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Case Report

Novel *IARS2* mutations in Japanese siblings with CAGSSS, Leigh, and West syndrome

Yusuke Takezawa [a], Hiromi Fujie [b], Atsuo Kikuchi [a,*], Tetsuya Niihori [c], Ryo Funayama [d], Matsuyuki Shirota [e], Keiko Nakayama [d], Yoko Aoki [c], Masayuki Sasaki [f], Shigeo Kure [a]

[a] *Department of Pediatrics, Tohoku University School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan*
[b] *Department of Pediatrics, Iwaki Kyoritsu General Hospital, 16 Kuzehara, Mimayamachi, Uchigo, Iwaki, Fukushima 973-8555, Japan*
[c] *Department of Medical Genetics, Tohoku University School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan*
[d] *Division of Cell Proliferation, United Centers for Advanced Research and Translational Medicine, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan*
[e] *Division of Interdisciplinary Medical Sciences, United Centers for Advanced Research and Translational Medicine, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan*
[f] *Department of Child Neurology, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo 187-8551, Japan*

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Abstract

Background: *IARS2* encodes isoleucine-tRNA synthetase, which is aclass-1 amino acyl-tRNA synthetase. *IARS2* mutations are reported to cause Leigh syndrome or cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal dysphasia syndrome (CAGSSS). To our knowledge, *IARS2* mutations and diseases related to it have only been reported in three families. Here we report a case of two Japanese siblings with Leigh syndrome, some features of CAGSSS, and West syndrome that are found to have compound heterozygous novel *IARS2* mutations.

Case report: A 7-month-old Japanese girl presented with infantile spasms. Brain magnetic resonance imaging (MRI) revealed diffuse brain atrophy and hyperintensity in the bilateral basal ganglia. Three years later, her younger sister also presented with infantile spasms. MRI revealed diffuse brain atrophy and hyperintensity of the bilateral ganglia, suggesting Leigh syndrome. The siblings were identified with compound heterozygous missense mutations in *IARS2*, p.[(Phe227Ser)];[(Arg817His)].

Conclusion: This is the first case study reporting Leigh syndrome concomitant with some features of CAGSSS in siblings with novel *IARS2* mutations, thereby broadening the phenotypic spectrum of *IARS2*-related disorders. Further studies are warranted to elucidate the nature of these disorders.

Keywords: CAGSSS; Whole-exome sequencing; Leigh syndrome; West syndrome; Mitochondrial disease

1. Introduction

IARS2 (OMIM 612801) encodes isoleucine-tRNA synthetase, which is a class I mitochondrial aminoacyl-tRNA synthetase (ARS) [1]. Pathogenic variants in genes encoding mitochondrial ARSs, such as EARS2, FARS2,

* Corresponding author at: Department of Pediatrics, Tohoku University School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.
E-mail address: akikuchi-thk@umin.ac.jp (A. Kikuchi).

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and NARS2, have been reported in a wide variety of neurological disorders [2]. *IARS2* mutations are reported to cause Leigh syndrome (OMIM 256000) or cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal dysphasia syndrome (CAGSSS; OMIM 616007) with autosomal recessive inheritance [3]. To our knowledge, till date, *IARS2*-related disorders have only been reported in a French-Canadian (p.Phe909Leu; CAGSSS), Scandinavian-Caucasian (p.Trp607Ter and p.Glu708Lys; Leigh syndrome), and Danish (p.Gly874Arg; CAGSSS) family [3,4]. Here we report a case of two Japanese siblings with Leigh syndrome, some features of CAGSSS, and West syndrome.

2. Case report

2.1. Patient II-1

Patient II-1 was the first child born to a healthy, non-consanguineous Japanese couple (Fig. 2A). She was delivered after 37 weeks of an uncomplicated gestational period, with an Apgar score of 9 at both 1- and 5-min following birth. However, at 28 gestational weeks, a sacral mass was noted. At birth, her weight, height, and head circumference were noted to be 2.130 kg [SD (standard deviation), −1.3], 45.0 cm (SD, −1.1), and 30.8 cm (SD, −1.3), respectively. No family history of neurodevelopmental diseases was noted and chest X-ray at neonate was unremarkable (Fig. 1A). She was diagnosed with a benign sacrococcygeal teratoma (Altman type II) and underwent complete resection at the age of 3 months. At 5 months of age, the patient developed infantile spasm clusters, and her EEG showed hypsarrhythmia (Supplementary Fig. 2). The patient underwent a subsequent developmental arrest. She was diagnosed with West syndrome and was treated with vitamin B6, valproic acid, and adrenocorticotropic hormone (ACTH), but only showed transient effects; she consequently developed intractable epilepsy. Brain magnetic resonance imaging (MRI) revealed diffuse, but mild cortical atrophy at 8 months of age; The patient subsequently developed severe cortical atrophy and bilateral hyperintensity in the basal ganglia on T2-weighted images at 21 months of age (Fig. 1B and Supplementary Fig. 1). Lactate and pyruvate analysis revealed an elevated lactate-to-pyruvate ratio of 25.2, with a plasma lactate concentration of 45.4 mg/dL and pyruvate concentration of 1.8 mg/dL at 1.8 years of age. Considering the high lactate level and the brain MRI findings, she was diagnosed with Leigh syndrome. The patient was analyzed for mitochondrial DNA (mtDNA) mutations, but no causative mtDNA mutations were detected. Her skeletal muscle biopsy demonstrated normal histology, and her serum amino acid analysis revealed results within the normal limits. She

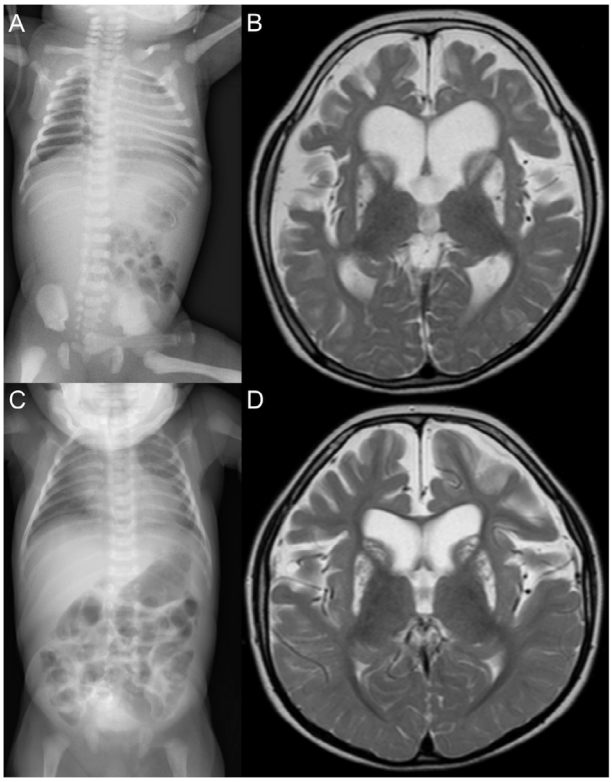

Fig. 1. X-ray and brain magnetic resonance imaging of the patients. (A) Radiographs of the trunk (Patient II-1). (B) T2-weighted brain magnetic resonance imaging at 21 months (Patient II-1). (C) Radiographs of the trunk (Patient II-2). (D) T2-weighted brain magnetic resonance imaging at 18 months (Patient II-2).

demonstrated hypotonic quadriplegia and was bedridden at 2 years of age. Cataracts were noted at 7.9 years of age. At her last follow-up (age, 8 years), her weight and height were noted to be 13.6 kg (SD, −5.1) and 97.3 cm (SD, −5.4SD), respectively. Analysis of the levels of serum fibroblast growth factor 21 (FGF-21) and growth differentiation factor 15 (GDF-15), which are useful biomarkers of mitochondrial disease [5–7], in the patient revealed high levels of both (774.3 pg/mL [cut-off: 300 pg/mL] and 675.4 pg/mL [cut-off: 550 pg/mL], respectively) [7]. She did not require any tube feeding or mechanical ventilation support during the follow-up period.

Supplementary table and figures associated with this article can be found, in the online version, at https://doi.org/10.1016/j.braindev.2018.06.010.

2.2. Patient II-2

Patient II-2 was the second child of the same couple and was Patient II-1's sibling (Fig. 2A). She was born after 38 weeks of uncomplicated gestation. Transient hypoglycemia was observed following delivery; she revealed an Apgar score of 6 at 1 min and 9 at 5 min

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