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CLINICAL REPORT

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Recessive *ACO2* variants as a cause of isolated ophthalmologic phenotypes

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Abstract

The mitochondrial aconitase gene (*ACO2*) encodes an enzyme that catalyzes the conversion of citrate to isocitrate in the tricarboxylic acid cycle. Biallelic variants in *ACO2* are purported to cause two distinct disorders: infantile cerebellar-retinal degeneration (ICRD) which is characterized by CNS abnormalities, neurodevelopmental phenotypes, optic atrophy and retinal degeneration; and optic atrophy 9 (OPA9), characterized by isolated ophthalmologic phenotypes including optic atrophy and low vision. However, some doubt remains as to whether biallelic *ACO2* variants can cause isolated ophthalmologic phenotypes. A review of the literature revealed five individuals from three families who carry biallelic *ACO2* variants whose phenotypes are consistent with OPA9. Here, we describe a brother and sister with OPA9 who are compound heterozygous for novel missense variants in *ACO2*; c.[487G>T];[1894G>A], p.[(Val163Leu)];[(Val632Met)]. A review of pathogenic *ACO2* variants revealed that those associated with OPA9 are distinct from those associated with ICRD. Missense variants associated with either OPA9 or ICRD do not cluster in distinct ACO2 domains, making it difficult to predict the severity of a variant based on position alone. We conclude that biallelic variants in *ACO2* can cause the milder OPA9 phenotype, and that the OPA9-related *ACO2* variants identified to date are distinct from those that cause ICRD.

KEYWORDS

ACO2, ICRD, infantile cerebellar-retinal degeneration, OPA9, optic atrophy, optic atrophy 9

1 | INTRODUCTION

The second step of the tricarboxylic acid cycle, the conversion of citrate to isocitrate, is catalyzed by aconitase (Martius, 1937). Mitochondrial aconitase is encoded by the nuclear gene *ACO2* (OMIM *100850) (Mirel et al., 1998). Autosomal recessive variants in *ACO2* have been purported to cause two distinct disorders; infantile cerebellar-retinal degeneration (ICRD; OMIM #614599) and optic atrophy 9 (OPA9; OMIM #616289) (Metodiev et al., 2014; Spiegel et al., 2012).

ICRD is characterized by progressive degeneration of the cerebrum, cerebellum and retina starting from infancy that results in a failure to meet normal developmental milestones, psychomotor retardation and vision loss. Symptoms can also include optic atrophy, retinal dystrophy, cerebellar ataxia, seizure disorders, strabismus, axial hypotonia, and athetosis. A few cases of spastic paraplegia have been described in patients that have many of the previously listed symptoms with or without optic atrophy (Bouwkamp et al., 2018; Marelli et al., 2018; Sharkia et al., 2019). To date, 26 individuals from 15 different families with ICRD have been published (Abela et al., 2017; Bouwkamp et al., 2018; Marelli et al., 2018; Metodiev et al., 2014; Sadat et al., 2016; Sharkia et al., 2019; Spiegel et al., 2012; Srivastava et al., 2017).

In contrast, a review of the literature revealed only five individuals from three families who carry biallelic *ACO2* variants and whose phenotypes are consistent with OPA9 (Chen et al., 2019; Kelman et al., 2018; Metodiev et al., 2014). Unlike ICRD, OPA9 is characterized only by ophthalmologic phenotypes including optic atrophy, low vision, dyschromatopsia, and exotropia. All previously described individuals with OPA9 have been compound heterozygous for a c.220C>G, p.(Leu74Val) [NM_001098.3] allele and a second variant. Here, we describe two previously unreported siblings who are compound heterozygous for novel, pathogenic missense variants in *ACO2* who have phenotypes consistent with OPA9. These cases provide further evidence that biallelic variants in *ACO2* can cause the milder OPA9 phenotype.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

Subjects 1 and 2 were enrolled in a research study approved by the institutional review board of Baylor College of Medicine. The procedures followed were in accordance with the ethical standards of the institution's committee on human research and were in keeping with international standards.

2.2 | Copy number variant analysis and exome sequencing

Array-based copy number variant (CNV) analysis and exome sequencing studies were performed on a clinical basis at Baylor Genetics (https://www.baylorgenetics.com/) (Wiszniewska et al., 2014; Yang et al., 2013, 2014). The following quality control metrics for exome sequencing are generally achieved: >70% of reads aligned to target with >95% of targeted bases covered at >20X, >85% of targeted bases covered at >40X, and mean coverage of targeted bases >100X.

3 | RESULTS

3.1 | Clinical descriptions

3.1.1 | Subject 1

Subject 1 is a 16-year-old male of Hispanic ancestry who was born to non-consanguineous parents. Pregnancy was complicated only by a vaginal infection treated with antibiotics for 5 days. He was born a 36 weeks gestation via spontaneous vaginal delivery. His gross motor development was normal—sitting at 6 months and walking at 12 months. With the exception of being late to speak at 18 months of age, he did not have development delay, intellectual disability, neurological problems or behavioral issues.

Over time, he was noted to have low vision and stable, bilateral optic nerve pallor (Figure 1a), intermittent exotropia, and myopia, for which he was prescribed corrective lenses. A brain MRI obtained at 6 years of age showed diminutive bilateral optic pathways with no evidence of midline defects. On exam, he was noted to have normal sized optic nerve heads with bilateral optic nerve pallor. A brain MRI performed at 10 years of age continued to show stable, severe reduction in the optic tracts and the optic chiasm. At 14 years of age, he had strabismus surgery to correct his intermittent exotropia.

Other medical issues included recurrent tonsillitis and epistaxis, a pituitary pars intermedia cyst and asymmetric kidney size with normal function. At 16 years, 5 months of age his height was 172.2 cm (38^{th} centile), his weight was 63.1 kg (51^{st} centile), and his head circumference was 56 cm (62^{nd} centile).

3.1.2 | Subject 2

Subject 2, the full-sister of Subject 1, is 14 years old. Her mother had an uncomplicated pregnancy and avoided teratogenic exposures. She was born at 36 weeks gestation via spontaneous vaginal delivery. Her developmental milestones were similar to her brother's, sitting at 7 months of age, walking at 12 months of age, and speaking her first words at 18 months of age. She had no other signs of development delay, intellectual disability, neurological problems or behavioral issues, and her current language ability is normal.

Over time, she was noted to have decreased vision and color vision, bilateral optic atrophy, astigmatism and myopia, exotropia, and amblyopia of her left eye. She has had surgery to remedy her exotropia, and she wears corrective lenses.

A brain MRI at 5 years old was reported to be normal, but an MRI at 7 years of age showed a mild reduction in the size of the optic nerves, chiasm, and optic tracts which was thought to also be present on the previous MRI. A renal ultrasound showed no abnormalities.

Her most recent anthropomorphic measurements, performed at 7 years, 9 months of age, were height 130.3 cm (74^{th} centile), weight 36.2 kg (96^{th} centile), and head circumference 53.5 cm (92^{nd} centile).

3.2 | Diagnostic and molecular studies

Subject 1 had a normal array-based copy number variant analysis. Subject 2 had an array-based copy number variant analysis that showed a loss on chromosome 20p12.1 (minimum deletion chr20:14,766,022–15,026,908, maximum deletion chr20:14,755,760–15,036,881; hg19) that is commonly seen in the general population (Database of Genomic Variants; http://dgv.tcag.ca/dgv/app/home), and was, therefore, felt to be non-contributory.

Exome sequencing performed on a clinical basis in both Subject 1 and Subject 2 revealed compound heterozygous variants in *ACO2*; a maternally-inherited c.1894G>A, p.(Val632Met) variant in *ACO2* and a non-maternally-inherited c.487G>T, p.(Val163Leu) variant (Table 1,

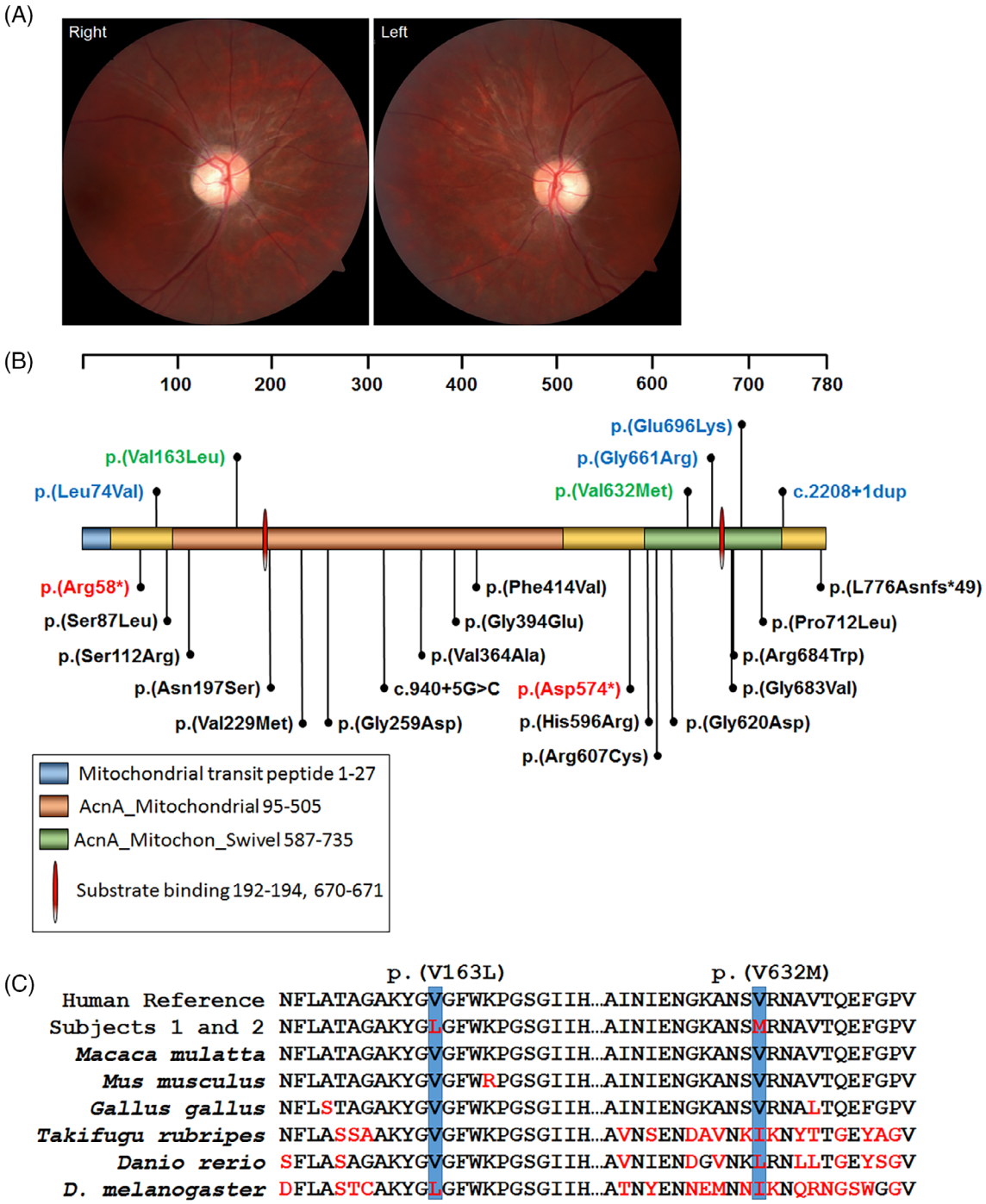

FIGURE 1 *ACO2* pathogenic variants and their effects. (a) Color fundus photos of Subject 1 demonstrate mild temporal pallor of the optic nerves bilaterally. (b) A schematic representation of ACO2 and its protein domains. The protein changes depicted above this representation are associated with OPA9 and include previously reported variants (blue) and the novel variants found in Subjects 1 and 2 (green). The protein changes depicted below the ACO2 protein have been associated with infantile cerebellar-retinal degeneration (ICRD) and include two stop-gain variants (red) that likely trigger nonsense-mediated mRNA decay, as well as missense, splice site, and frameshift variants (black). (c) The *ACO2* missense variants seen in Subjects 1 and 2 affect amino acids that are conserved in mammals [Color figure can be viewed at wileyonlinelibrary.com]

Figure 1b). All *ACO2* variants described in this report are based on transcript NM_001098.3. A DNA sample was not available from the father, however, it is most likely that the recurrent c.487G>T, p.(Val163Leu) variant was inherited from him. These variants alter amino acids that are conserved in mammals (Figure 1c) and have high Combined Annotation Dependent Depletion scores (CADD; https://cadd.gs.washington.edu/); 22.6 for c.487G>T, p.(Val163Leu) and 24.3 for c.1894G>A, p.(Val632Met).

TABLE 1 Clinical and molecular data from patients with OPA9-associated variants in *ACO2*

Study (patient identifier), age	*ACO2* variants [NM_001098.3] (paternal; maternal)	OA/optic disc pallor	Reduced visual acuity	Dyschromatopsia	Other ophthalmological phenotypes	MRI results	Development	Other medical problems; dysmorphic features
Metodiev et al. (2014) (P1), 41y	c. 1981G>A, p.(Gly661Arg); c. 220C>G, p.(Leu74Val)	+	+	+	Bilateral reduction in temporal and inferior RNFLs with preservation of nasal RNFLs	N/D	Normal	None; none
Metodiev et al. (2014) (P2), 36y	c. 1981G>A, p.(Gly661Arg); c. 220C>G, p.(Leu74Val)	+	+	+	Bilateral reduction in temporal and inferior RNFLs with preservation of nasal RNFLs	N/D	Normal	None; none
Kelman et al. (2018) (Sib.1), 7y	c.2208+1dup (likely paternal); c.220C>G, p.(Leu74Val)	+	+	+	Fine horizontal nystagmus, hypermetropia, P-VEP amplitudes at lower limit of normal, cystic spaces within inner nuclear layer	Bilateral atrophic optic nerves	Walked at 18 m, otherwise normal	Asthma; none
Kelman et al. (2018) (Sib. 2), 9y	c.2208+1dup (likely paternal); c.220C>G, p.(Leu74Val)	+	+	+	Hypermetropia, P-VEP amplitudes at lower limit of normal, significant thinning of RNFL, mostly temporally	N/D	Walked at 18 m, otherwise normal	Asthma; none
Chen et al. (2019) (P30), age of onset 5y	c.220C>G, p.(Leu74Val); c.2086G>A, p.(Glu696Lys)	+	+	N/D	N/D	Normal	Normal	N/D; N/D
This study (S1), 16y5m	c.487G>T, p.(Val163Leu) (likely paternal); c.1894G>A, p.(Val632Met)	+	+	N/D	Myopia, intermittent exotropia	Severe hypoplasia of the optic nerves, chiasm and optic tracts, pituitary pars intermedia cyst	First words at 18 m, otherwise normal	Asymmetric kidney size with normal function; none
This study (S2), 14y1m	c.487G>T, p.(Val163Leu) (likely paternal); c.1894G>A, p.(Val632Met)	+	+	+	Astigmatism, myopia, exotropia, amblyopia of left eye	Mild hypoplasia of the optic nerves, chiasm, and optic tracts	First words at 18 m, otherwise normal	None; none

Abbreviations: m, months; N/D, not determined/not reported; OA, Optic Atrophy; P, patient; P-VEP, Pattern Visual Evoked Potential; RNFL, Retinal Nerve Fiber Layer; S, Subject; Sib., Sibling; y, years.

In gnomAD (https://gnomad.broadinstitute.org/), the c.487G>T, p.(Val163Leu) variant is seen 31 times in the heterozygous state, with no homozygotes being identified. This allele is seen in 20/10,244 (0.2%) of Ashkenazi Jewish alleles, 5/34,930 (0.014%) of Latino alleles, 5/127,466 (0.004%) of non-Finnish European alleles and 1/7,096 (0.014%) of "other" alleles. A second allele, c.487G>C, that encodes for the same amino acid change, is reported in gnomAD in 1/24,472 (0.004%) of African alleles and in 6/127,466 (0.005%) non-Finnish European alleles. These variants were all in the heterozygous state. In contrast, the c.1894G>A, p.(Val632Met) is not seen in gnomAD.

Both Subject 1 and Subject 2 carried changes in other genes associated with autosomal recessive ophthalmologic disorders, but none were considered causative based on their inheritance pattern and/or the absence of a second variant in trans. These changes included a heterozygous c.724C>G, p.(Leu242Val) [NM_001098] variant in *CNNM4* (OMIM #607805; inheritance pattern not determined), and two, presumably paternal variants in *LCA5* (OMIM *611408); a c.511C>T, p.(Leu171Phe) [NM_181714] variant and a c.38A>G, p.(Glu13Gly) [NM_181714] variant in cis. Subject 2 also carried a heterozygous c.2189C>T, p.(Ala730Val) [NM_172364] variant in *CACNA2D4* (OMIM *608171) that was not seen in Subject 1.

4 | DISCUSSION

Pathogenic variants that affect mitochondrial proteins have been shown to cause genetic forms of optic atrophy that are inherited as autosomal dominant, mitochondrial, and autosomal recessive disorders. Optic atrophy 1 (OPA1; OMIM #165500) is a common form of autosomal dominant optic atrophy caused by pathogenic variants in *OPA1*, that encodes a mitochondrial dynamin-related GTP protein that plays a key role in mitochondrial fusion (Alexander et al., 2000; Cipolat, Martins de Brito, Dal Zilio, & Scorrano, 2004; Delettre et al., 2000; Kjer, Eiberg, Kjer, & Rosenberg, 1996; Yu-Wai-Man et al., 2010). Although the age of onset and level of vision loss associated with OPA1 varies widely among individuals, it usually presents as an insidious decrease in visual acuity starting between 4 and 6 years of age, and typically leads to moderate vision loss (Delettre-Cribaillet, Hamel, & Lenaers, 1993). Similarly, optic atrophy 5 (OPA5; OMIM #610708) is caused by autosomal dominant, pathogenic variants in *DNM1L*, that encodes a dynamine GTPase required for mitochondrial fusion (Barbet et al., 2005; Gerber et al., 2017; Smirnova, Griparic, Shurland, & van der Bliek, 2001). It is characterized by a slow decrease in visual acuity starting in the first to third decade of life. Leber optic atrophy (OMIM #535000), also referred to as Leber hereditary optic neuropathy (LHON), is caused by missense variants that affect a variety of mitochondrial gene-encoded proteins, and is characterized by bilateral, painless, subacute visual failure that typically develops during young adult life (Meyerson, Van Stavern, & McClelland, 2015; Yu-Wai-Man & Chinnery, 1993). The atrophic phase of LHON is characterized by optic atrophy and usually develops within 6 weeks of the onset of visual loss. The optic atrophy associated with optic atrophy 7 (OPA7; OMIM #612989) is variable in its onset and severity, and is caused by autosomal recessive variants in *TMEM126A* that encodes a mitochondrial inner membrane protein of unknown function (Hanein et al., 2009; Hanein et al., 2013).

We present two Hispanic full siblings with isolated ophthalmologic phenotypes that were noted in childhood and included optic atrophy with resulting low vision, dyschromatopsia, exotropia, amblyopia, astigmatism, and myopia. They both carry compound heterozygous missense variants, c.[487G>T];[1894G>A] [NM_001098.3], p.[(Val163Leu)];[(Val632Met)], in *ACO2*, the gene that encodes mitochondrial aconitase (Mirel et al., 1998). These variants alter amino acids that are conserved in mammals and have high CADD scores; 22.6 and 24.3, respectively. Sequence variants that result in the p.(Val163Leu) amino acid substitution are found at a low level (allele frequency ≤ 0.2%) in individuals from several populations catalogued in gnomAD. In contrast, the c.1894G>A, p.(Val632Met) is not seen in gnomAD.

A review of the literature revealed five other individuals who carry biallelic *ACO2* variants whose phenotypes are consistent with OPA9 (Table 1). All five of these individuals carried a c.220C>G, p.(Leu74Val) (CADD = 22.7) variant in trans with either a c.1981G>A, p.(Gly661Arg) missense variant (CADD = 29.9), a c.2208+1dup splice site variant, or a c.2086G>A, p.(Glu696Lys) missense variant (CADD = 33) (Chen et al., 2019; Kelman et al., 2018; Metodiev et al., 2014) (Figure 1b; Table 1). The c.220C>G, p.(Leu74Val) variant is seen frequently in gnomAD with a total allele frequency of 0.37% (1,055/282,256), and is most common among non-Finnish Europeans (839/128,790 alleles, 0.65%) with four homozygotes. The other changes are very rare, with the missense variants each being seen only once, and the splice variant not being identified in gnomAD. Taken together, these data suggest that biallelic variants in *ACO2* can cause the milder OPA9 phenotype.

The OPA9-associated *ACO2* alleles identified to date are distinct from those associated with ICRD (Figure 1b) that include loss-of-function variants, splice site variants, and missense variants with high CADD scores (Abela et al., 2017; Bouwkamp et al., 2018; Marelli et al., 2018; Metodiev et al., 2014; Sadat et al., 2016; Sharkia et al., 2019; Spiegel et al., 2012; Srivastava et al., 2017). Previously performed functional studies of *ACO2* variants suggest that alleles associated with OPA9 have greater residual ACO2 activity than those associated with ICRD (Bouwkamp et al., 2018; Marelli et al., 2018; Metodiev et al., 2014; Sadat et al., 2016; Sharkia et al., 2019; Spiegel et al., 2012).

Missense variants associated with either OPA9 or ICRD do not cluster in distinct ACO2 domains (Figure 1b), making it difficult to predict the severity of a variant based on position alone. This underscores the importance of describing the phenotypic consequences associated with individual *ACO2* variants and their combinations. It also suggests that in the absence of known associations and/or functional studies, physicians need to be cautious when providing prognostic information to families carrying *ACO2* variants.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

K.G.Y, V.R.S. and D.A.S. clinically evaluated the subjects, K.G.Y. provided fundus photographs, M.S.A and S.R.L consented the subjects for research, S.G. and D.A.S. analyzed the data, D.A.S. prepared the figures, S.G. performed the literature review and wrote the initial draft of the manuscript, D.A.S. provided general oversight, and S.G., M.S.A, S.R.L., K.G.Y, V.R.S. and D.A.S. reviewed, edited and approved the manuscript.

DATA AVAILABILITY STATEMENT

The *ACO2* variants seen in Subjects 1 and 2 have been submitted to the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/).

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