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A boy with Coffin-Siris syndrome with a novel frameshift mutation in ARID1B

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Abstract

Coffin-Siris syndrome (OMIM #135900) is an autosomal dominant inherited disorder, characterized by dysmorphic features, congenital anomalies, and developmental delay. We report the clinical and molecular findings in a patient with Coffin-Siris syndrome. A 3-year-and-6-month-old boy presented with developmental delay, distinctive facial features, hypertrichosis, partial agenesis of the corpus callosum, fifth digit nail hypoplasia, congenital anomalies, and growth retardation. Targeted gene panel sequencing identified a novel heterozygous frameshift mutation c.2147_2148insAC in *ARID1B* which was predicted as a premature stop codon p. (Gln717Argfs*29). This is the second report of Coffin-Siris syndrome in Korea. Targeted gene panel sequencing can be used as an effective tool for the diagnosis of rare complex syndromes such as Coffin-Siris syndrome.

CASE REPORT

INTRODUCTION

Coffin-Siris syndrome (CSS; OMIM#135900) is an autosomal dominant inherited multisystem disease. Fewer than 200 cases with genetically confirmed CSS have been reported to date (Mannino *et al.* 2018). The characteristic findings of CSS are dysmorphic features (sparse scalp hair, bushy eyebrows, broad nasal bridge, wide mouth with prominent lips, and fifth digit nail and/or toenail hypoplasia or aplasia), congenital anomalies (brain/spine anomalies, cardiac defects, malformation of genitourinary systems), recurrent respiratory infections, and developmental delay. Other features include growth insufficiency, feeding problems, ophthalmologic impairment, and audiologic abnormalities (Levy & Baraitser 1991; Pranckeniene *et al.* 2019; van der Sluijs *et al.* 2019). CSS is caused by a heterozygous pathogenic variant in various genes, including *ARID1A, ARID1B, SMARCA4, SMARCB1, SMARCE1, SOX11, PHF6,* and *DPF2* (Wieczorek *et al.* 2013; Lee *et al.* 2020). *ARID1B* is the most common gene involved in reported cases of CSS (37%) (Tsurusaki *et al.* 2012). The exact prevalence and incidence are not known but they are likely underestimated. Due to the variety in phenotypes, it is challenging to clinically diagnosis CSS. Here, we present a novel *ARID1B* mutation detected by targeted gene panel sequencing in a 3-year-and-6-month-old

boy with developmental delay, distinctive facial features, hypertrichosis, partial corpus callosal agenesis, fifth digit nail hypoplasia, congenital anomalies, and growth retardation.

CASE REPORT

The patient was born to nonconsanguineous healthy Korean parents by vaginal delivery at 39 weeks of gestation age. Birth weight was 2430 g (< 3rd percentile) and birth height was 47 cm (10-25th percentile). Apgar scores were 8 points at one minute and 9 points at 5 minutes. There was no specific family history, and his older sister did not show any abnormalities. Prenatal ultrasonography revealed partial corpus callosum malformation. On the third day after birth, he was hospitalized due to breathing difficulties and poor sucking power. Physical examination showed a systolic murmur, grade 3 on the left upper sternal border and axial hypotonia with head lag. Echocardiography showed large patent ductus arteriosus (PDA). Brain MRI revealed partial corpus callosal agenesis suspected in prenatal ultrasonography and posterior fossa cerebrospinal fluid space widening (Fig. 1). After ligation of PDA, he was discharged with an improved general condition. At the age of 1 month, the patient was hospitalized again due to a seizure. The seizure was a complex partial type, including lip cyanosis, eyeball deviation, and loss of consciousness. Electroencephalography revealed a spike and sharp wave on the left or right temporal area. After that, he experienced several episodes of seizures despite taking antiepileptic medication.

At the age of 11 months, he received orchiopexy. At the time, intubation was difficult. Laryngeal microscopy identified laryngomalacia and subglottic stenosis. The larynx was magnified and granulation tissues were removed. After that, he frequently exhibited inspiratory stridor and was hospitalized due to recurrent respiratory infections. He started to sit unassisted around this time. At 19 months, speech-language evaluation revealed that his receptive and expressive language was at the level of a 4 to 6 month old.

At the age of 2 years and 2 months, he was referred to our clinic for a coarse face and slow growth. His height, weight, and head circumference were 87.3 cm (SD -0.47), 12.2 kg (SD -0.24) and 50.5 cm (SD 1.46), respectively. He showed hypertrichosis with loose hair, and thick eyebrows and eyelashes, a broad nasal bridge, a large mouth with thick lips, hypoplastic digit/nail of the fifth finger. He also had a hemangioma on the left leg and trunk and exotropia. He showed babbling and could stand with support. Laboratory investigations were as follows: complete blood count, electrolytes, liver enzymes, alkaline phosphatase, renal function, and thyroid function test were all within normal ranges. Insulin-like growth factor 1 was 8.7 ng/ml [32.2-255.4]. Bone age was advanced, at 3 years and 3 months. Chromosomal analysis revealed 46, XY. Abdominal ultrasonography was normal. Vision and hearing were also normal. Bayley scales of infant development exhibited delayed mental (developmental age: 2 months) and motor function (developmental age: 7 months).

To make a diagnosis and identify the underlying genetic defect related to the coarse face, hypertrichosis,

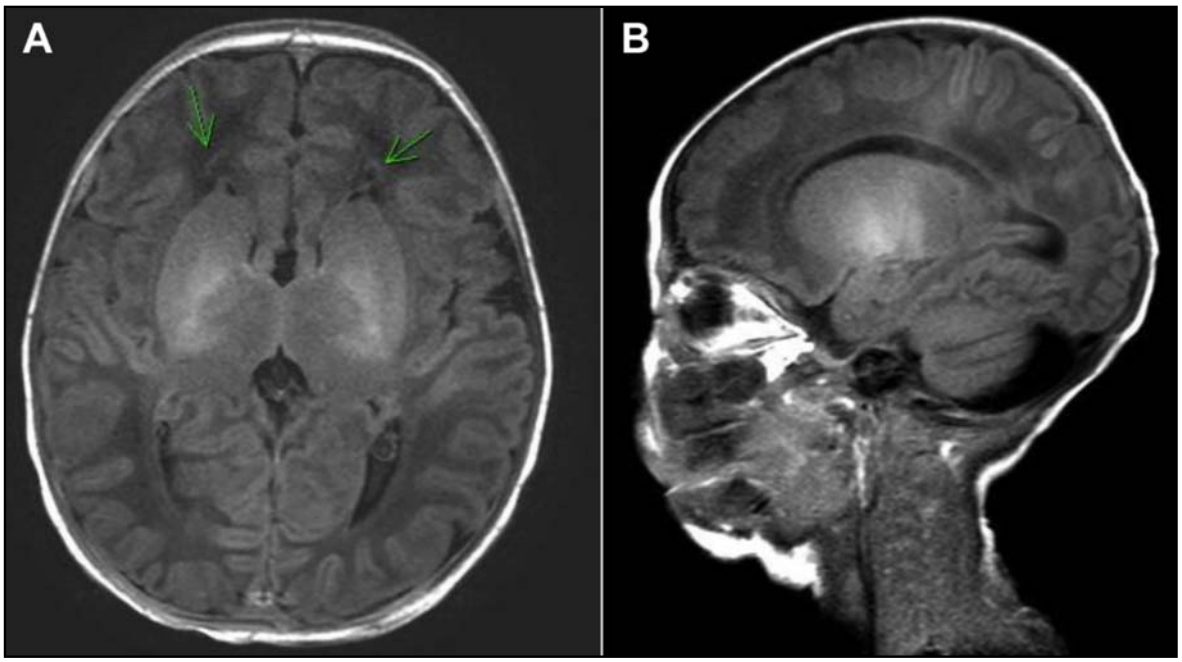

Fig. 1. T1-weighted brain magnetic resonance imaging of the patient, showing the partial corpus callosal agenesis (green arrow: genu and anterior body) and posterior fossa cerebral space showing widening of the fluid. (A) Axial image; (B) sagittal image

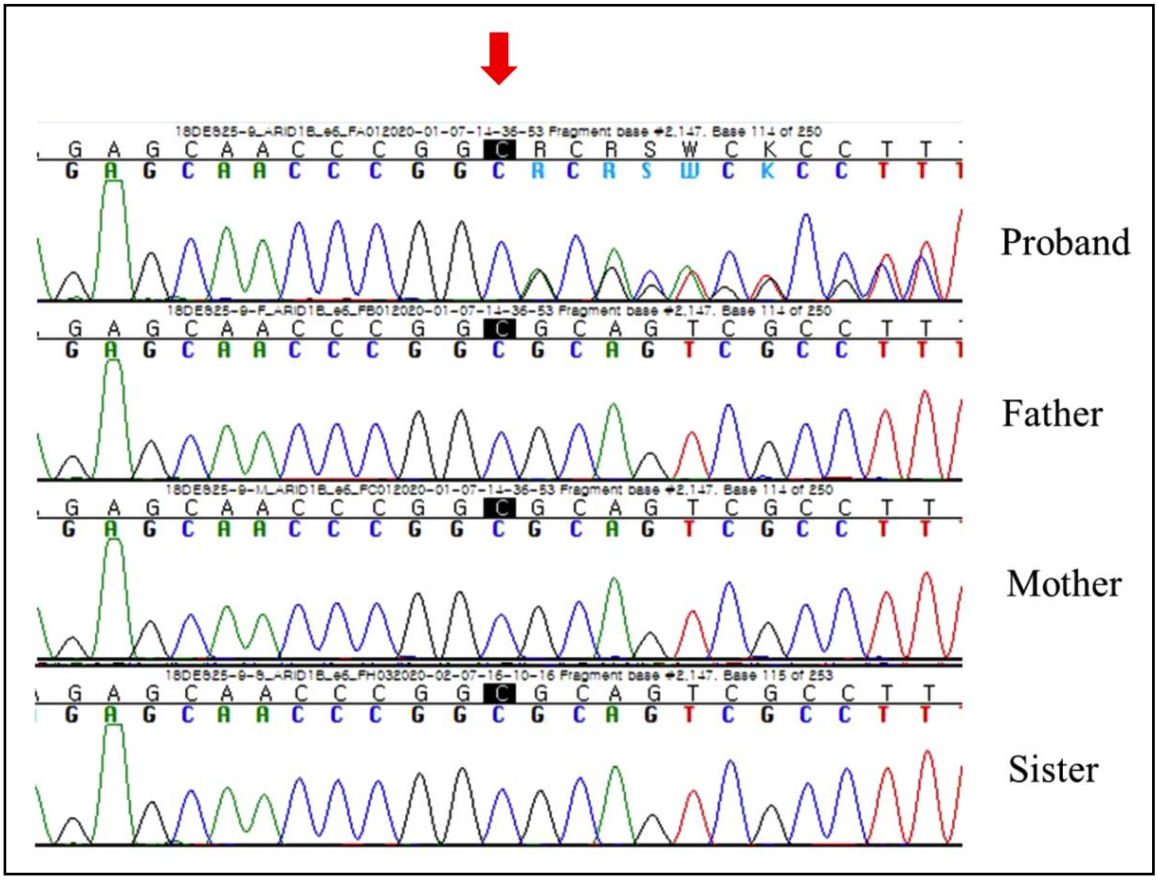

Fig. 2. Chromatogram obtained from Sanger sequencing: c.2147_2148insAC (p. Gln717Argfs*29) in exon 6 of *ARID1B*. No variants were found in the patient's father, mother, and sister (red arrowhead: mutation site).

partial corpus callosal agenesis, small nail, congenital anomalies (PDA and cryptorchidism), growth retardation, and developmental delay, targeted gene panel sequencing was performed.

Informed consent was obtained from the patient and parents. Genomic DNA was extracted from peripheral blood leukocytes using the chemagicTM Magnetic Separation Module I (MSM I) method (PerkinElmer chemagen, Baesweiler, Germany) with the DNA Blood 200 µl. Kit. xGen Inherited Disease Panel (Integrated DNA Technologies, Inc., Coralville, Iowa, USA) was used for library preparation, and sequencing was performed on the Illumina NextSeq500 platform (Illumina Inc., San Diego, CA) generating 2 × 150 bp paired-end reads. The obtained sequence reads were aligned to the hg19 human reference sequence using the Burrow–Wheeler Aligner (BWA version 0.7.12). Duplicated reads were removed with Picard tools (version 1.96, http://picard.sourceforge.net). Local realignment, recalibration, and variant calling were performed with the Genome Analysis Tool Kit (GATK version 3.5), and annotation was done with VEP88 (Variant Effect Predictor), dbNSFP v3.3. We identified a novel heterozygous frameshift mutation c.2147_2148insAC in exon 6 of *ARID1B* predicting a premature stop codon p.(Gln717Argfs*29), and there was no pathogenic variant in other genes. Sanger sequencing revealed the presence of the mutation in the proband, his parents and his sister (Fig. 2). This variant has not been reported previously. The pathogenicity of the variants was analyzed based on the American College Medical Genetics and Genomics (ACMG) guidelines (Richards *et al.* 2015).

When the patient was 3 years old, he could walk unassisted but sometimes his gait was unstable. He could swallow liquid formula but still could not say meaningful words.

DISCUSSION

We found a novel frameshift mutation in *ARID1B* in a Korean boy with CSS. This is the second report of Korean CSS with the *ARID1B* mutation. At first, our patient showed partial corpus callosum agenesis, hypotonia, congenital heart defects, and feeding difficulties. As the patient aged, he showed developmental delay, seizures, and recurrent infections. His height remained short and coarse facial features became clearer. Targeted gene panel sequencing confirmed the clinical diagnosis of CSS, identifying a novel *de novo* variant in *ARID1B*.

CSS is recognized as the human Brahma associated factor (BAF, also known as SWItch/ Sucrose Non-Fermenting, SWI/SNF) complex disorder

(Mannino *et al.* 2018). In recent studies (Tsurusaki *et al.* 2012; Van Houdt *et al.* 2012; Santen *et al.* 2013), demonstrated associations between variants in BAF complex components and intellectual disability syndromes. The BAF complex is a chromatin remodeling structure and is crucial for transcription, cell differentiation, DNA repair, and tumor suppression (Hargreaves & Crabtree 2011; Hoyer *et al.* 2012; Tsurusaki *et al.* 2012; Tsurusaki *et al.* 2014). *ARID1* is the largest subunit of the BAF complex and is expressed as two isoforms: *ARID1A* and *ARID1B* (Tsurusaki *et al.* 2014; Vasileiou *et al.* 2015). Furthermore, *ARID1B* is expressed mostly in the brain and in embryonic stem cells (Hoyer *et al.* 2012). The *ARID1B* encodes 20 exons and produces a transcript of 9648 bp (NM_020732.3). The *ARID1B* protein is made of 2249 amino acids (NP_065783.3). Loss of *ARID1B* expression leads to aberrant chromatin remodeling and; therefore, is causative of CSS.

Up until recently, 245 disease-causing mutations have been identified according to HGMD (version 2020.01). The most common types of reported *ARID1B* mutations are frameshift (45.7%), followed by nonsense (24.4%) and gross deletion (18.5%). In line with this, the vast majority of reported pathogenic variants are truncating (Santen *et al.* 2012; Tsurusaki *et al.* 2012; Santen *et al.* 2013; Sim *et al.* 2015; van der Sluijs *et al.* 2019).

Individuals with pathogenic *ARID1B* variants are generally at the milder end of the spectrum of CSS. Facial features are mild and distal digital hypoplasia is usually limited to the fifth digit. Two-thirds of the patients reported moderately severe feeding problems, while seizures and hypoplasia of the corpus callosum are noted in fewer cases (Santen *et al.* 2014; Tsurusaki *et al.* 2014). Our patient exhibited most of the characteristic features of CSS such as developmental delay, partial corpus callosal agenesis, congenital anomalies (PDA and cryptorchidism), epilepsy, hypoplastic digits/nails, hypertrichosis, and facial dysmorphism. However, he did not show vision or hearing impairments.

As CSS is not a severely fatal and curable disease, regular evaluation by a pediatrician and multidisciplinary therapeutic interventions are recommended. In particular, attention to developmental progress and growth issues are needed. If slow growth persists, hormonal evaluation such as thyroid function, growth specific factors, and bone age studies should be completed to assess poor growth velocity. Feeding difficulties should also be tracked. Regular follow-ups for ophthalmologic and hearing abnormalities should be included in surveillance.

In conclusion, this report describes a novel frameshift mutation in *ARID1B* in a 3-year-and-6-month-old Korean boy with CSS. Patients with the following features should be assessed for CSS: developmental delay, brain anomalies, hypotonia, characteristic facial features, hypertrichosis with sparse scalp hair, hypoplasia or aplasia of the fifth digit nail and/or toenail, and congenital anomalies. Early medical attention to patients diagnosed with CSS is needed to provide timely multidisciplinary management, considering developmental issues, congenital problems, growth insufficiency, and genetic counseling for the next generation. In addition, targeted gene panel sequencing can be used as an effective tool for the diagnosis of rare complex syndromes such as Coffin-Siris syndrome.

ETHICAL STATEMENT

Informed consent was obtained from the parents of the patient and this research was approved by the Institutional Review Board of Samsung Medical Center (approval number: 2012-05-080-015).

CONFLICTS OF INTEREST

There is no conflict of interest.

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