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Title

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Permalink

<https://escholarship.org/uc/item/2748x5x5>

Journal

Ophthalmic Genetics, 39(1)

ISSN

1381-6810

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Publication Date

2018-01-02

DOI

10.1080/13816810.2017.1350723

Peer reviewed



Published in final edited form as:

Ophthalmic Genet. 2018 ; 39(1): 99–102. doi:10.1080/13816810.2017.1350723.

Retinopathy and optic atrophy: expanding the phenotypic spectrum of pathogenic variants in *AARS2* gene

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Abstract

Background—Optic atrophy may be the sequela of optic nerve injury due to any insult, including isolated and syndromic genetic diseases. Alanyl-tRNA synthetase 2 (*AARS2*) pathogenic variants have been reported to cause leukodystrophy with ovarian failure, and cardiomyopathy (#615889) as well as combined oxidative phosphorylation deficiency-8 (#614096). We report a young child who presented with decreased vision due to optic atrophy and was found to harbor missense variants in the *AARS2* gene expanding the phenotypic expression of *AARS2* gene.

Materials and Methods—Single observational case report with genetic testing, laboratory testing, neurologic and ophthalmic clinical examinations, and neuroimaging performed at a tertiary academic medical center

Results—An 18-month old Korean boy was noted to have a progressive decline in visual function. Physical exam revealed bilateral optic atrophy, peripheral retinal bone spicule pigmentation, and absent patellar reflexes. Electromyography was consistent with a demyelinating polyneuropathy. Magnetic resonance imaging (MRI) of the brain and spine showed cerebellar and supratentorial white matter multifocal changes with areas of restricted diffusion, and dorsal column signal abnormalities. Whole exome sequencing revealed two missense variants in the *AARS2* gene [c.1519G>C (p.V507L) and c.2165G>A (p.R722Q)], found to be *in trans* on parental testing.

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Declaration of Interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Conclusions—Missense variants in the *AARS2* gene are the likely cause of the retinopathy and optic atrophy in this patient. This finding expands the phenotypic spectrum of *AARS2* gene.

Keywords

optic atrophy; retinopathy; leukodystrophy; *AARS2*

Background

Optic atrophy (OA) may be the sequela of optic nerve injury due to any insult including isolated and syndromic genetic diseases. Mitochondrial disease can lead to optic atrophy and/or retinopathy in multiple genetic conditions, including Leber Hereditary Optic Neuropathy (LHON), neuropathy, ataxia, and retinitis pigmentosa (NARP) and Kearns-Sayre syndrome.^{1,2} Pathogenic variants in the genes responsible for the mitochondrial respiratory chain have been implicated in multiple neurometabolic diseases, with the majority of mitochondrial diseases arising from pathogenic variants in nuclear genes rather than mitochondrial DNA.³ Whole exome sequencing has been proposed as a way to identify defective genes which influence mitochondrial function, and lead to mitochondrial diseases.³

The mitochondrial aminoacyl transfer RNA (tRNA) synthetases have been identified as important players in the development of mitochondrial disease, and the alanyl-tRNA synthetase 2 gene (*AARS2*) has been shown to cause progressive leukoencephalopathy and ovarian failure, previously called “ovarioleukodystrophy.”⁴⁻⁵ *AARS2* pathogenic variants have also been found in patients with axonal spheroids and pigmented glia (ALSP).⁶ Beyond the leukoencephalopathies, *AARS2* pathogenic variants have also been demonstrated in cases of lethal mitochondrial cardiomyopathy.^{3,7,8} Here we report that missense variants in *AARS2* can also present with retinopathy and optic atrophy in a young child, in addition to previous associations with progressive leukoencephalopathy, ovarian failure, and lethal cardiomyopathy.

Case Report

We report a Korean boy with an uncomplicated birth history other than mild jaundice, who presented initially with decreased vision at 18 months of age. His parents noted progressive difficulties with vision, and at the age of 2.5 years was evaluated by a pediatric ophthalmologist. He underwent a detailed ophthalmologic evaluation which revealed visual acuities of central, steady, and maintained in both eyes, without a relative afferent pupillary defect; however, he was noted to have bilateral optic atrophy prompting an MRI of the brain, orbits, and cervical spinal cord with and without gadolinium. This revealed bilateral optic nerve atrophy with cerebellar and supratentorial multifocal white matter changes with restricted diffusion. Dorsal column signal abnormalities were present as well, and the overall appearance was thought to be suggestive of a metabolic disease. He underwent extensive genetic work up for optic neuropathies and leukodystrophies including urine organic acids, plasma amino acids, urine acylglycines, very long chain fatty acids, biotinidase enzyme analysis, pyruvate, and acylcarnitine, all of which were unremarkable. Plasma lactate was elevated (31.7 mg/dl) and carnitine status was suboptimal. A lumbar puncture for routine

studies and oligoclonal bands was performed which was unremarkable. Laboratory and genetic investigations including mitochondrial testing for Leber's hereditary optic neuropathy, dominant optic atrophy (*OPA1* sequencing and deletion/duplication analysis), congenital disorders of glycosylation, lysosomal storage disease enzyme screen, leukodystrophy gene panel, thyroid studies, fibroblast studies for metachromatic leukodystrophy, and neuronal ceroid lipofuscinosis studies were all negative or normal.

A repeat MRI of the brain performed at three years of age revealed mild interval progression of disease with increasing signal abnormalities in the left frontal and parietal periventricular white matter. [Figure 1]

A trial of intravenous high dose solumedrol was given at an outside facility for possible demyelinating disease. There was no improvement in vision or MRI imaging.

Evaluation by a pediatric neuro-ophthalmologist revealed best-corrected distance visual acuities of 5/125 OD and 5/150 OS, bilateral optic nerve pallor as well as pigmentary abnormalities and bone spicules in the periphery. [Figure 2] An ERG performed at three years of age revealed no discernable waveform in either photopic or scotopic conditions indicating widespread retinal dysfunction.

On follow up evaluation by a pediatric neurologist, he was noted to have absent patellar reflexes with normal strength and sensation. An EMG revealed findings consistent with a motor predominant demyelinating polyneuropathy. A muscle biopsy was considered, but determined to be too invasive and nonspecific due to the lack of ragged red fibers and respiratory enzyme chain deficiencies seen in other patients with *AARS2* related disease.

A subsequent contrast-enhanced MRI of the brain at four years of age showed new lesions in the left anterior frontal white matter, pericallosal white matter, and in the middle cerebellar peduncle. [Figure 3]

Whole exome sequencing was performed, which revealed two missense variants [c1519G>C (p.V507L) and c.2165G>A (p.R722Q)] identified in the *AARS2* gene. These variations were found to be in *trans* on parental testing. The patient was also found to be a carrier for variants in the *ARSA* and *SLC25A20* genes. There were no copy number variations detected in these genes. The allele frequencies for the *AARS2* variants in ExAC database were as follows. The c1519G>C (p.V507L) was 0.00003296, with a frequency of less than 1 in 10,000 in all populations, and 0.0003467 in East Asian population. The c.2165G>A (p.R722Q) was 0.00007446 with frequency of less than 1 in 10,000 in all populations and 0.0002315 in East Asian population. Functional studies were recommended, but were not performed due to cost. Lactate was repeated at five years of age and was found to be normal.

Conclusions

The *AARS2* gene has been implicated in progressive leukoencephalopathy with ovarian failure, lethal cardiomyopathy, and adult-onset leukoencephalopathy with axonal spheroids and pigmented glia in previous investigations.^{3,5-8} In this report we describe a patient with optic atrophy, retinopathy, leukoencephalopathy, and demyelinating polyneuropathy in

which missense variants in *AARS2* are the most likely cause for his clinical findings. Although these missense variants have not previously been published, given that they are in *trans* with allele frequencies of less than 1 in 10,000 and the MRI findings that are suggestive of *AARS2* associated leukoencephalopathy changes, we propose that these are the most likely cause for the clinical presentation in our patient.

It is difficult in this case to determine if the optic atrophy is primary to the patient's underlying condition, or if it is secondary to the widespread retinal dysfunction. Previous reports of *AARS2* related mitochondrial diseases have not reported retinopathy or optic atrophy as phenotypic expressions of these genetic pathogenic variants. One report included a patient who suffered a visual disturbance, which was not further characterized by the authors.⁶ It is possible that previous reports simply have not focused on optic atrophy or retinopathy as a manifestation of *AARS2* pathogenic variants. The only reported muscle enzyme finding in *AARS2* is a decrease in cytochrome c oxidase activity.⁴ In the literature, functional yeast studies were more confirmatory but were cost prohibitive in our patient.⁴

Interestingly recently described novel *YARS* variants have demonstrated in similar wide spectrum findings including hypotonia, failure to thrive, developmental delay, thin corpus callosum, frontal atrophy, and elevated plasma triglycerides.⁹ *YARS* autosomal dominant variants are typically associated with Charcot-Marie-Tooth disease. These findings suggest that variants in the aminoacyl-transferRNA synthetases may have a wide spectrum of clinical presentation.

Functional studies in the future or additional cases with similar genotype and phenotype would reinforce the pathogenicity of these variants as the likely cause of the retinopathy and optic atrophy in our patient. This patient expands the phenotypic spectrum of *AARS2* gene pathogenic variants.

Acknowledgments

This study was supported in part by Research to Prevent Blindness, Inc., New York, New York (an unrestricted grant to the Department of Ophthalmology, Emory University); and the National Eye Institute, National Institutes of Health, Bethesda, Maryland (core grant no.: P30-EY006360 [Department of Ophthalmology, Emory University]).

References

1. Newman NJ. Hereditary optic neuropathies. In: Miller NR, Newman NJ, Biousse V. , et al., editors Walsh and Hoyt's Clinical Neuro-Ophthalmology. 6th. Vol. 1. Baltimore, MD: Williams & Wilkins; 2005. 465–501.
2. Chinnery PF. Mitochondrial disorders overview. In: Pagon RA, Adam MP, Ardinger HH. , et al., editors GeneReviews. Seattle: University of Washington, Seattle; 2000. (updated 2014)
3. Taylor RW, Pyle A, Griffin H, et al. Use of whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiencies. *JAMA*. 2014; 312(1):68–77. [PubMed: 25058219]
4. Dallabona C, Diodato D, Kevelam SH, et al. Novel (ovario) leukodystrophy related to *AARS2* mutations. *Neurology*. 2014; 82:2063–2071. [PubMed: 24808023]
5. Hamtani M, Jingami N, Tsurusaki Y, et al. The first Japanese case of leukodystrophy with ovarian failure arising from novel compound heterozygous *AARS2* mutations. *J Hum Genet*. 2016; 61(10): 899–902. [PubMed: 27251004]

6. Lynch DS, Zhang WJ, Lakshmanan R, et al. Analysis of mutations in *AARS2* in a series of *CSF1R*-negative patients with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia. *JAMA Neurol.* 2016; 73(12):1433–1439. [PubMed: 27749956]
7. Mazurova S, Magner M, Kucerova-Vidrova V, et al. Thymidine kinase 2 and alanyl-tRNA synthetase 2 deficiencies cause lethal mitochondrial cardiomyopathy: case reports and review of the literature [Published online November 14, 2016]. *Cardiol Young.*
8. Götz A, Tynnismaa H, Euro L, et al. Exome sequencing identifies mitochondrial alanyl-tRNA synthetase mutations in infantile mitochondrial cardiomyopathy. *Am J Hum Genet.* 2011; 88(5): 635–642. [PubMed: 21549344]
9. Nowaczyk MJ, Huang L, Tarnopolsky M, et al. A novel multisystem disease associated with recessive mutations in the tyrosyl-tRNA synthetase (*YARS*) gene. *Am J Med Genet A.* 2017; 173:126–34. [PubMed: 27633801]

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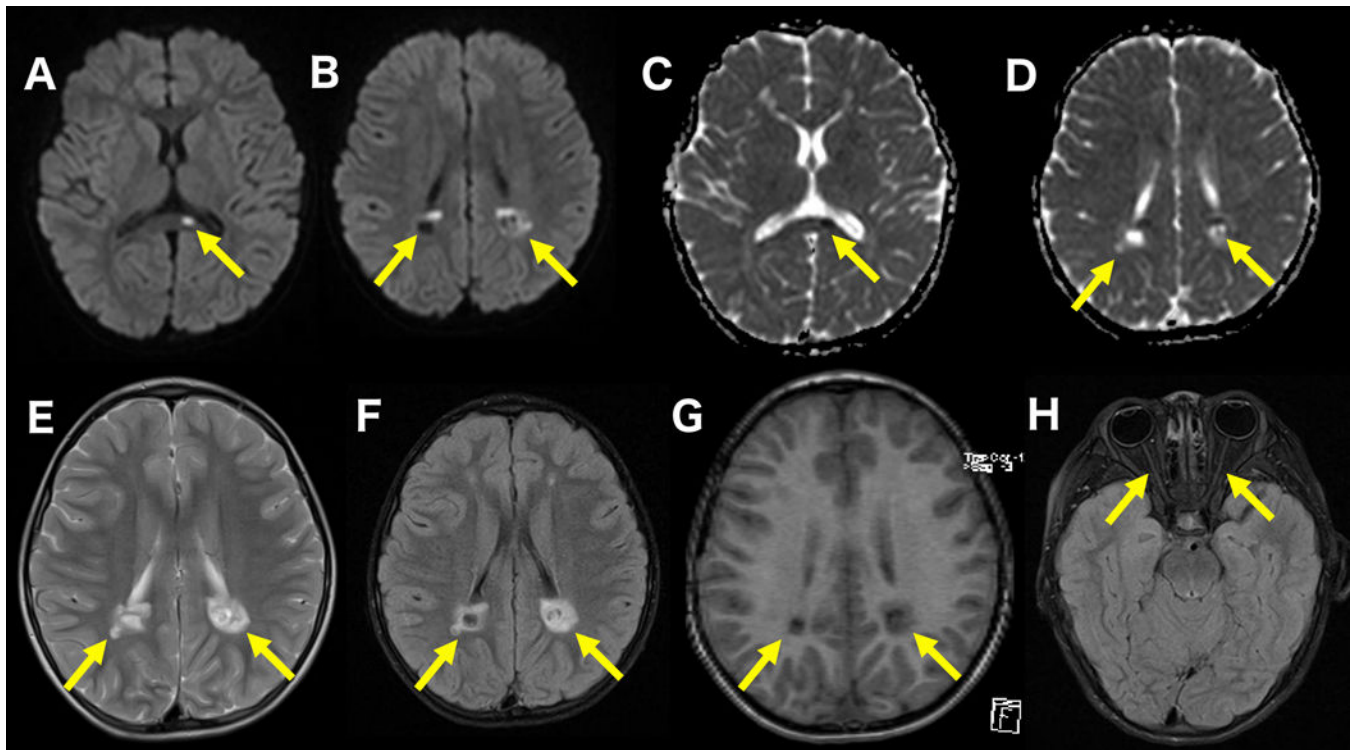


Figure 1.

MRI of the brain at age three: (A) Axial DWI image shows ovoid lesion with restricted diffusion in the callosal splenium (arrow). (B) Axial DWI shows additional lesions with restricted diffusion in the bilateral posterior periventricular white matter. (C) Axial ADC map of “A” confirming restricted diffusion (arrow). (D) Axial ADC map of “B” showing acute and chronic lesions superimposed. (E) Axial T2- weighted image of periventricular lesions. (F) Axial T2-FLAIR image of periventricular lesions showing central cavitation. (G) Axial T1-weighted image of periventricular lesions shows central cavitation indicating chronicity. (H) Axial T2-FLAIR image shows bilateral optic nerve atrophy or hypoplasia without abnormal signal intensity.

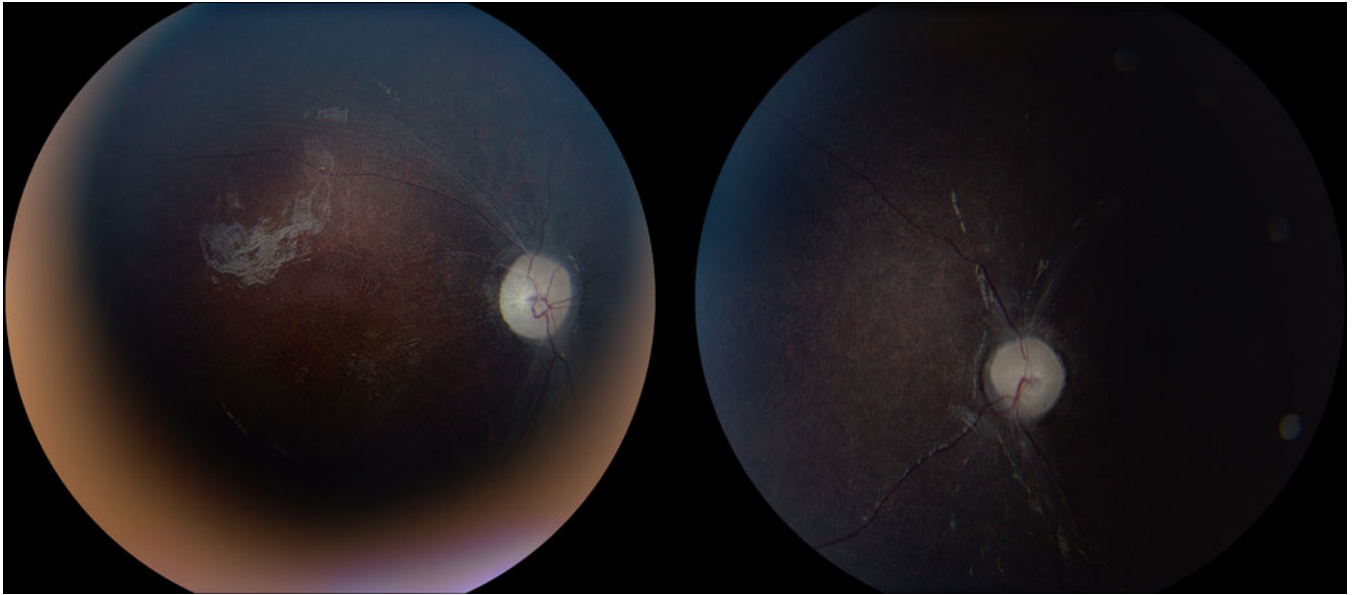


Figure 2. Fundus photographs depicting bilateral optic atrophy from bilateral optic neuropathies as well as peripheral retinal pigmentary changes and bone spicules.

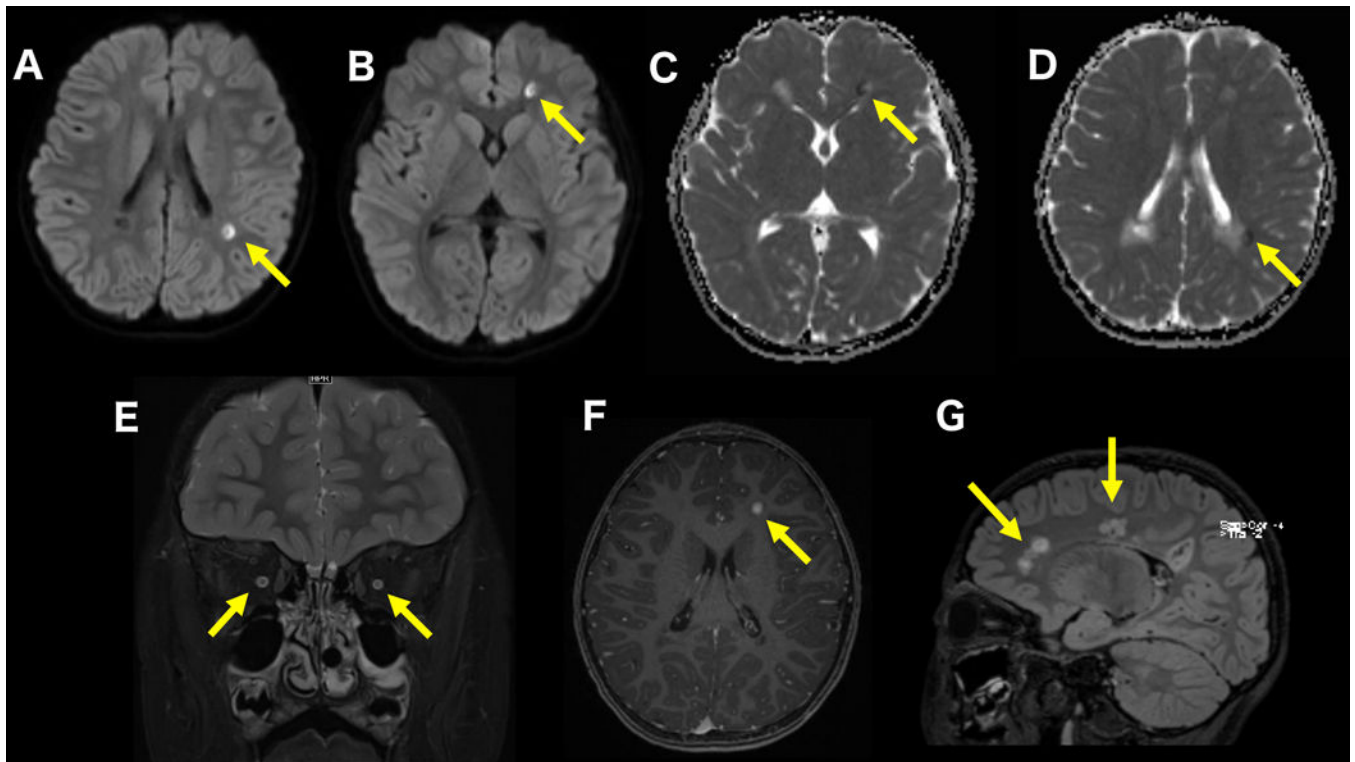


Figure 3.

Subsequent MRI of the brain at age four: (A) Axial DWI image shows new lesion with restricted diffusion in the left parietal white matter. (B) Axial DWI image shows new lesion with restricted diffusion in the left anterior frontal white matter. (C) Axial ADC map of “B” confirming restricted diffusion. (D) Axial ADC map of “A” showing acute and chronic lesions superimposed. (E) Coronal T2-weighted fat suppressed image shows bilateral optic nerve atrophy or hypoplasia without abnormal signal intensity. (F) Axial contrast-enhanced T1-weighted image shows enhancement of a left anterior frontal white matter lesion. (G) Sagittal T2-FLAIR image shows periventricular lesions.