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Clinical and genetic characteristics of Korean patients with *IARS2*-related disorders

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Purpose: Genetic defects in the nuclear-encoded mitochondrial aminoacyl-tRNA synthetases were first identified as causes of various disorders in 2007. Variants in *IARS2*, which encodes a mitochondrial isoleucyl-tRNA synthetase, were first reported in 2014. These variants are associated with diverse phenotypes ranging from CAGSSS (CAtaracts, Growth hormone deficiency, Sensory neuropathy, Sensorineural hearing loss, and Skeletal dysplasia) and Leigh syndrome to isolated nonsyndromic cataracts. Here, we describe the phenotypic and genetic spectrum of Korean patients with *IARS2*-related disorders.

Materials and Methods: Using whole-exome sequencing followed by Sanger sequencing, we identified five patients with *IARS2* mutations. Their medical records and brain magnetic resonance images were reviewed retrospectively.

Results: All five patients presented with developmental delay or regression before 18 months of age. Three patients had bilateral cataracts, but none had hearing loss or sensory neuropathy. No evidence of skeletal dysplasia was noted, but two had short stature. One patient had cardiomyopathy and another exhibited renal tubulopathy and hypoparathyroidism. Their brain imaging findings were consistent with Leigh syndrome. Interestingly, we found the recurrent mutations p.R817H and p.V105Dfs*7 in *IARS2*.

Conclusion: To our knowledge, this is the first report of Korean patients with *IARS2*-related disorders. Our findings broaden the phenotypic and genotypic spectrum of *IARS2*-related disorders in Korea and will help to increase clinical awareness of *IARS2*-related neurodegenerative diseases.

Key words: Amino acyl-tRNA synthetases, Cataract, *IARS2*, Leigh disease.

Introduction

Mitochondrial structure and function are under dual genetic control and involving the interplay of the mitochondrial and nuclear genomes. Thirteen mitochondrial respiratory chain subunits are encoded in the mitochondrial genome, and their translation requires nuclear-encoded mitochondrial aminoacyl-tRNA synthetases (mtARSs) [1-3]. These enzymes are encoded by the

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nuclear genome, translated in the cytoplasm, and transported into mitochondria. A total of 37 nuclear-encoded aminoacyl-tRNA synthetases are found in the cytoplasm and mitochondria of human cells, including two dual-localized synthetases, glycyl-tRNA synthetase (GARS) and lysyl tRNA synthetase (KARS) [1-6].

The 17 mtARSs are described using the nomenclature for aminoacyl-tRNA synthetases as a single-letter code for the recognized amino acid, followed by 'ARS' and '2', which indicates its function in mitochondria [1-3]. *DARS2* and *RARS2* mutations were first identified in 2007 [7]; since then, mutations have been reported in *YARS2*, *HARS2*, *SARS2*, *EARS2*, *MARS2*, *FARS2*, *IARS2*, *LARS2*, *AARS2*, *VARS2*, *TARS2*, *CARS2* and, more recently, *WARS2*, *PARS2*, and *NARS2* [5,6]. Notably, despite their ubiquitous expression, mtARSs seem to cause tissue-specific phenotypes or even gene-specific brain neuroimaging patterns [1-6]. Encephalopathy is the most common phenotype, but involvement of the heart, kidney, muscle, ear, or ovary is also relatively common.

Among the mtARS genes, mutations in *IARS2* (OMIM *612801), which encodes mitochondrial isoleucyl-tRNA synthetase, were first reported in a French-Canadian family with the syndrome abbreviated as CAGSSS (CAtaracts, Growth hormone deficiency, Sensory neuropathy, Sensorineural hearing loss, and Skeletal dysplasia) in 2014 [8]. A few reports since then [8-12], have shown that the clinical spectrum ranges from Leigh syndrome with or without West syndrome to isolated cataracts. Here, we discuss five unrelated patients with mutations in *IARS2*. Our findings expand the understanding of the phenotypic and genotypic spectrum of *IARS2*-related disorders.

Materials and Methods

This study was approved by Seoul National University Hospital Institutional Review Board (IRB No.1902-125-1013). Blood samples were obtained from the five enrolled patients whose parents provided informed consent. Given the clinical diagnosis of Leigh syndrome for these five unrelated patients, mitochondrial genome analysis was followed by whole-exome sequencing (WES). The genetic variants identified were validated using Sanger sequencing. Segregation studies were also performed using parental DNA samples whenever possible. The variants identified were considered to be pathogenic or likely pathogenic according to the 2015 American College of Medical Genetics and Genomics guidelines [13]. Clinical data for the five patients with *IARS2* mutations were analyzed by retrospective review of their medical records. Their brain magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS) findings were also reviewed.

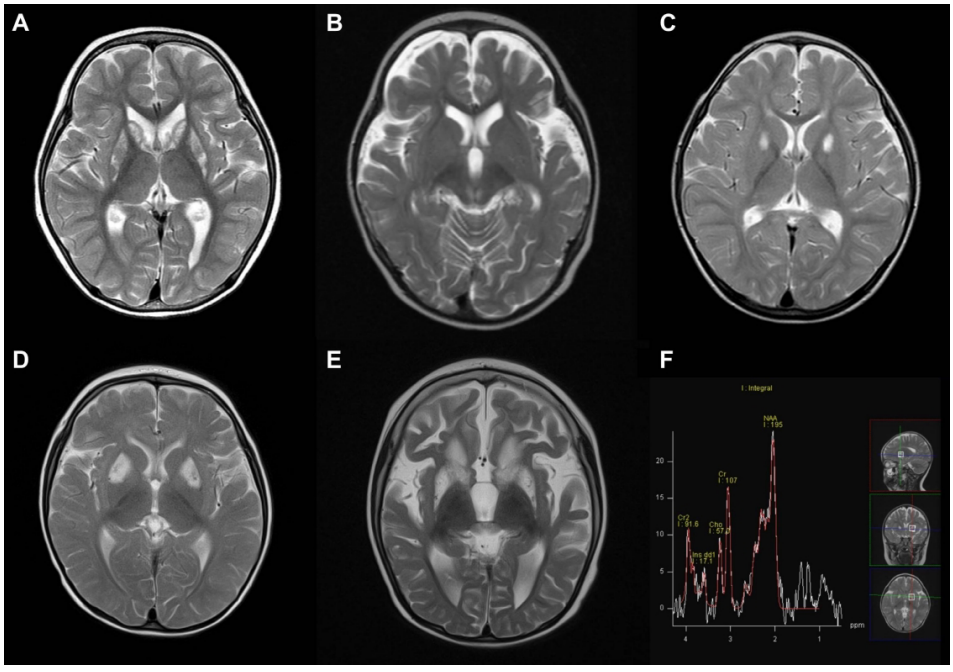

Fig. 1. Brain magnetic resonance (MR) axial T2-weighted images (A-E) of Patients 1 to 5 show high signal intensity lesions involving: (A) both the caudate nucleus and basal ganglia at 42 months of age in Patient 1, (B) periaqueductal area and midline of the midbrain at 15 months of age in Patient 2, (C, D) basal ganglia at 37 months in Patient 3 and at 22 months of age in Patient 4, (E) both caudate nucleus and basal ganglia at 47 months of age in Patient 5, together with diffuse cerebral atrophy and white matter volume loss. (F) Brain MR spectroscopy of Patient 3 shows the lactate peak in the putamen.

Results

1. Case presentations

1) Patient 1

A 3-year-old girl visited our hospital because of developmental regression starting at 18 months of age, when she developed gait abnormality and hypotonia after a prolonged fever. Thereafter, she presented with developmental regression. On visiting our clinic at 3 years of age, no ophthalmologic abnormality or hearing loss was noted. No skeletal dysplasia was found. The work-up for kidney and heart function was normal. At 42 months of age, her height was 91.4 cm (about 10 percentile) and weight was 17.2 kg (75th to 90th percentile). Serum lactate level was elevated at 3.8 mmol/L (reference: 0.7 to 2.0 mmol/L). Brain MRI and MRS at 42 months of age showed a T2-weighted high signal intensity lesion involving both the caudate nucleus and basal ganglia with swelling and a suspicious lactate peak in the basal ganglia lesion (Fig. 1A). Muscle biopsy at 42 months of age showed no specific findings. Mitochondrial genome analysis found no abnormalities. WES was performed and identifed compound heterozygous *IARS2* variants of c.1195A>G (p.M399V) and c.2052delT (p.Q685Kfs*15). Sanger sequencing was validated in the proband but was not performed in her parents because they refused. The patient is now aged 13 years. She can walk with assistance but speaks no words, although her receptive language is tolerable. She has not exhibited seizures.

2) Patient 2

A 15-month-old girl visited our hospital because of developmental delay and hypotonia. At 11 months of age, she could sit with assistance. At 10 months of age, her height, weight, and head circumference were 72.8 cm (25th to 50th percentile), 11.8 kg (>97th percentile), and 45.2 cm (50th to 75th percentile), respectively. Her oldest brother is healthy, but the second brother, who also had developmental delay, died from hypertrophic cardiomyopathy at the age of 19 months; however, he had not received an accurate diagnosis. The patient was found to have unspecified hypertrophic cardiomyopathy. Not long after her first visit to a neurology outpatient clinic, she was admitted for lethargy and respiratory difficulty, which had been preceded by fever. Even with intensive care, she died 3 weeks later. A nerve conduction study was normal and no cataracts were found. The results of a hearing exam were not available. Brain MRI showed T2-weighted high signal intensity lesions in the periaqueductal area and midline of the midbrain, together with diffuse brain atrophy (Fig. 1B). Muscle biopsy showed microvesicular fatty changes in myofibers on light microscopy and increased lipid vacuoles and small mitochondria on electron microscopy, which were suggestive of metabolic myopathy. Mitochondrial genome analysis identified no abnormalities. WES was performed and identifed c.550G>A (p.A184T) and c.1967T>C (p.F656S) in *IARS2*. Sanger sequencing was validated in the proband but was not performed in her parents because they refused.

3) Patient 3

A 24-month-old boy was transferred to our hospital because of developmental delay. He had exhibited nystagmus at 11 months of age. He started to stand alone at 20 months of age. At age 24 months, he underwent bilateral cataract surgery. The serum lactate level was slightly elevated at 2.3 mmol/L (reference: 0.7 to 2.0 mmol/L). An audiology examination and cadiology work-up showed no abnormalities. At 37 months of age, his height, weight, and head circumference were 89.7 cm (5th to 10th percentile), 14 kg (25th to 50th percentile), and 49 cm (25th to 50th percentile), respectively. Brain MRI and MRS at 37 months of age showed T2-weighted high signal intensity lesions in both the basal ganglia (putamen) and a lactate peak in the putamen (Fig. 1C and F). Muscle biopsy at 37 months of age showed findings consistent with nonspecific myopathy, including myofibers with mild size variation, mild endomysial fibrosis, and fatty changes. Mitochondrial genome analysis identified no abnormalities. WES was performed and identified c.314_318delTAAAG (p.V105Dfs*7) and c.2450G>A (p.R817H) in *IARS2*. The variants were validated with Sanger sequencing, and his unaffected parents were found to be heterozygous carriers of each variant. The results of a nerve conduction study at 7 years of age were normal. He developed no seizures and did not display short stature. He is currently age 8 years. He could walk by himself from 5 years of age, but he speaks no words.

4) Patient 4

A 22-month-old boy visited our neurology clinic because of developmental delay starting around 9 months of age and microcephaly. At that time, he had started to sit alone but could not stand even with assistance, and he spoke no words. At 21 months age, his height, weight, and head circumference were 76 cm (<3rd percentile), 10.3 kg (10th to 15th percentile), and 45 cm (<3rd percentile), respectively. At 23 months of age, he underwent operations for bilateral cataracts. He has been taking two antiepileptic drugs (levetiracetam and vigabatrin) for seizures (flexor spasms) from 22 months of age. The serum lactate

Table 1. Clinical features and genotypes of the five patients with *IARS2*-related disorders

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	F	F	M	M	M
Onset age	18 mo with dev regression	11 mo with dev delay	11 mo with nystagmus	9 mo with dev delay	5 mo with severe dev delay
Current age (surviving)	13 yr	Died at 16 mo	8 yr	36 mo	5 yr
Current status (development)	- Walk with assistance - No speech, except receptive language		- Walk alone (5 yr) - No speech	- Sit up and stand with assistance - No speech	- Nearly bedridden - No babbling
CNS Sx	Dev regression	- Dev delay - Hypotonia	Dev delay	- Dev delay - Microcephaly - Seizures (flexor spasms)	- Severe dev delay - Microcephaly - Seizures
PNS Sx	Test not done, but no suspicion of neuropathy	NCS normal	NCS normal	Test not done, but no suspicion of neuropathy	Test not done, but no suspicion of neuropathy
Ocular findings	–	–	+ (nystagmus, cataract)	+ (cataract)	+ (cataract)
Auditory findings	–	N/A	–	–	Inconclusive
Endocrine findings	GH test not done				- GH test not done - Hypoparathyroidism
Skeletal findings	–	–	–	Short stature	Short stature
Cardiology findings	–	Cardiomyopathy	–	–	–
Renal findings	–	–	–	–	Renal tubulopathy
Neuroimaging findings	c/w Leigh syndrome	c/w Leigh syndrome	c/w Leigh syndrome	c/w Leigh syndrome	c/w Leigh syndrome
Genetic variants in *IARS2* (pathogenicity)	P: c.1195A>G (p.M399V) P: c.2052delT (p.Q685Kfs*15)	LP: c.550G>A (p.A184T) LP: c.1967T>C (p.F656S)	P: c.314_318del (p.V105Dfs*7) P: c.2450G>A (p.R817H)	P: c.971_972del (p.S324*) P: c.2450G>A (p.R817H)	P: c.314_318del (p.V105Dfs*7) P: c.2450G>A (p.R817H)

CNS, central nervous system; Sx, symptom; PNS, peripheral nervous system; F, female; M, male; Dev, developmental; GH, growth hormone; c/w, consistent with; NCS, nerve conduction study; N/A, not available; P, pathogenic; LP, likely pathogenic.

level was elevated at 4.2 mmol/L (reference: 0.7 to 2.0 mmol/L). Audiology evaluation showed no definite abnormalities. Brain MRI at 22 months of age showed bilateral symmetric T1-weighted low and T2-weighted high signal intensity lesions in the putamen and delayed myelination (Fig. 1D). Muscle biopsy performed at 23 months of age showed findings consistent with nonspecific myopathy but no evidence of mitochondrial myopathy. Mitochondrial genome analysis found no etiology, and WES identifed two *IARS2* variants of c.971_972delCT (p.S324*) and c.2450G>A (p.R817H). The variants were validated with Sanger sequencing, and his unaffected parents were heterozygous carriers of each variant. He is currently aged 36 months, and he can sit up and has started to stand with assistance.

5) Patient 5

A 47-month-old boy visited our neurology clinic because of severe psychomotor retardation starting at 5 months of age and microcephaly. His developmental milestones included incomplete head control. He was nearly completely bedridden, could maintain eye contact for only a very short time, and did not babble. At 37 months of age, he had undergone operations for bilateral cataracts. He was found to have hypoparathyroidism with manifestations of tonic spasms and startle responses at 46 months of age. He has been taking medications for hypocalcemia. He has also been taking one antiepileptic drug (zonisamide) for seizures. The serum lactate level was slightly elevated at 2.2 mmol/L (reference: 0.7 to 2.0 mmol/L). Renal tubulopathy was also noted. The cardiology work-up was normal. Brain MRI showed bilateral symmetric T2-weighted hyperintensities and atrophic changes in both the putamen and caudate nucleus, diffuse cerebral atrophy, and loss of white matter volume (Fig. 1E). Mitochondrial genome analysis identified no abnormalities. WES was performed and identifed c.314_318delTAAAG (p.V105Dfs*7) and c.2450G>A (p.R817H) in *IARS2*. The variants were validated with Sanger sequencing, and his unaffected parents were heterozygous carriers of each variant. Inconclusive audiology test results were obtained and will need to be repeated. He is currently age 5 years. He has short stature (98.1 cm, <1st

percentile), but a growth hormone test has not been performed. He is still nearly completely bedridden.

2. Genetic results

Through WES, seven different variants were identified from unrelated five patients (Table 1). Among them, three truncated mutations (p.S324*, p.Q685Kfs*15, p.V105Dfs*7) and three missense pathogenic variants (p.M399V, p.A184T, p.F656S) were novel, which have not been previously reported and were not detected in the Human Gene Mutation Database (genetic variants without detailed clinical information were submitted in other journal for Leigh syndrome cohort). Segregation analysis was done for three families, but two patients' parents refused their genetic testing (Fig. 2).

Discussion

In addition to the two bifunctional enzymes GARS and KARS, 17 nuclear genes encode mtARSs, which are involved in mitochondrial translation by charging specific tRNAs with their cognate amino acids [2,6]. Since the first report of *DARS2* mutations by Scheper et al. [7] in 2007, the genetic defects associated with mtARSs have been identified as a cause of various mitochondrial diseases [5,6]. There is debate about whether these enzymes have a tissue-specific phenotype [1-6].

The mechanism underlying the tissue specificity remains unclear. However, a threshold effect has been observed in organs requiring high energy, and tissue-specific differences have been noted for mitochondrial chaperone activities, levels of uncharged tRNAs, and additional non-canonical functions of mtARSs [1-6]. The phenotypic spectrum has been expanding as more cases are reported. For example, *AARS2* mutations were originally found to be associated with severe infantile cardiomyopathy but were later described in association with ovarioleukodystrophy [14]. *IARS2* mutations were first identified in patients with CAGSSS in 2014 [8] and later in those with Leigh syndrome, and more recently in patients with isolated non-syndromic cataracts or cataracts accompanied by skeletal dysplasia [9-12]. It remains unclear how the *IARS2* mutations are related to the diversity in the severity and variability of phenotypes. The relationship between phenotype and genotype remains unclear. Some epigenetic factors or individual differences in genetic background may influence the phenotype.

To date, 10 patients from six families with pathogenic variants in *IARS2* have been reported [8-12]. These patients have presented with a broad range of clinical phenotypes. Not all of these patients fulfill the criteria for a specific syndrome and some also display features of other syndromes [11]. Our five patients showed the phenotypic diversity of *IARS2*-related disorders. All presented with developmental delay or regression, although one initially manifested with nystagmus followed by developmental delay. They all manifested the associated symptoms before 2 years of age, and the neuroimaging findings were consistent with Leigh syndrome. Three of them could stand with holding or walk alone, but were unable to speak. None of these patients have developed peripheral neuropathy, although nerve conduc-

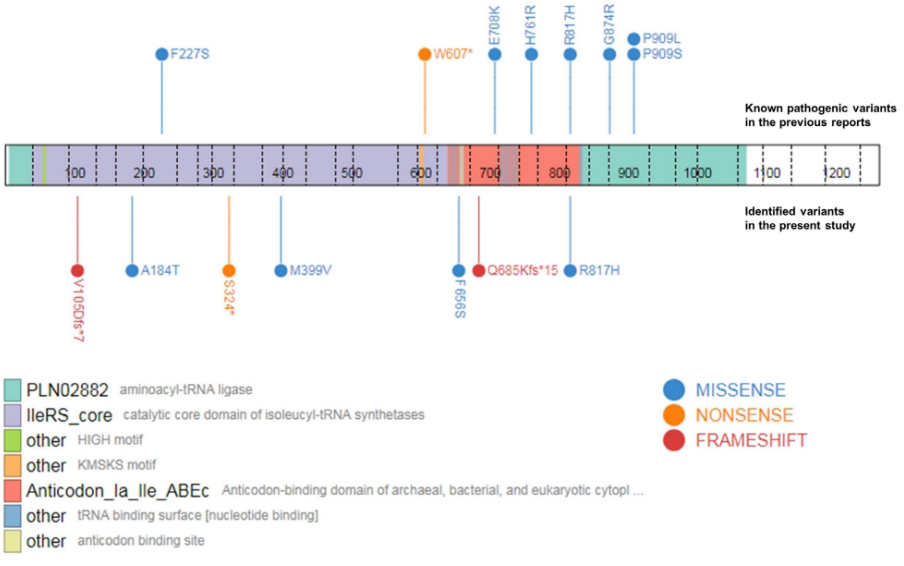

Fig. 2. Schematic representation of the variants identified in the present study and in previous reports.

tion study results were not available for three patients. Additionally, none had exhibited hearing loss, and only one showed inconclusive audiology test results. Sensorineural hearing loss can develop at a later age, and regular follow-up will be needed for these patients. None of the patients exhibited skeletal abnormalities. Three had congenital bilateral cataracts around 2 to 3 years of age. Two had short stature, although a growth hormone test was not performed. One patient had cardiomyopathy and one renal tubulopathy and hypoparathyroidism.

Our findings expand the genotypic spectrum with the six novel variants of *IARS2* observed: M399V, Q685Kfs*15, A184T, F656S, V105Dfs*7, and S324*. Interestingly, we found the recurrent mutations p.R817H and p.V105Dfs*7 in *IARS2*. The R817H mutation has recently been reported in Japanese patients with Leigh syndrome, CAGSSS, and West syndrome [12]. Consistent with the suggestion that disease manifestations caused by genetic mutations in mtARSs are tissue-specific [1-6], our findings represent the spectrum of *IARS2*-related Leigh syndrome, both with and without cataracts. By contrast, the expanded phenotype to include cardiomyopathy, renal tubulopathy, and hypoparathyroidism may explain the opposite aspects. As Vona et al. [11] reported, the expanded clinical features of *IARS2*-related mitochondrial disease include central adrenal insufficiency and esophageal achalasia, and we have broadened the phenotype of *IARS2*-related disorders. To our knowledge, no one has reported cardiomyopathy, renal tubulopathy, or hypoparathyroidism caused by genetic defects in *IARS2*, although the molecular defects might show a variety of phenotypes involving tissues with high energy demand, including heart problems, endocrinologic abnormalities, or neurological disorders. However, more than one patient with the same phenotype would be needed to replicate the findings.

In conclusion, our findings show the diverse phenotypic and genotypic spectrum of patients with *IARS2*-related Leigh syndrome. Given the extreme clinical and genetic heterogeneity, it can be challenging to identify the molecular defects in such mitochondrial diseases. The recent advances in genomic technologies may help to identify other specific genetic defects and the pathological mechanisms responsible for mitochondrial translation-associated diseases.

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Appendix 1. Genes that encodes mtARSs localized in mitochondria

AARS2	Alanyl-tRNA synthetase, Mitochondrial
CARS2	Cysteinyl-tRNA synthetase, Mitochondrial
DARS2	Aspartyl-tRNA synthetase, Mitochondrial
EARS2	Glutamyl-tRNA synthetase, Mitochondrial
FARS2	Phenylalanyl-tRNA synthetase, Mitochondrial
HARS2	Histidyl-tRNA synthetase, Mitochondrial
IARS2	Isoleucyl-tRNA Synthetase, Mitochondrial
LARS2	Leucyl- tRNA synthetase, Mitochondrial
MARS2	Methionyl-tRNA synthetase, Mitochondrial
NARS2	Asparaginyl-tRNA synthetase, Mitochondrial
PARS2	Prolyl-tRNA synthetase, Mitochondrial
RARS2	Arginyl-tRNA synthetase, Mitochondrial
SARS2	Seryl-tRNA synthetase, Mitochondrial
TARS2	Threonyl-tRNA synthetase, Mitochondrial
VARS2	Valyl-tRNA synthetase, Mitochondrial
WARS2	Tryptophanyl-tRNA synthetase, Mitochondrial
YARS2	Tyrosyl-tRNA synthetase, Mitochondrial