Adult Cerebellar Ataxia, Axonal Neuropathy, and Sensory Impairments Caused by Biallelic SCO2 Variants

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Neurol Genet 2021;7:e630. doi:10.1212/NXG.0000000000000630

SCO2 encodes a 266-amino-acid metallochaperone involved in copper supply for the assembly of cytochrome c oxidase or complex IV (CIV). CIV is the terminal enzyme of the energy-transducing respiratory chain that transfers electrons from reduced cytochrome c to oxygen via 3 copper ions.1 SCO2 pathogenic variants were first identified in children with hypertrophic cardiomyopathy, often associated with developmental delay and lactic acidosis2 (Figure, A). SCO2 variants were then reported in children with Leigh syndrome3 and early-onset axonal neuropathy,4 possibly associated with cerebellar ataxia5 (Figure, A). Here, we report heterozygous missense SCO2 variants in a 48-year-old patient presenting with a complex neurologic and sensory phenotype comprising cerebellar ataxia, sensory neuronopathy, deafness, pigmentary retinopathy, and cataract.

Case Presentation

Our patient’s family history was unremarkable except for hearing loss in his father in his third decade. At age 40 years, our patient was diagnosed with left hearing loss. At age 41 years, he developed slowly progressive gait abnormalities. At age 45 years, he reported vision impairment—score of 12/40 on the Scale for the Assessment and Rating of Ataxia—, areflexia, and a positive Romberg sign. Brain MRI showed bilateral supratentorial white matter abnormalities and cortical atrophy (eFigures 1, links.lww.com/NXG/A477). Nerve conduction studies revealed a severe bilateral axonal sensitive neuropathy of the 4 limbs. Audiometry showed bilateral perceptive hypoacusis.

Our patient had normal 20/20 visual acuity, but slit lamp examination demonstrated atypical bilateral lens inclusions with opacities. Fundus examination appeared grossly normal, but autofluorescence of the fundus revealed bilateral hyper-autofluorescence of the posterior pole and a patchy area of peripheral hyper fluorescence in the left eye. High-definition optical coherence tomography (OCT) disclosed bilateral hyper reflectivity of the retro-foveal region, located just below the ellipsoid line, with heterogeneity of the photoreceptor line. The electroretinogram revealed alteration of retinal electrogensis in scotopic conditions consistent with the alterations observed on OCT (Figure, B).

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Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by Pitié-Salpêtrière Hospital.

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CK enzymes were mildly but constantly elevated (range 320–376 U/L, N = 25–195 U/L). Metabolic investigations were normal, as well as molecular analyses of ATXN 1, 2, 3, 6, 7, and 17, FXN, and NOP56. Muscle biopsy showed a few fibers with lipid overload (i.e., lipid droplets) and a few COX negative or pale fibers. Spectrophotometric determination of mitochondrial respiratory chain enzyme activities as a ratio to citrate synthase activity showed isolated decreased activities of CIV in muscle and fibroblasts (Table).

We then analyzed our patient’s leukocyte genomic DNA, after informed consent was obtained, using a next-generation sequencing panel (Roche NibelGen, Madison, WI), comprising the entire coding region and exon-intron junctions of 244 genes associated with mitochondrial diseases, and identified 2
heterozygous missense variants in SCO2 (NM_005138.3: c.[179G>A];[577G>A]) (Figure, A and eFigure 2, links.lww.com/NXG/A478): (1) a variant of unknown significance—ACMG grading (PM2, PM3, PP2, and BP4)—, c.179G>A p.(Arg60Gln), which modifies a conserved amino acid of the N-terminal domain and predicted as possibly pathogenic by Polyphen; and (2) the c.577G>A p.(Gly193Ser) variant, reported as pathogenic and associated with infantile cardiocencephalopathy. Each parent was heterozygous for a SCO2 variant. Blue native polyacrylamide gel electrophoresis on the patient’s fibroblasts showed an almost complete absence of the CIV band, confirming isolated CIV deficiency (Figure, C). Given the discrepancy between our patient’s phenotype and all pediatric patients reported so far with SCO2 deficiency, the patient and his parents underwent whole-genome sequencing. These independent analyses retrieved both SCO2 variants, but no other known pathogenic variants associated with cerebellar ataxia, peripheral neuropathy, hearing loss, or retinopathy.

### Discussion

We present an adult-onset form of CIV deficiency related to bilateral SCO2 variants manifesting with a slowly progressive cerebellar ataxia after age 40 years, an axonal sensitive polyneuropathy, and bilateral sensory deficits with deafness, pigmentary retinopathy, and cataract.

Most of the damages caused by CIV deficiency are early and fatal, as reported so far with SCO2 pathogenic variants with pediatric and rapidly progressive disorders except for 2 children with a slower neurologic course. A possible explanation for the more moderate phenotype of our patient relates to his genotype as he carries 2 missense variants, only 1 of which is located in the thioredoxin domain. Instead, pediatric cases carry either 2 missense variants in the thioredoxin domain or the association of one missense variant in the thioredoxin domain with a truncating variant (Figure, A). Unlike pediatric cases, our patient displayed both hearing and vision impairments with pigmentary retinopathy. Of interest, heterozygous SCO2 variants were also identified in dominant forms of severe myopia.

### Acknowledgment

The authors thank Sandrine Filaut et Laura Legrand for their help with NGS.

### Study Funding

No targeted funding reported.

### Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/NG for full disclosures.

### References

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Neurol Genet 2021;7;
DOI 10.1212/NXG.00000000000000630

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