Movement Disorders
CLINICAL PRACTICE
CASE REPORT

# Levodopa Responsive Dystonia Parkinsonism, Intellectual Disability, and Optic Atrophy Due to a Heterozygous Missense Variant in *AFG3L2*

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*AFG3L2* mutations are associated with several neurodegenerative disorders.[1–5] The ATP-dependent mitochondrial AAA+ metalloprotease (*m*-AAA) has 2 subunits: AFG3L2 and paraplegin. AFG3L2 is encoded by the gene *AFG3L2* and paraplegin is encoded by the gene, *SPG7*.[6] AFG3L2 subunits form homo-oligomeric complexes or hetero-oligomeric complexes with paraplegin, located in the mitochondrial inner membrane, essential for protein quality control.[6]

We report the first family with *AFG3L2*-related autosomal dominant optic atrophy (DOA) and intellectual disability with two members having the additional manifestation of dopamine responsive dystonia parkinsonism.

**Video 1.** Segment 1 demonstrates the dystonia and mild parkinsonism of III-3 at 7.5-years-old. There is gait dystonia, bradykinesia, shuffling when turning and asymmetric dystonic posturing of his upper limbs. Segment 2 shows III-3 on 4 mg/kg/day of levodopa. There is significant improvement in the gait but with some subtle arm posturing and left foot inversion still present whilst running with his unaffected sibling, Segment 3 shows III-3 at 13-years-old with more prominent parkinsonism. He has a bradykinetic, stooped gait. Segment 4 shows subtle gait dystonia with bilateral feet inversion and reduced right arm swing and subtle posturing in III-4 prior to levodopa.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13538

## Case Report

The proband is a 13-year-old boy with optic atrophy and moderate intellectual disability diagnosed at 5-years of age. At 7.5-years of age, he presented with progressive limb dystonia, where symptoms worsened towards the end of the day when he would require assistance for mobilizing. He walked at an appropriate age, though always with in-toeing and intermittent toe-walking. At 7.5 years of age, examination showed dystonic

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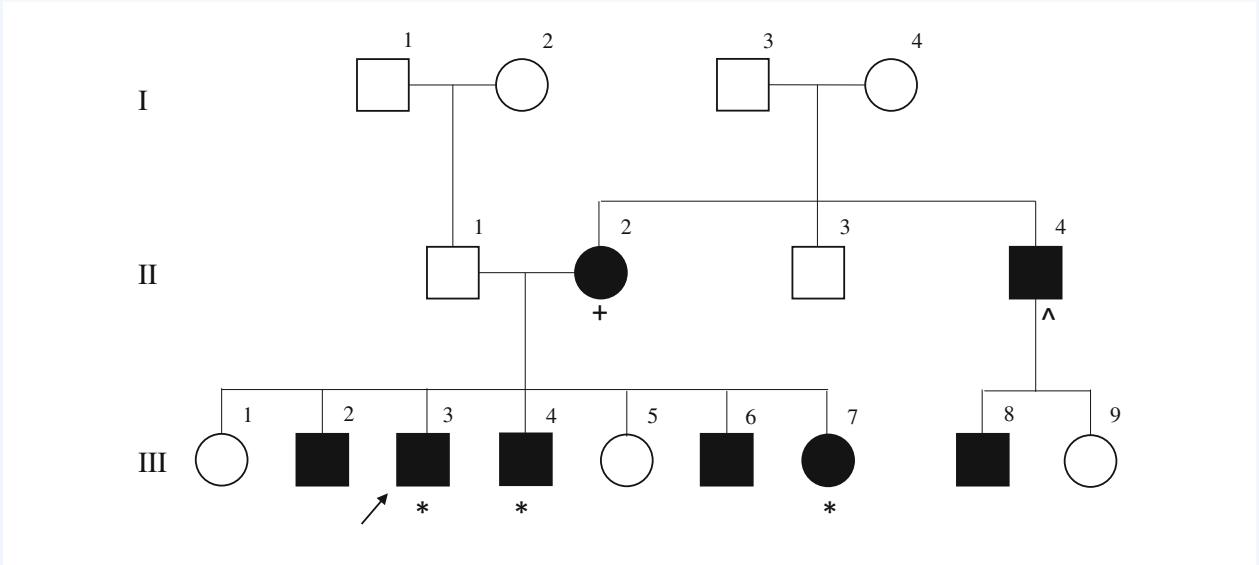


FIG. 1. Family pedigree. Black symptoms indicate individuals with the *AFG3L2* missense variant c.1064C>T; p.(Thr355Met). Arrow indicates proband. *indicates presence of dystonia. ^indicates presence of sensorineural hearing loss, complex ophthalmoplegia and spastic ataxia. +indicates presence of dysarthria, ataxia and sensorineural hearing loss.

lower limb posturing at rest, a dystonic gait with foot inversion, toe walking, arm flexion, and loss of arm swing, and parkinsonian features of paucity of facial expression, bradykinesia, shuffling when turning and postural instability (Video 1, segment 1).

MRI head showed isolated hypoplastic optic nerves. Cerebrospinal fluid analysis revealed low biopterin 14.96 nmol/L (25.00–45.00), homovanillic acid 0.259 μmol/L (0.345–0.716) and HVA:5-HIAA ratio 1.46 (2.30–4.00) with normal protein, glucose, lactate, and amino acids. These findings were consistent with a potential diagnosis of GTP cyclohydrolase deficiency, which was not supported by genetic analysis as outlined below. Serum alpha-fetoprotein, copper, caeruloplasmin, uric acid and thyroid function testing and urine metabolic screen were normal. Chromosome microarray was normal. Next generation sequencing in 2016 using a 130-gene movement disorder panel (TruSight One panel [FC-141-1007] on an Illumina NextSeq550) did not identify any pathogenic or likely pathogenic variants, including full coverage of all known disorders of monoamine metabolism.

Levodopa trial at 4 mg/kg/day resulted in significant, but incomplete improvement in dystonia (Video 1, segment 2) enabling maintenance of independent ambulation throughout the day. However, his dystonia gradually worsened with escalating levodopa requirements. At recent review at 13-year-old on levodopa 12.5 mg/kg/day, the patient had more prominent

**TABLE 1** *Clinical details of family members carrying the* AFG3L2 *variant*

| Pedigree number | Sex | Age (years) | Optic atrophy | Cognition | Additional manifestations |
|---|---|---|---|---|---|
| II-2 | Female | 39 | Yes | Learning disability | Sensorineural hearing loss<br>Dysarthric speech (cerebellar)<br>Gait ataxia (cerebellar) |
| II-4 | Male | 41 | Yes | Learning difficulties | Sensorineural hearing loss<br>Complex ophthalmoplegia<br>Spastic ataxia<br>Right ankle deformity |
| III-2 | Male | 17 | Yes | Mild intellectual disability | Nil |
| III-3 | Male | 13 | Yes | Moderate intellectual disability | Dopa responsive dystonia<br>Parkinsonism |
| III-4 | Male | 12 | Yes | Moderate intellectual disability | Dopa responsive dystonia |
| III-6 | Male | 7 | Yes | Global developmental delay | Nil |
| III-7 | Female | 5 | Pending review | Pending review | Mild dystonia |
| III-8 | Male | 13 | Yes | Moderate intellectual disability | Nil |

parkinsonism with a stooped posture and difficulty initiating movements (Video 1, segment 3).

Whole genome sequencing conducted as part of Economic and Psychosocial Impacts of Caring for Families Affected by Intellectual Disability study, ethics reference no: HREC/16/HNE/309, identified a heterozygous pathogenic missense variant in *AFG3L2* (NM_006796.2:c.1064C>T; p.(Thr355Met)), previously reported in a family with DOA and hyperkinetic movements, ataxia and dystonia.[1] The variant was absent from the gnomAD database and classified as pathogenic (ACMG with modifications; PP1_strong, PM2, PS4_supporting, PM1_supporting, PP3).[7]

Several family members had optic atrophy and variable intellectual disability (Fig. 1): proband (III-3), mother (II-2), three brothers (III-2, III-4, III-6), maternal cousin (III-8) and maternal uncle (II-4). Dystonia emerged in III-4 at 11-years of age (Video 1, segment 4), partially responsive to 3 mg/kg/day levodopa. III-7 had mild limb dystonia when running at 5-years of age but no optic atrophy or intellectual disability and remains under review. II-2 and II-4 had sensorineural hearing loss and ataxia with ophthalmoplegia only seen in II-4. The *AFG3L2* variant segregated to affected family members and was absent in II-1, III-1, III-5 and III-9 (Fig. 1). Clinical details of individuals with the *AFG3L2* variant are shown in Table 1 and Video 2.

# Discussion

Previously, heterozygous variants in *AFG3L2* were described in DOA and autosomal dominant spinocerebellar atrophy type 28 (SCA28), while homozygous or compound heterozygous variants were described in distinct neurodegenerative disorders, including spastic ataxia type 5 (SPAX5).[1–5] SCA28 manifests as adult-onset, slowly progressive cerebellar ataxia and SPAX5 has a severe phenotype of early-onset spasticity, cerebellar ataxia, oculomotor apraxia and progressive myoclonic epilepsy with basal ganglia and cerebellar abnormalities on brain MRI.[2,5] DOA associated with *AFG3L2* variants was described in 12 families, with some individuals exhibiting additional phenotypic features of intellectual disability, sensorineural deafness, spasticity, cerebellar signs, dystonia, myoclonus or chorea.[1] This included an individual with the same mutation as this report (p.T355M) and an overlapping phenotype but no details on levodopa response. AFG3L2 interacts with *OPA1*, which encodes a mitochondrial GTPase responsible for the fusion of the inner mitochondrial membrane, and disease-causing variants in *OPA1* are responsible for 75% of cases of autosomal dominant DOA.[8]

Many monogenic disorders of dopamine biosynthesis, such as GTP cyclohydrolase 1 deficiency remain stable in severity and levodopa response, while levodopa responsiveness can also be noted in otherwise progressive disorders, like some cases of ataxia telangiectasia and neuronal intranuclear inclusion disease.[9] Progressive dystonia has been reported in *AFG3L2*-related disorders, but levodopa responsive dystonia had not been previously reported. However, a 25-year-old female with heterozygous variants in both *AFG3L2* and *SPG7* (*AFG3L2*: p.R468C and *SPG7*:p.Glu127SerfsTer2) was described with progressive manifestations of optic atrophy, cognitive impairment, spastic ataxia and levodopa responsive parkinsonism.[10] The *AFG3L2* variant in this individual had been reported in DOA with mild intellectual disability suggesting concurrent AFG3L2 and paraplegin defects likely cause a distinct defect resulting in a complex, neurodegenerative phenotype. Our proband did not have variants in *SPG7* or *OPA1*.

It has not been explicitly described how dysfunction of the AFG3L2 subunit results in altered neurotransmitter levels in the central nervous system and dopamine responsiveness of the subsequent movement disorder. We postulate that this effect may be mediated through two possible pathways. The first possible mechanism is by the dysregulation of $Ca^{2+}$ homeostasis, as mitochondria play a crucial role in modulation of neuronal cell $Ca^{2+}$ levels, which can result in altered neurotransmitter release.[11] Secondly, Magri et al[10] demonstrated abnormal dopaminergic uptake in the basal ganglia on single photon emission computed tomography (SPECT)/dopamine transporter (DaT) scan in their proband with concurrent *AFG3L2* and *SPG7* variants. Additionally, Baderna et al[8] showed in functional studies that a variant in *AFG3L2* close to the AAA domain of the protein (as in our family) resulted in destabilization of the long isoforms of OPA1 leading to mitochondrial fragmentation. Finally, variants in the *OPA1* gene have been causative for genetic forms of Parkinson's disease with functional studies showing the mitochondrial dysfunction associated with this results in a significant loss of dopaminergic synapses.[12] Whilst this is still postulation, the relationship between some *AFG3L2* variants and OPA1 dysfunction may be a factor in the dopamine responsive nature demonstrated in our family.

To our knowledge, our index case is the first described patient with *AFG3L2*-related, progressive levodopa responsive dystonia parkinsonism in a family with *AFG3L2*-related DOA, intellectual disability, and additional neurological manifestations. We propose that in addition to optic atrophy, dystonia, with or without parkinsonism, may be a prominent manifestation of *AFG3L2*-related disease and a trial of levodopa therapy is warranted.

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# Author Roles

1. Research project: A. Conception, B. Organization, C. Execution
2. Manuscript preparation: A Writing of the first draft, B. Review and Critique

WW: 1A, 1B, 1C, 2A, 2B.
CT: 1A, 1C, 2B.
RCD: 1A, 2B.
TR: 1C, 2B.

MF: 1C, 2B.
EP: 1C, 2B.
EMM: 1C, 2B.
KRK: 1B, 1C, 2B.
SSM: 1A, 1B, 1C, 2B.

# Disclosures

**Ethical Compliance Statement:** The use of diagnostic and clinical information of patients in this study complied with the requirements of the clinical ethics committee of the Children's Hospital at Westmead. Verbal and written informed consent for use of information and videos was gained from the patients (when adult consent was possible) or the parents of the patients for those under the age of 14 years of age. All authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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# Supporting Information

Supporting information may be found in the online version of this article.

**Table S1** Characteristics of individuals reported with AFG3L2 variants with manifestations of dystonia or parkinsonism


**Video 2.** Full video from the 2021 Video Challenge discussion of this case.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13538