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# Novel homozygous *OPA3* mutation in an Afghani family with 3-methylglutaconic aciduria type III and optic atrophy

**Eric D Gaier, MD, PhD**[1,2,3,4], **Inderneel Sahai, MD**[3,5], **Janey L Wiggs, MD, PhD**[2,3], **Brian McGeeney, MD**[3,6], **Jodi Hoffman, MD**[7,8], **Crandall Peeler, MD**[7,9,10]

[1]Department of Ophthalmology, Boston Children's Hospital, Boston, MA

[2]Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, MA

[3]Harvard Medical School, Boston, MA

[4]Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA

[5]Departments of Genetics and Pediatrics, Massachusetts General Hospital, Boston, MA

[6]Department of Neurology, Brigham and Women's Hospital, Boston, MA

[7]Boston University School of Medicine, Boston, MA

[8]Department of Genetics, Boston Medical Center, Boston, MA

[9]Department of Ophthalmology, Boston Medical Center, Boston, MA

[10]Department of Neurology, Boston Medical Center, Boston, MA

## Abstract

**Purpose:** To describe and distinguish clinical phenotypes with the overlapping feature of optic atrophy caused by distinct mutations in the same gene, *OPA3*. We report 3 affected siblings in a consanguineous family harboring a novel *OPA3* mutation causing 3-methylglutaconic aciduria type III with optic atrophy.

**Methods:** Retrospective case series.

**Results:** Three siblings (2 male, 1 female) among 6 children in a consanguineous Afghani family developed decreased vision from early childhood. Both parents and all extended family members were unaffected. All 3 affected siblings suffered from severe visual impairment ranging from visual acuities of 20/150 to counting fingers. All had spastic lower extremity weakness and ataxia. Two of the three affected siblings also had a history of seizures, and the female sibling had limited cognition with diffuse atrophic changes on brain MRI. Two of the three individuals also had migraine-like headaches. Urine organic acid analysis revealed mildly elevated 3-methylglutaconic acid for the male siblings. Whole exome sequencing and subsequent PCR confirmation revealed a

**Corresponding Author:** Crandall Peeler, MD, Department of Ophthalmology, Boston Medical Center, Boston, MA, Phone: 617-414-4020, Crandall.Peeler@bmc.org.

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novel variant in *OPA3* (intron1, c.142+2_142+3dupTG), affecting the consensus sequence of the splice site, for which all 3 clinically affected siblings were homozygous.

**Discussion:** Mutations in *OPA3* can cause optic atrophy in a dominant pattern of inheritance associated with cataract or in a recessive pattern associated with spastic paresis and ataxia. The novel recessive variant and clinical presentations described herein further support how different mutation types affecting *OPA3* can produce distinct clinical phenotypes and underscore the critical and susceptible role of mitochondrial health in optic nerve function.

### Keywords

Optic Atrophy; Ataxia; Costeff Syndrome; OPA3; 3-methylglutaconic aciduria type III

## Introduction

Hereditary optic neuropathies are characterized by primary optic atrophy and are caused by mutations in multiple genes. Mutations in *OPA3* are associated with optic atrophy in distinct contexts (1–3). Heterozygous mutations in *OPA3* cause autosomal dominant optic atrophy with associated cataract (OMIM#165300), while mutations in both *OPA3* alleles cause autosomal recessive 3-methylglutaconic aciduria type III (MGA3; Costeff Syndrome; OMIM#258501), a neuro-degenerative disorder characterized by optic atrophy, extrapyramidal signs, spastic paraparesis and ataxia.

We present a family with consanguineous, unaffected parents and 3/6 affected siblings who were referred for neuro-ophthalmic and genetic evaluation due to optic atrophy, spastic lower extremity weakness and ataxia. Whole-exome sequencing revealed novel homozygous mutations of *OPA3* in all 3 affected siblings, 2 with elevated urine levels of 3-methylglutaconic acid, consistent with MGA3. We review the distinct clinical entities caused by dominant and recessive *OPA3* mutations.

## Clinical Features

The family emigrated from northwestern Afghanistan to the United States 2 years prior to their initial evaluation (Figure 1A). All 3 affected siblings (2 male, 1 female) had histories of progressive optic atrophy, extrapyramidal signs, ataxia, and peripheral neuropathy since childhood. The 3 unaffected female siblings had multiple unaffected children.

By history aided through a live Farsi interpreter, all affected siblings reportedly had normal neurodevelopment until the age of 2 to 3 years when the first symptoms of visual difficulty began. Of note, the 2 male siblings were reported to have fevers which preceded the visual loss and typically lasted ~2 days and recurred every 2–3 weeks for 1 year.

Following initial vision loss in early childhood, affected family members exhibited difficulty walking. The female and younger male (II5) siblings developed seizures in the 2$^{nd}$ decade of life, controlled with valproate and levetiracetam, respectively. Both male siblings also described headaches, one (II3) with associated photophobia. In each affected brother, headaches were improved with amitriptyline and rescued with sumatriptan, respectively.

On examination, best-corrected visual acuities were: II3: 20/150 OD, 20/300 OS; II4: 20/500 OD 20/500 OS; II5: 20/150- OD, counting fingers 4’ OS. The male siblings were mildly myopic (Manifest refraction: II3: −2.50 +1.00 x080 OD, −3.00 +1.50 x085 OS; II5 −4.00 +0.50 x025 OD, −2.00 sphere OS), whereas the female sibling was highly myopic secondary to bilateral posterior staphylomas (II4 −15.75 +5.00 x086 OD, −9.50 +2.75 x086 OS). Only II5 was noted to have a relative afferent pupillary defect (OS), and he was only able to identify the Ishihara control plate OD (II3 and II5 could not identify the Ishihara control plate with either eye). Extraocular motility was full. The male siblings each exhibited a 35–45 PD comitant exotropia. There was no nystagmus. Automated static and manual kinetic perimetry showed marked diffuse depression and constriction. All 3 siblings exhibited primary optic atrophy on funduscopic examination (Figure 1B–D). The siblings’ mother had normally appearing optic nerves.

All 3 siblings were alert and oriented to person, place, and time. The female sibling had some cognitive limitations and was not independent. Each had up-slanting palpebral fissures and periorbital fulness. Dysarthria was apparent in all 3 siblings. All 3 siblings had short stature and diffusely decreased muscle bulk. Upper extremity strength was intact bilaterally with 1+ deep tendon reflexes (DTR), and lower extremities were spastic with 3–4+ DTR in all 3 siblings. Somatosensory testing was normal to light touch and pin prick. All 3 siblings exhibited an ataxic gait. MRI of the brain for the female sibling showed mild diffuse cerebral and cerebellar volume loss without signal abnormality.

## Genetic and Metabolic Testing

Chromosomal microarray for all 3 affected siblings showed multiple regions of homozygosity, ranging from 3.72–8.54%, reflective of consanguinity. The one region of homozygosity shared by all was arr[hg19] 19q13.13q13.33(38,588,976–48,026,667) which includes *OPA3*. Whole exome sequencing for II5 revealed a homozygous variant in *OPA3* (intron1, c.142+2_142+3dupTG), affecting the consensus sequence of the splice site (Figure 2). The other two siblings (II3, II4) were homozygous for this variant on sequencing of *OPA3*, and the mother was heterozygous. The unaffected siblings and father (presumed deceased) were unavailable for testing.

Plasma amino acid analysis for all 3 affected siblings was unremarkable. Urine organic acid analysis revealed mildly elevated 3-methylglutaconic acid for male siblings II3 and II5 at 12 μmol/mmol creatinine (Reference 2–8 μmol/mmol creatinine) but was normal for female sibling II4 on two separate occasions.

## Discussion

This consanguineous family exemplifies a clinical phenotype consistent with MGA3 with segregation of a novel slice site variant in *OPA3*. Affected siblings exhibited a constellation of profound optic atrophy, lower extremity weakness and ataxia. Two of the three individuals also had a history of seizures beginning later in life, and the female sibling had limited cognition with diffuse atrophic changes on brain MRI. Two of the three individuals also had migraine-like headaches.

Mutations in *OPA3* can manifest with optic atrophy “plus” phenotypes in dominantly and recessively inherited forms (1–4). In 1989, Hanan Costeff first described 19 cases of infantile optic atrophy and early movement disorder, spastic paraparesis, ataxia and cognitive impairment inherited in an autosomal recessive pattern in the Iraqi Jewish community in Israel (5). Three of these cases also exhibited seizures. The common Iraqi Jewish founder mutation c.142–3G>C (IVS1–3G>C) at the intron1-exon2 junction is in the acceptor splice site for the predominant transcript (Transcript 2) and results in reduced expression (2). The variant identified in our family c.142+2_142+3 dupTG (IVS1+2_IVS1+3dupTG) is in the donor splice site at the exon1-intron1 junction (Figure 2). Another variant at this donor splice site, c.142+5G>C [IVS1+5G>C], has been reported in heterozygous form with another variant in two siblings with *OPA3*-related MGA3, and it is predicted to reduce/obliterate exon1-intron1 as a splice donor site (4). Nucleotide variants within the consensus splice site are relatively common causes of aberrant splicing, and the variant found in our family may similarly reduce splicing at the exon1-intron1 junction thereby affecting both transcripts. Thus, there is very strong evidence supporting the pathogenicity of the novel variant reported herein (6). To date, 6 distinct mutations in *OPA3* have been associated with MGA3 (1). Outside of the Iraqi-Jewish population, these include a Pakistani family with 2 affected individuals with *OPA3* missense mutations, and Turkish-Kurdish and Indian patients with nonsense mutations (1).

In 2004, Reynier et al. (3) reported the first dominant *OPA3* mutation in a family with optic atrophy and early onset cataract, and four additional missense *OPA3* mutations have been reported since (1). These mutations can also cause a “plus” phenotype characterized by axonal peripheral neuropathy, gastrointestinal dysmotility, autonomic dysfunction and hearing loss. While recessive mutations associated with MGA3 have loss-of-function effects, dominant *OPA3* mutations presumably impart a dominant-negative or pathologic gain-of-function effect that produces the autosomal dominant inheritance pattern and early-onset cataract. This presumption is supported by the absence of phenotypic features of optic atrophy in individuals who are known carriers of loss-of-function (recessive) mutations.

The rodent *Opa3* protein product localizes to mitochondria and is expressed in the retina, extraocular muscles, cornea and lens (7). In mice with homozygous *Opa3* mutation, retinal mitochondrial cristae are disorganized and fragmented. Likewise, cultured skin fibroblasts from patients with either dominant or recessive *OPA3* mutations display fragmented mitochondrial networks (1, 4), supporting mitochondrial dysfunction as the pathophysiologic root of optic atrophy and neurologic dysfunction in patients with *OPA3*-related disease.

In conclusion, mutations in *OPA3* can impart distinct phenotypes carried through dominant or recessive inheritance patterns but with the common universal feature of optic atrophy, underscoring the critical and susceptible role of mitochondrial health in optic nerve function. The novel recessive mutation and clinical presentations described herein further support how different mutation types affecting *OPA3* can produce distinct clinical phenotypes.

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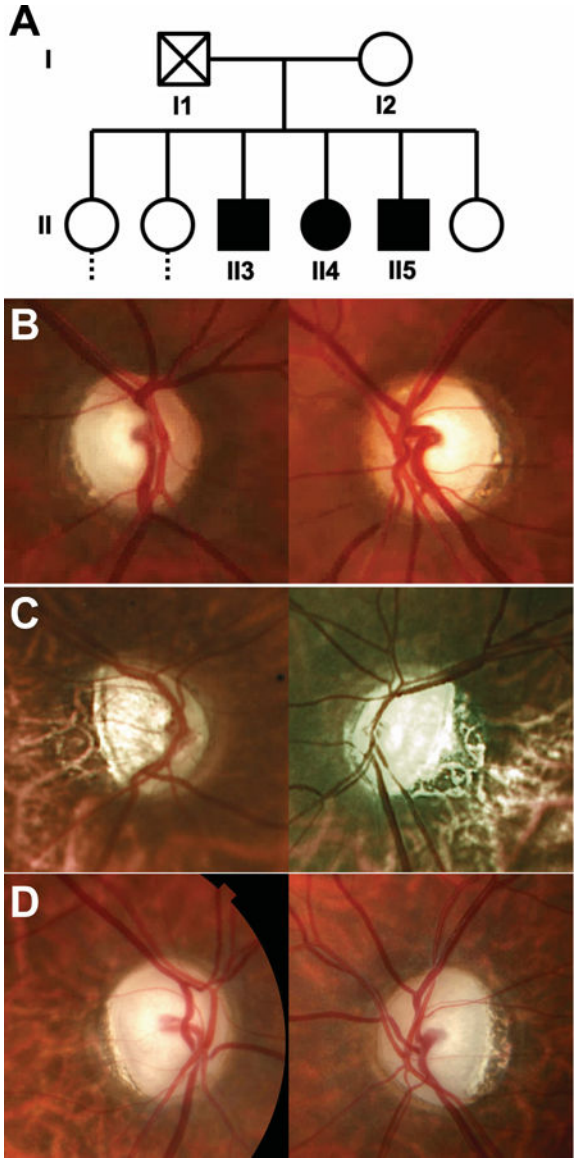


**Figure 1. Presentation of affected family members.**

(**A**) Nuclear family tree including both unaffected parents, 3 unaffected siblings, and 3 affected siblings. Of note, the parents are 1st cousins, and no other extended family members are reportedly affected. Unaffected siblings II1 and II2 have unaffected children (represented by dashed lines). (**B-D**) Fundus photographs centered on the optic nerves of affected siblings II3 (B; Topcon), II4 (C; Optos), and II5 (D; Topcon).

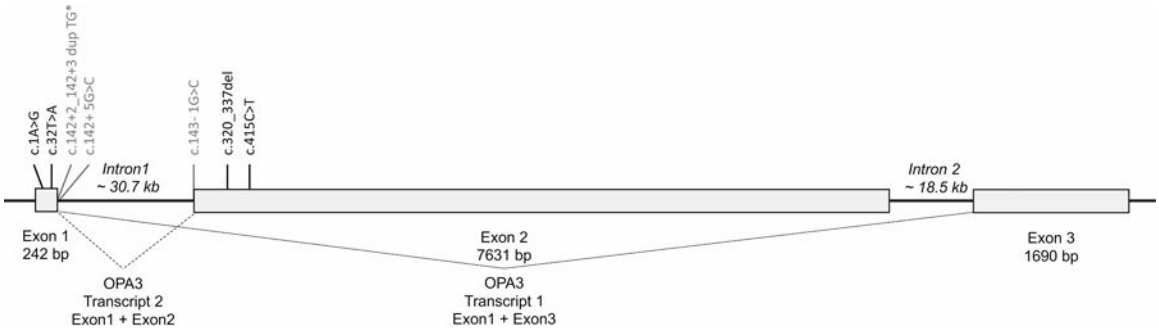


**Figure 2. Schematic of *OPA3* and *OPA3*-related 3-Methylglutaconic aciduria (MGA3) sequence variants.**

The *OPA3* gene [NC_000019.9], showing the 3 exons as boxes and introns as lines (not to scale). The 2 *OPA3* mRNA transcripts generated by splicing at the intron-exon junctions: Transcript Variant 2 [GenBank NM_025136] and Transcript Variant 1 [Gen Bank NM_001017989]. Sequence variants associated with *OPA3*-related MGA3 are shown. Mutations in the coding region are shown in black while those in the intronic splice sites are in gray. * denotes the novel variant reported in this case study.