaired color vision, and optic disc pallor. The magnetic resonance imaging of the brain, heavy metal screen, autoimmune work-up, B12, B6, folate, erythrocyte sedimentation rate, rapid plasma reagin, and Lyme titer were all normal. Optical coherence tomography of the macula and electroretinogram were normal; the visual evoked potential was unrecordable in both eyes. She denied a family history of similar ocular issues, and genotyping of the OPA1 gene revealed a novel previously unreported mutation at IVS12+10T >C.

Key words: Dominant optic atrophy (group together), OPA1, IVS12+10T >C

Access this article online	
Quick Response Code:	Website: www.ijo.in
	DOI: 10.4103/0301-4738.146043

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Manuscript received: 02.07.14; Revision accepted: 01.09.14

Dominant optic atrophy (DOA) is the most common inherited optic neuropathy, and its incidence is 1 in 50,000 persons in the United States and 1 in 10,000 persons in Denmark. Vision loss in DOA is related to retinal ganglion cell loss from mitochondrial dysfunction. DOA is a heterogeneous disease that has been mapped to chromosome 3q28, and *OPA1* has been identified as the responsible gene. *OPA1* codes for a dynamin-related GTPase protein targeted to the mitochondrial inner membrane, which regulates the fusion, oxidative phosphorylation, and cell death. Of the 204 different reported *OPA1* mutations in DOA, 82 are truncative N-terminal mutations; 55 are missense mutations; and 55 are splice variants.[1-3]

Case Report

A 39-year-old healthy woman complained of difficulty focusing. She stated things have not been clear at distance or near and colors, were not vivid. This has slowly been getting worse over the last 4 years. She denied any other ocular symptoms. She went to multiple optometrists and ophthalmologists who stated that nothing was wrong with her eyes except for a slightly abnormal visual field. Her vision could not be corrected with glasses.

Her past ocular history is completely unremarkable. She used artificial tears as needed for comfort. She denied any known family history of decreased vision or glaucoma. Her past medical history is only notable for migraines, carpal tunnel syndrome, cholecystectomy, nephrolithiasis, rhinoplasty, and breast augmentation. She uses oral pregabalin and meclizine and has no medication allergies. She is a nonsmoker and nondrinker. Review of systems is only positive for her typical headaches.

Prior to her presentation, a magnetic resonance imaging of her brain and orbits were done with and without contrast, and the interpretation was normal. A neurology evaluation demonstrated a normal electroencephalogram, electromyogram, and nerve conduction velocities. A heavy metal screen, B12, B6, folate, erythrocyte sedimentation rate, rapid plasma reagin, and Lyme titer were normal.

Her best-corrected visual acuities vision were 20/80 oculus dexter (OD) and 20/70 oculus sinister (OS). Her external examination was unremarkable. Color vision in each eye was 1/8 Ishihara plates. Her applanation pressures were 14 mm Hg Oculus uterque (OU). Confrontation visual fields were normal in both eyes. The pupils were sluggish bilaterally with no relative afferent pupillary defect. Ocular motility was full. Slit lamp examination was unremarkable. The macula, retinal vessels and periphery were normal. The optic discs were pale bilaterally with pallor out of proportion to cupping.

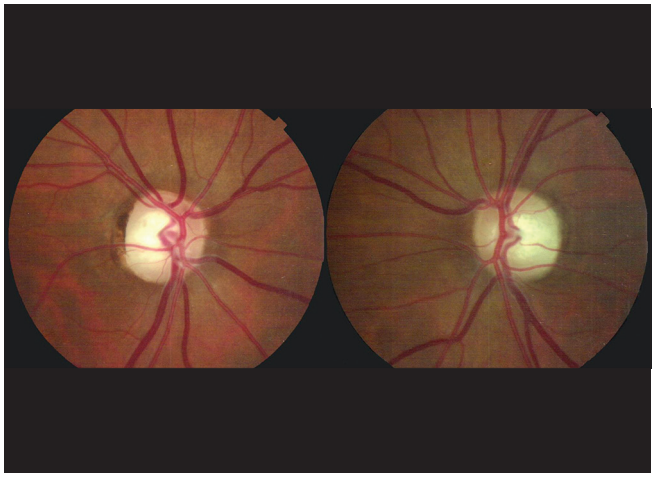


Figure 1: Optic nerve photos demonstrate pallor out of proportion to cupping OU and a temporal crescent in the right eye

There was a temporal crescent and peripapillary atrophy in the right eye [Fig. 1]. Automated perimetry demonstrated severe general depression bilaterally with a possible inferior arcuate defect in the left eye [Fig. 2].

The ERG was normal; the visual evoked potential (VEP) was unrecordable in both eyes. Optic nerve optical coherence tomography (OCT) demonstrated symmetric severe retinal nerve fiber layer (RNFL) thinning (average 59 µm OD and 58 µm OS), most superiorly and inferiorly with temporal sparing [Fig. 3]. OCT of the macula revealed a preserved photoreceptor inner segment/outer segment junction and a normal fovea. *OPA1* gene sequencing at Athena diagnostics® (Worcester, MA, USA) revealed DNA variant transition T >C at nucleotide position IVS12+10. There is currently no published research on this gene variant.

Discussion

The *OPA1* mutation that this patient has, T >C at nucleotide position IVS12+10 has not previously been reported in clinical cases of DOA. While this mutation is in the noncoding region of the *OPA1* gene, the patient has a clinical phenotype of DOA, making this possibly clinically significant.

Dominant optic atrophy can insidiously present as mild to moderate vision loss, typically in school-aged children ages 4-6 years of age, with a potential for progressive vision loss later in life (30-50%). About 40% of patients have a visual acuity of 20/60 or better; 45% are between 20/60 and 20/200; and 15% are below 20/200.[4,5] Visual fields commonly demonstrate central

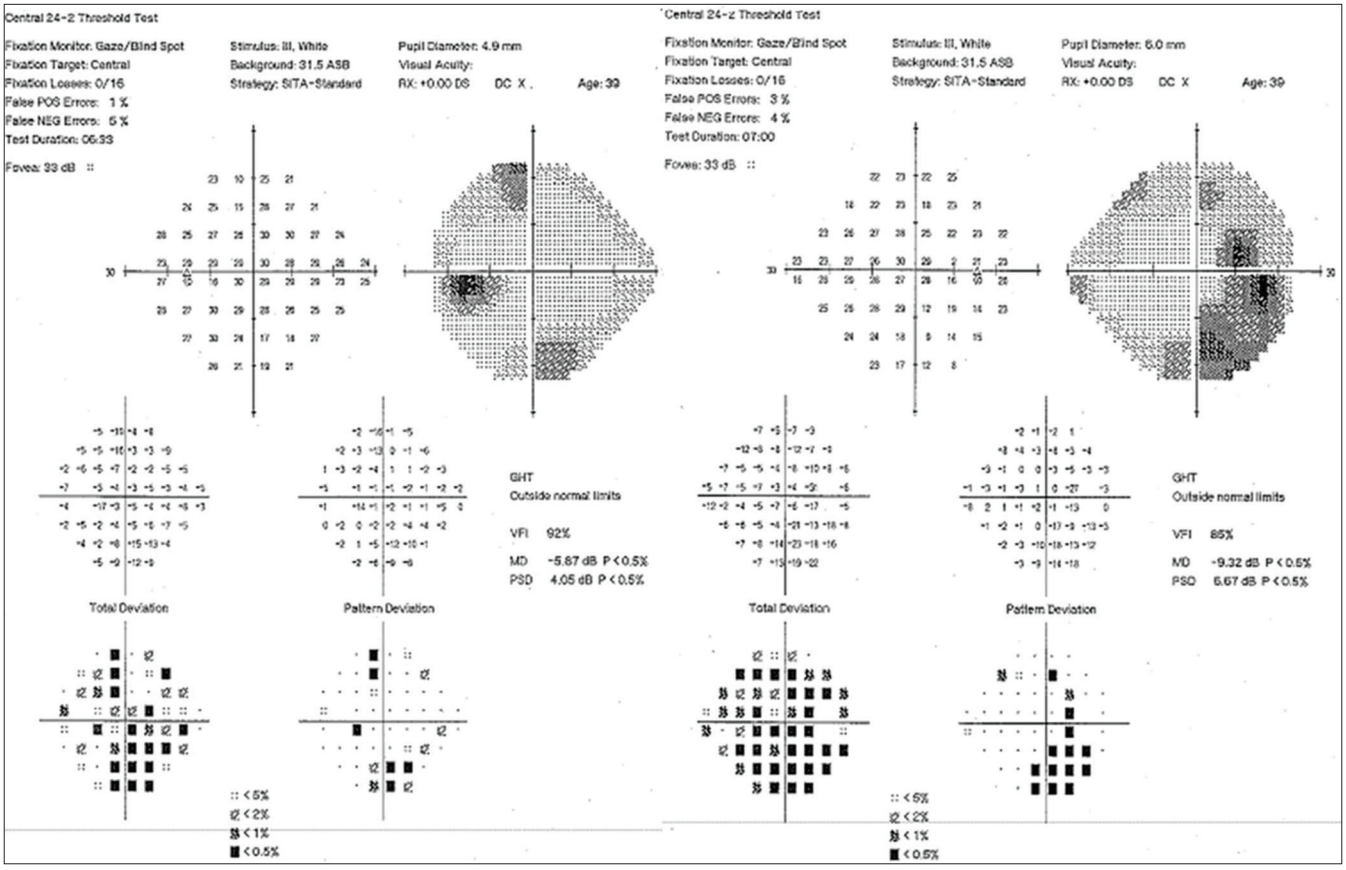
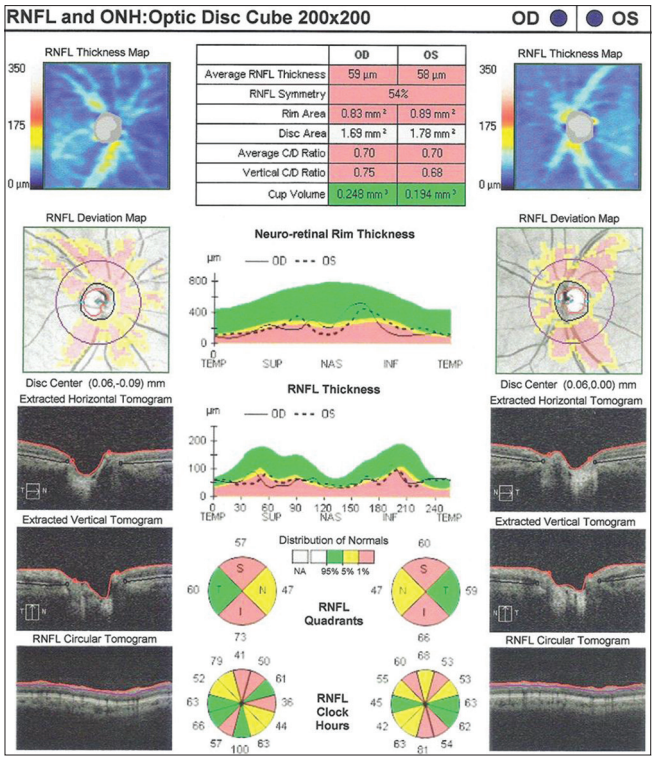


Figure 2: Humphrey visual fields demonstrates generalized depression and an inferior arcuate defect in the left eye



	OD	OS
Average RNFL Thickness	59 µm	58 µm
RNFL Symmetry	54%	
Rim Area	0.83 mm²	0.89 mm²
Disc Area	1.69 mm²	1.78 mm²
Average C/D Ratio	0.70	0.70
Vertical C/D Ratio	0.75	0.68
Cup Volume	0.248 mm³	0.194 mm³

Figure 3: Optical coherence tomography of the retinal nerve fiber layer demonstrated severe thinning in both eyes

and cecocentral visual field defects, but altitudinal defects have also been reported.[6] Generalized, blue-yellow, and red-green dyschromatopsias have been described. Optic nerve pallor has been described to affect only the temporal nerve (52%) and the entire nerve (48%), as seen in this patient.[5] Other clinical findings reported in DOA patients include peripapillary atrophy (69%), a temporal grey crescent (31%), and an enlarged cup to disc ratio, >0.5 (48%).[3] In addition, up to 20% of *OPA1*-mutated patients develop "*OPA1* plus" phenotype with deafness, progressive external ophthalmoplegia and myopathy, starting from the third decade of life onward.[1]

This patient had a subacute decrease in visual acuity, diffusely depressed visual fields, severe diffuse bilateral RNFL loss, symmetric dyschromatopsia, peripapillary atrophy with a temporal crescent, enlarged cup to disc ratio, and a VEP that was nonrecordable. Sequencing of the *OPA1* gene revealed a novel mutation that describes a classic phenotype of DOA.

Acknowledgment

The authors than Dr. Kang Zhang for his analysis of the genetic mutation.

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Cite this article as: Ramkumar HL, Savino PJ. A novel mutation in a case of dominant optic atrophy?. Indian J Ophthalmol 2014;62:1034-6.

Source of Support: Nil. **Conflict of Interest:** None declared.