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CASE REPORT

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Genotype–phenotype correlation in IARS2-related diseases: A case report and review of literature

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Abstract

Isoleucyl-tRNA synthetase 2 *(IARS2)* encodes mitochondrial isoleucine-tRNA synthetase. Pathogenic variants in the *IARS2* gene are associated with mitochondrial disease. We report a female with *IARS2* compound heterozygous variants, p.Val499Glyfs*14 and p.Arg784Trp who presented with infantile spasms, Leigh disease and Wolff-Parkinson White (WPW) pattern. This report expands the phenotypic spectrum of *IARS2*-related disease.

KEYWORDS

CAGSSS, IARS2, mitochondrial disease, West syndrome, WPW

1 | INTRODUCTION

Mitochondria produce energy through oxidative phosphorylation (OXPHOS) via the respiratory chain complex. Thirteen polypeptides make up the electron transport chain, they are encoded by the mitochondrial genome and are synthesized within the mitochondrial translation system. There are two rRNA and 22 tRNA molecules necessary for mitochondrial translation encoded by the mt-DNA. Other proteins used in mitochondrial translation are encoded by the nuclear genome. These include ribosomal proteins, tRNA modifying enzymes, translation factors, and aminoacyl-tRNA synthetases (mt-ARSs).[1] Specifically, mt-ARSs are involved in the biogenesis of mitochondrial tRNA by catalyzing amino acid attachment to their corresponding tRNA to form an aminoacyl tRNA.[2,3] There are 19 aminoacyl-tRNA synthetases, which have been implicated in human diseases.[4–6] Among the mt-ARSs, pathogenic variants in *IARS2* (Isoleucyl-tRNA synthetase 2), which encodes mitochondrial isoleucine-tRNA synthetase (MIM #612801), have been known to result in neurological dysfunction as well as a spectrum of extra-neurological affects. The disease is comprised of a broad phenotypic spectrum. Pathogenic variants in the

IARS2 gene have been reported to cause 2 distinct clinical phenotypes including cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal dysplasia (CAGSSS) and Leigh syndrome with autosomal recessive inheritance.[7,8]

Isoleucyl-tRNA synthetase 2-related disease was first described in 1993 in two first cousins of French–Canadian descent, who demonstrated clinical features consistent with the previously described CAGSSS phenotype.[8] Pathogenic variants in *IARS2* are rare, and fewer than 30 patients have been reported in the literature. CAGSSS has been described in seven patients from four families with broad clinical variability. Other reported clinical manifestations of CAGSSS include dysmorphic facial features (thick eyebrows, midface retrusion, prognathism, and deep-set eyes), brachydactyly, pes planus, and tapering fingers, adrenal insufficiency, and hypoglycemic episodes.[7,8] From 2018 to 2021, eighteen individuals with pathogenic variants in *IARS2* gene have been noted with a wide clinical spectrum.[9–11] Among 26 reported patients from nineteen families with differing ethnic backgrounds, 15 patients (58%) have neurologic manifestations, 12 patients (46%) have Leigh disease,[7,9–12] 4 patients (15%) have West syndrome,[9,11] 4 patients (15%) have sideroblastic anemia,[9] 3 patients (12%) have cardiomyopathy,[9,12] and 3 patients (12%) have isolated cataract.[13] However, approximately 27% of the patients with pathogenic variants in *IARS2* have CAGSSS spectrum.[7,14,15] Prognosis is favorable among CAGSSS individuals. All individuals with CAGSSS are alive at most recent follow-up, their ages range from 6 yr to 35 yr, and no intellectual disability was reported in this group. Mortality is high among patients with neurological phenotype which is primarily attributed to progressive neurologic disease; 4 patients died from neurologic regression, 1 patient died from cardiomyopathy, and 7 patients have a range of disabilities from profound intellectual disability, absent speech to non-ambulation.[7,9,11,12] Genotype–phenotype correlation has not been well established due to the rarity of this disease.

We report a female infant with novel compound heterozygous pathogenic variants, c.1493dupA (p.Val499Glyfs*14) and c.2350C>T (p.Arg784Trp) in *IARS2* gene detected by Exome Sequencing (ES), who presented with developmental regression, infantile spasms, hypotonia, abnormal brain MRI, and WPW pattern on EKG. This is the first report of WPW in *IARS2*-related mitochondrial disorder.

2 | LITERATURE SEARCH

We perform a literature search through PubMed, Embase, and Google Scholar. The following search terms were used: *IARS2*, *IARS2*-related disorders, *IARS2*-related mitochondrial disease, aminoacyl-tRNA synthetases, CAGSSS, Leigh disease, cardiac diseases in mitochondrial disorder, WPW in mitochondrial disorder, and ventricular pre-excitation in mitochondrial disorder.

3 | CLINICAL REPORT

The proband is a 41-month-old African American female patient who presented with infantile spasm, progressive neurological deterioration associated with Leigh syndrome. She was the first child of non-consanguineous parents, a 21-year-old mother and a 22-year-old father. The family history was noncontributory. The pregnancy was uncomplicated. Birthweight was 3005 g (37th centile), and length was 53.3 cm (93rd centile). Post-natal period was uncomplicated. The patient began to roll over at 6 months of age and to sit without support at age 7 months. She was subsequently delayed in her development and began to exhibit regression including the loss of the ability to babble and sit unsupported around 8 months of age, 2 months prior to the onset of infantile spasms.

At 10 months of age, she presented with infantile spasms. Examination at age 10 months revealed normal growth parameters; weight 8.79 kg (60th centile), height 74 cm (70th centile), and head circumference 45.4 cm (66th centile). She had no evidence of craniofacial dysmorphic features. Her neurological examination was notable for marked axial and appendicular hypotonia with poorly elicitable deep tendon reflexes. EEG at this time demonstrated high-voltage, disorganized background activity with multifocal epileptiform discharges consistent with hypsarrhythmia and two infantile spasms. She was treated with a course of high-dose oral methylprednisolone which resolved her infantile spasms clinically and the hypsarrhythmia electrographically. Brain MRI at 10 months of age revealed restricted water diffusion in the periaqueductal gray area of the midbrain and upper dorsal pons, medial thalamus and mamillary bodies as well as edema in the periaqueductal gray region consistent with Leigh syndrome (Figure 1A,B).

The patient's EKG was also abnormal with intermittent ventricular pre-excitation (VPE) consistent with WPW (Figure 2). Echocardiogram showed normal cardiac anatomy and function. Holter monitoring revealed pre-excited atrial tachycardia in the 230 bpm range. The patient was started on propranolol. She did not have any documented supraventricular arrhythmias on telemetry or on subsequent Holter monitor studies at 23 months of age. An ophthalmological examination was normal without retinal abnormalities. An audiological evaluation was normal.

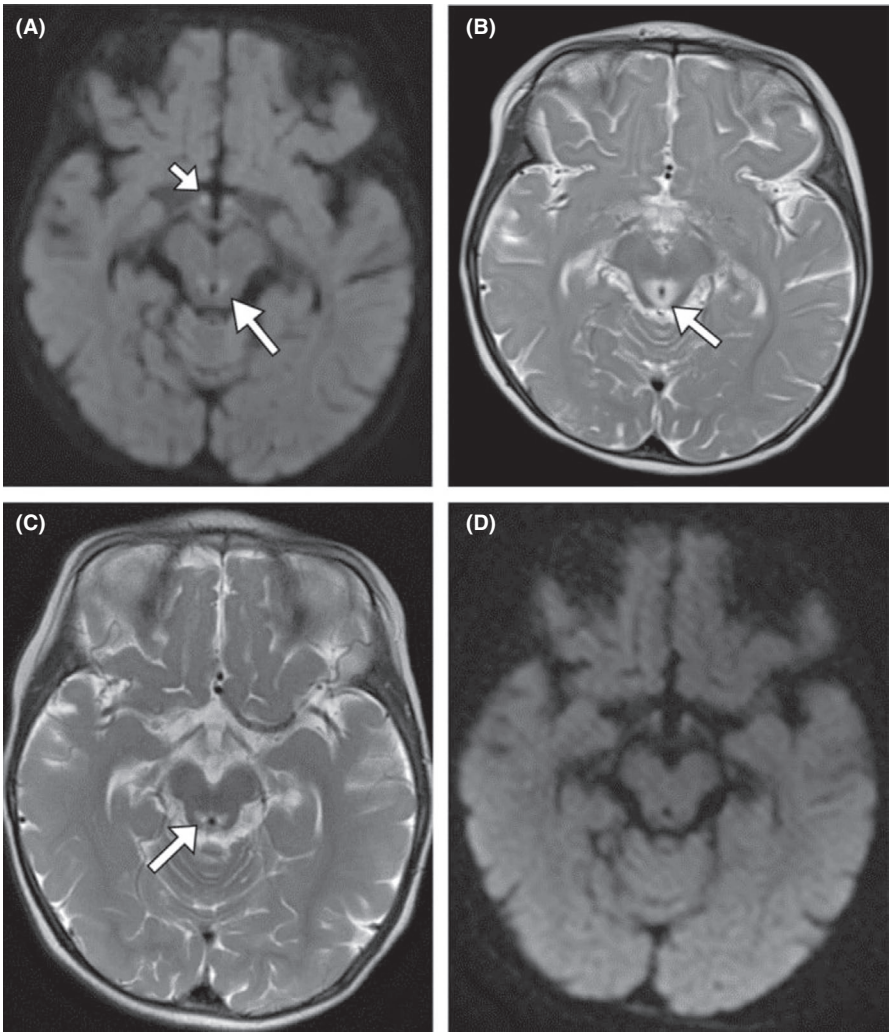

FIGURE 1 Brain MRI of the patient at age 10 months. (A) Diffusion weighted imaging of the brain showing restricted diffusion within the mammillary bodies (short arrow) and periaqueductal gray region of the midbrain (long arrow). (B) Axial T2 weighted image of the brain at 10 months of age demonstrating edema within the periaqueductal gray region of the midbrain (arrow). (C) Axial T2 imaging demonstrating periaqueductal gray gliosis with residual increased signal (arrow). (D) Axial Diffusion Weighted Imaging demonstrating resolution of restricted diffusion changes seen at 10 months of age

Initial genetic testing including chromosome microarray, plasma amino acid analysis, urine organic acid analysis, *MECP2* gene sequencing, and an epilepsy gene panel was non-diagnostic. However, urine organic acid analysis revealed elevated lactic acid, pyruvic acid, fumaric acid, 2-ketoglutaric acid, methylmalonic acid, 3-OH-butyric acid, and acetoacetic acid. Plasma amino acid analysis demonstrated a mild elevation of alanine. Blood lactic acid and pyruvic acid were elevated at 4.6 mmo/L (0.5–2.2 mmol/L) and 0.126 mmol/L (0.03–0.107 mmol/L), respectively. Given the history of developmental regression, abnormal MRI brain findings, intermittent VPE, elevated blood lactic acid, pyruvic acid and persistent elevation of lactic acid and TCA cycle intermediates in the urine, a mitochondrial disorder was suspected. Exome Sequencing (ES) by next-generation sequencing method found compound heterozygous variants in the *IARS2* gene, which included a pathogenic variant c.1493dupA (p.Val499Glyfs*14) inherited from her mother and a likely pathogenic variant c.2350C>T (p.Arg784Trp) inherited from her father. A frameshift variant, p.Val499Glyfs*14, predicted to result in protein truncation or nonsense-mediated decay and this variant is not observed in large population cohorts.[16] A likely pathogenic variant, p.Arg784Trp is not observed at a significant frequency in large population cohorts[16] and in silico analysis PROVEAN (Protein Variation Effect Analyzer) supports a deleterious effect. Mitochondrial genome sequencing and deletion/duplication analysis were normal.

Follow-up brain MRI at 16 months of age showed resolution of the diffusion-weighted imaging abnormalities as well as improvement of the T2 signal abnormality in the periaqueductal region and upper dorsal pons (Figure 1C,D). A follow-up MRI of the brain at 34 months of age revealed new cytotoxic edema lesions within the putamen nuclei bilaterally (Figure 3A,B).

At her most recent follow-up at 41 months of age, her weight was 12.3 kg (9th centile), length was 94 cm (24th centile) and head circumference was 48 cm (26th centile). She has global developmental delay but was now cooing and babbling once again. She was able to sit unsupported and was able to pull to a stand but is not

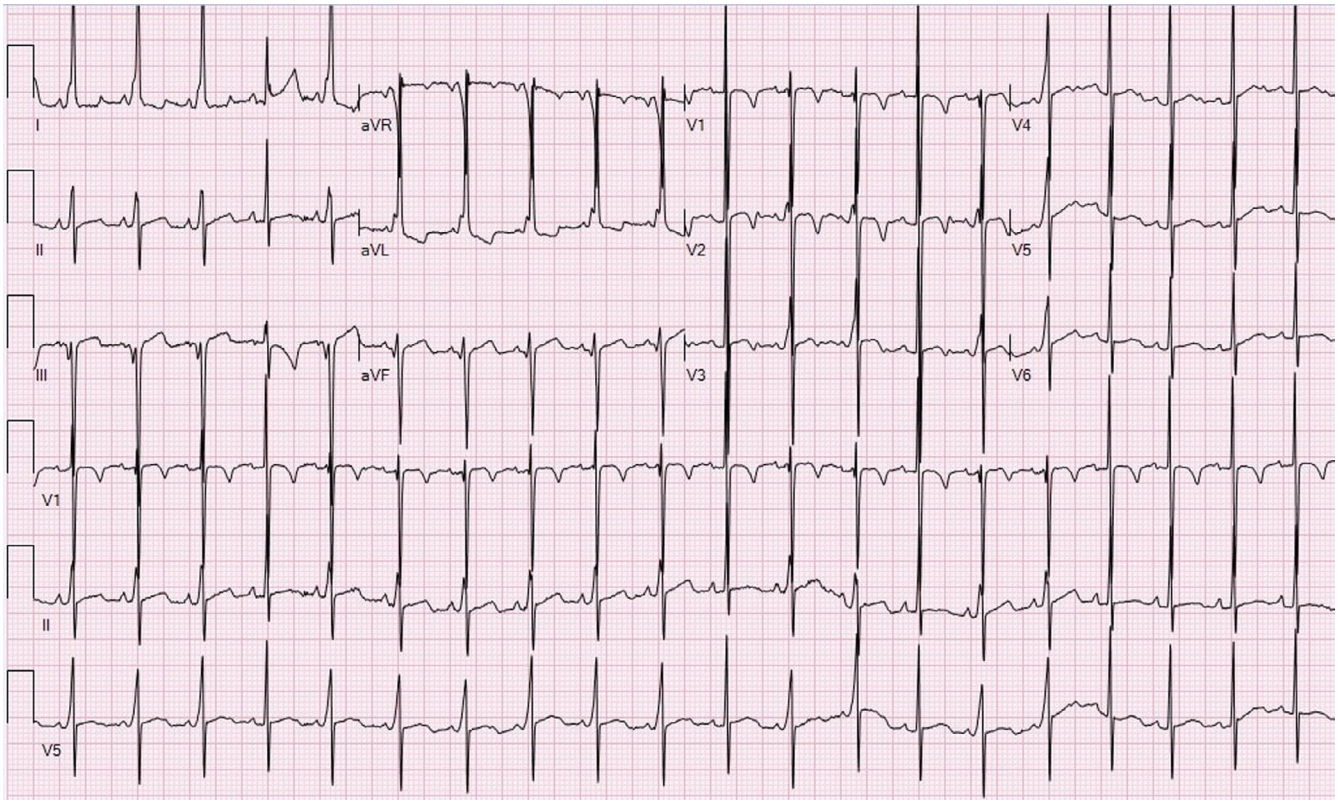

FIGURE 2 12-lead ECG demonstrating intermittent centricular pre-excitation (several beats with short PR with delta-wave and wide QRS complexes) consistent with PWP pattern

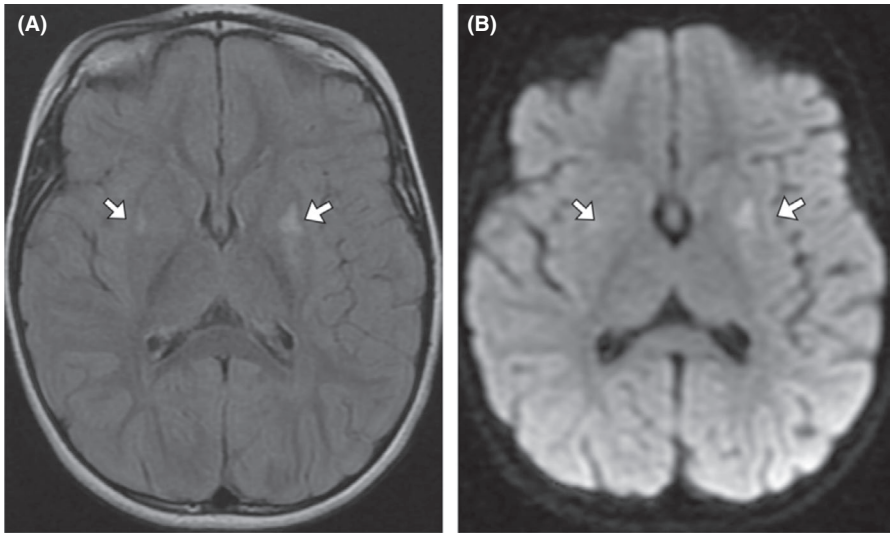

FIGURE 3 MRI of the Brain at 34 months of age. (A) Axial T2 imaging demonstrating new areas of edema within the putamen nuclei (arrows). (B) Corresponding axial Diffusion Weighted images demonstrating cytotoxic edema in the bilateral putamen nuclei (arrows)

walking without support. Her neurological examination was notable for good visual fixation and tracking with full extraocular movements. There was no nystagmus or ptosis. Bulbar function was intact. She continued to have axial and appendicular hypotonia along with quadriceps weakness. Her deep tendon reflexes were absent. EKG at 41 months showed sinus rhythm without evidence of atrial ectopic tachycardia.

Due to proximal leg weakness and absent deep tendon reflexes, nerve conduction studies and EMG were performed. The results demonstrated mild conduction velocity slowing without reduced amplitude in both sensory and motor nerves of the upper extremities and normal velocities and amplitudes in sensory and motor nerves of the lower extremities, possibly suggestive of a demyelinating sensory-motor neuropathy.

4 | DISCUSSION

Isoleucyl-tRNA synthetase 2-related mitochondrial disease is a rare genetic disease impacting mitochondrial isoleucyl-tRNA synthase. Given the broad spectrum of phenotypes among 27 patients including our patient, it is indicative that allelic disorders linked to *IARS2* may include isolated cataract, CAGSSS, and neurological phenotype which involves multiorgan systems with prominent neurological symptoms (Table 1). Here, we report an African American female patient with novel pathogenic and likely pathogenic variants in *IARS2* gene, who has a neurological disorder. At the time of this publication, our patient is 41 months of age and is making slow developmental progress without regression. Previously undescribed in other reports, our patient has VPE on EKG in addition to Leigh syndrome and West syndrome. Moreover, our patient has electrophysiological evidence for a mild sensorimotor demyelinating polyneuropathy that may become more progressive over time. Generally, mitochondrial dysfunction affects organs and tissues which are highly

TABLE 1 Summary of clinical characteristics in 27 patients with pathogenic/likely pathogenic variants in IARS2 gene categorized by phenotypes

Phenotype	Characteristic features	Frequency
CAGSSS ($N = 7$)	Developmental delay in early life	5/7
	Leigh syndrome	0/7
	Seizure	0/7
	Neuropathy	5/7
	Normal intelligence at most recent follow-up	7/7
	Cataract	7/7
	Corneal opacification	6/7
	Bilateral nystagmus	7/7
	Adrenal insufficiency	2/7
	GH deficiency	4/7
	Short stature	7/7
	SEMD	6/6
	Scoliosis	4/7
	Bilateral hip dislocation	4/7
	Dysmorphic features	7/7
	Hearing loss	5/7
	Type 2 Achalasia	2/7
Neurological phenotype ($N = 17$)	Developmental delay	16/16
	Hypotonia	14/14
	Leigh syndrome	14/17
	Seizure	9/13
	West syndrome	3/13
	Cardiomyopathy	4/10
	WPW	1/10
	Sideroblastic anemia	5/7
	Cataract	8/13
	Hearing loss	8/8
	Short stature	2/11
	Scoliosis	2/11
	Hypoparathyroidism	3/7
	High serum lactate	11/11
	High CSF lactate	5/5
	Death	5/13

metabolically active, including the heart and nervous system. Cardiac involvement is frequent in pediatric patients with mitochondrial disorders.[17] Cardiovascular manifestations of mitochondrial disease often include cardiomyopathy (dilated cardiomyopathy and hypertrophic cardiomyopathy),[18] conduction abnormalities (prolonged QT, right bundle branch block, supraventricular tachycardia, ventricular tachycardia, VPE), and left ventricular dysfunction.[19,20] Among cardiac conduction disturbances, VPE is more prevalent in patients with mt-DNA mutation, especially in patients MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes).[19,21–24] However, VPE has been described in a myriad of mitochondrial diseases caused by pathogenic variants in both the nuclear and mitochondrial genome.[18,25] Majority of children with VPE are asymptomatic.[26] Nonetheless, asymptomatic patients are still at risk of sudden cardiac death.[27] Among individuals with Leigh syndrome, sudden and unexpected death have been described.[28,29] The cause of sudden death is complex including fulminant metabolic acidosis, cerebral necrosis, conduction defects, aspiration etc.[29] Among cardiac conduction disturbances, VPE is more prevalent in patients with mtDNA mutation, especially in patients MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes).[19,21-24] In addition, VPE is well recognized to contribute to development of a dilated cardiomyopathy as a result of the recurrent and sustained tachyarrhythmia.[30,31] Our case has been asymptomatic so far from cardiac standpoint. This is the first report of VPE in *IARS2*-related disease.

By integrating the genotypic and phenotypic information from seven patients with CAGSSS, three patients with isolated cataract, as well as from seventeen patients with neurological manifestations, we were able to explore the potential correlation between the domains affected by pathogenic variants and the phenotypes (Figure 4). All seven

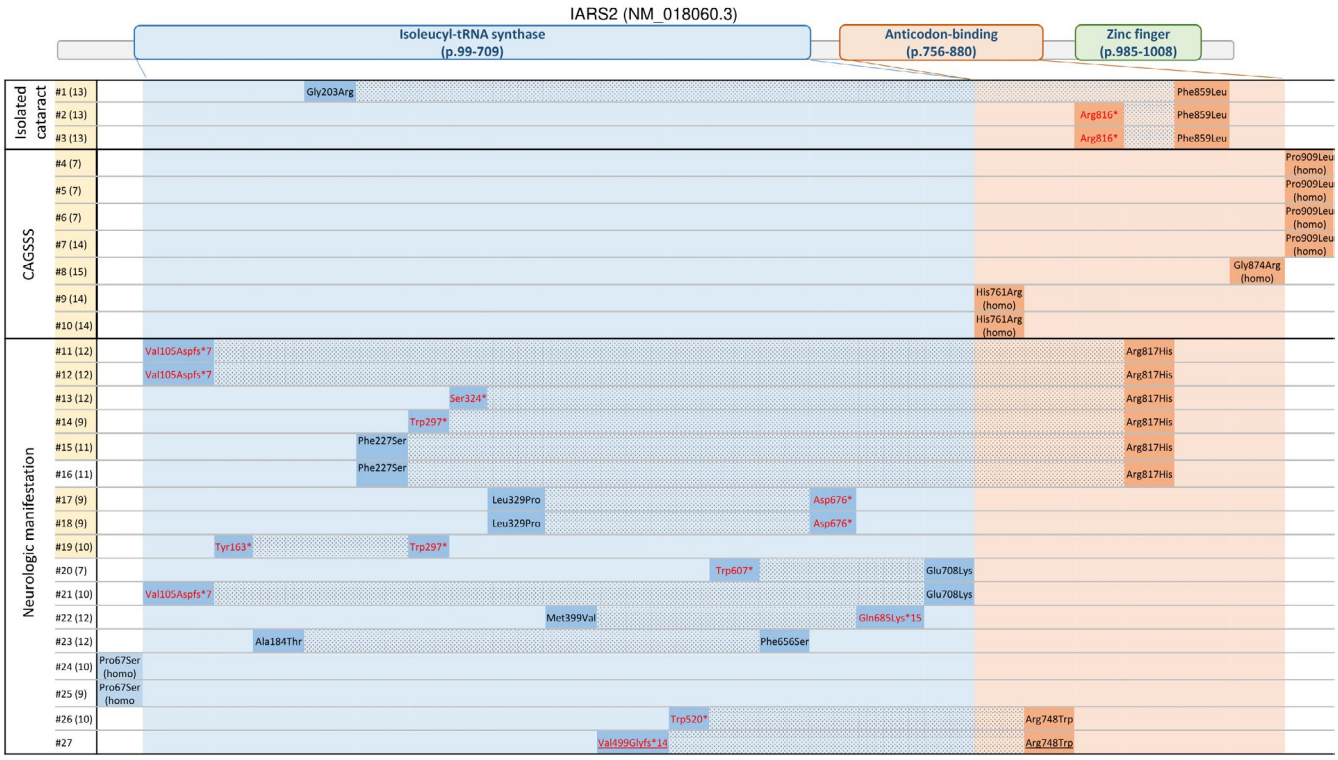

FIGURE 4 Distribution of reported pathogenic and likely pathogenic variants in *IARS2* gene. The reported pathogenic and likely pathogenic variants of *IARS2* gene are plotted around three functional domains in the schematic gene structure, including Isoleucyl-tRNA synthase domain (blue), Anticodon-binding domain (orange), and Zinc Finger domain (green). Twenty-seven reported patients in this figure are grouped into three phenotypic groups, including isolated cataract, CAGSSS, and neurological manifestation, in which all patients reported with cataract are highlighted in yellow. Each variant is listed in a box with the filled color corresponding to the functional domains. Homozygous variants are indicated with *homo* in the parenthesis, and the compound heterozygous variants are connected by dotted shadows for each patient. Frameshift and nonsense variants are highlighted in red font, and variants in the present case are underlined. NOTE: Likely due to a strong divergent feature of the anticodon-binding domain[32] different sources characterize the size of this domain differently. To reflect the opinion from the original report[14] of the variant Pro909Leu, Pro909Leu was orange color-coated as other variants in the anticodon-binding domain. To align towards our reference (Alamut Visual) used to unify the variant nomenclature, Pro909Leu was placed out of the light orange backdrop for the anticodon-binding domain. References are in brackets

patients of CAGSSS where the result of homozygous missense pathogenic variants around the anticodon-binding domain, although one study also differentially included Pro909Leu/Pro909Ser in the anticodon-binding domain,[14] which might result from the strong divergence in this domain.[32] Interestingly, SNP genotypes revealed regions of homozygosity of varying size involved in all variants of these CAGSSS individuals, including Pro909Leu (3 patients), Pro909Ser (1 patient), His761Arg (2 patients), and Gly874Arg (1 patient).[7,14,15] The shared clinical phenotype (CAGSSS) and the variant/region homozygosity suggested that the homozygous *IARS2* variants in anticodon-binding domain might be essential for the CAGSSS phenotype.[7,14] Aminoacyl-tRNA synthetases, such as *IARS2*, facilitate the pairing of tRNAs to its corresponding amino acid according to the anticodon triplet on each tRNA.[33] Since the above mentioned homozygous variants in the anticodon-binding domain will introduce different protein structures to the tRNA synthetases through various amino acid alterations over different mutation sites, we postulate that the spectrum of phenotypic presentations in CAGSSS could be the result of different structural variations of the tRNA synthetase. It is worth noting that at least one pathogenic variant in the anticodon-binding domain was detected in cataract cases including 3 cases with isolated cataract, 7 cases with CAGSSS, and 5 cases with neurological manifestation.[7,13,14] It would be interesting to explore the correlation between pathogenic variants in the anticodon-binding domain and cataracts in the future studies. In addition, seventeen cases with neurological manifestations, including the present case, were found to have at least one pathogenic variant in the aminoacyl-tRNA synthetase functional domain. Interestingly, one of these 17 cases reported with two pathogenic variants shares an amino acid alteration with the present case, in which the missense variant Arg784Trp is identical to the one presented here. Additionally, another nonsense variant in the same case, Trp520*, is a similar truncation event to the frameshift variant Val499Glyfs*14 in present case.[10] Conversely, a Pro67Ser homozygote was also reported with similar neurological manifestations, it should be noted that codon 67 is still proximal to aminoacyl-tRNA synthetase domain.[9] As it is characterized by the domain functions, mutations in the catalytic aminoacyl-tRNA synthetase domain likely affect the essential translation fidelity.[9] This catalytic domain might primarily contribute to the more severe phenotypic presentation resulting in neurological manifestation than those pathogenic variants in other parts of the protein, which result in the less severe, isolated, and cataract CAGSSS cases. Further functional evaluation would confirm the potential mechanism observed in this case series. It is possible that clear genotype–phenotype correlations will emerge, as a larger number of patients are studied.

Our report describes a patient with Leigh syndrome caused by *IARS2* variants. Our patient does not have features of CAGSSS with the exception of a possible mild demyelinating sensory-motor neuropathy. This suggests that allelic disorders linked to *IARS2* include CAGSSS, neurological disorder and also isolated cataracts. Furthermore, the intermittent VPE identified in this patient and hypertrophic cardiomyopathy described in other cases highlight the need to clinically evaluate cardiac conduction defect and cardiomyopathy in *IARS2*-related mitochondrial disease. Therefore, physicians should be aware of the potential for cardiac abnormalities and neuropathy in patients with similar MRI findings and suggestive metabolic abnormalities. Considering the risk of sudden cardiac death in the patients with Leigh syndrome, periodic EKG, and echocardiogram should be carried out for patients with *IARS2*-related mitochondrial disease.

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CONFLICTS OF INTERESTS

All authors declare no conflict of interest in connection with the current report.

AUTHOR CONTRIBUTION

JU involved in planning, conducting, and reporting the work described in the article. YL, NW, SD, KG, and HA involved in reporting and revising the work described in the article.

ETHICAL APPROVAL

No ethical approval was required.

CONSENT

The written consent was obtained from the patient's mother for publication of this case report.

DATA AVAILABILITY STATEMENT

All data related to this article are available upon request.

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