CASE REPORT

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Early Diagnosed Infant: Coffin Siris Syndrome by Novel Frameshift Mutation in ARID1B

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Abstract

Coffin Siris Syndrome (CSS) is a rare neurodevelopmental disorder characterized by intellectual disability, developmental delay, and dysmorphic features. We reported an infant at 3 months of age, attended with unable to meet the milestones. He had thick-arched eyebrows, long eyelashes, bulbous nasal tip, hypertrichosis, thick and everted lips. We studied for different cardiac, genitourinary, gastrointestinal, and ophthalmological abnormalities. Whole exome sequencing of the patient revealed a gene responsible for CSS, a novel de novo frameshift mutation in ARID1B. We identified a novel heterozygote variant c.3955dupC in the ARID1B (p.Gln1319ProfsTer14). Clinicians should consider the coexistence of genetic syndromes in patients with generalized hypotonia, dysmorphological features, and intellectual disability. Early diagnosis is crucial for treatable diseases. For this reason, consultations should be requested from genetics departments for more comprehensive genomic testing.

Keywords: hypotonic infant, ARID1B, Coffin Siris syndrome, WES.

Introduction

Coffin Siris Syndrome (CSS) is a rare neurodevelopmental disorder characterized by intellectual disability, developmental delay, and dysmorphic features. Heterozygous germline mutations that are mostly in the AT-rich interaction domain-containing protein 1B (ARID1B) gene on chromosome 6q25 result in the syndrome. The mutations in these genes cause impaired function in chromatin remodeling complexes. These complexes are essential in controlling and maintaining the activities of genes (1). To date, the mutations in the genes encoding chromatin remodeling complex subunits are ARID1A, ARID1B, ARID2, DPF2, SMARCA4, SMARCC2, SOX11, SOX4, SMARCE1, SMARCD1 and SMARCB1 (2,3).

Coffin Siris syndrome is one of the common causes of intellectual disability (4).The features of CSS are development delay, hypertrichosis, sparse hair, unique course facial features as bushy eyebrows, wide mouth with thick lips. Gene mutations of CSS may lead to brain defects and the tendency for brain tumors. In 1970, Coffin and Siris described the syndrome at first in three females with mental retardation and absence of the fifth distal phalanges (5).

Here, we present one of the few cases of CSS diagnosed at an early age in the literature. A new frameshift ARID1B Mutation was detected in the whole-exome sequencing of the patient, who was diagnosed at the age of three months, due to his dysmorphic features and developmental delay. By examining the parental samples, we determined that the mutation was de novo.

Case Report

Physical examination was performed at the age of 3 months. He has short stature of 60 cm (-0.48 SDS) and his weight is 4.9 kg (-1.72 SDS). Occipital Frontal Circumference is 40.5 cm (-0.44 SDS). Facial phenotype includes coarse facial features with low anterior hairline, thick arched eyebrows and long eyelashes, flat nasal bridge and bulbous nasal tip, wide mouth, hypertrichosis over the frontal region of his head, thick and everted lips (Figure 1A, B). He has bilateral protruding ears, without abnormal implantation. He has short distal phalanges of fingers, and hypoplastic toenails (Figure 1 C, D). He has generalized hypotonia with hypermobile joints.

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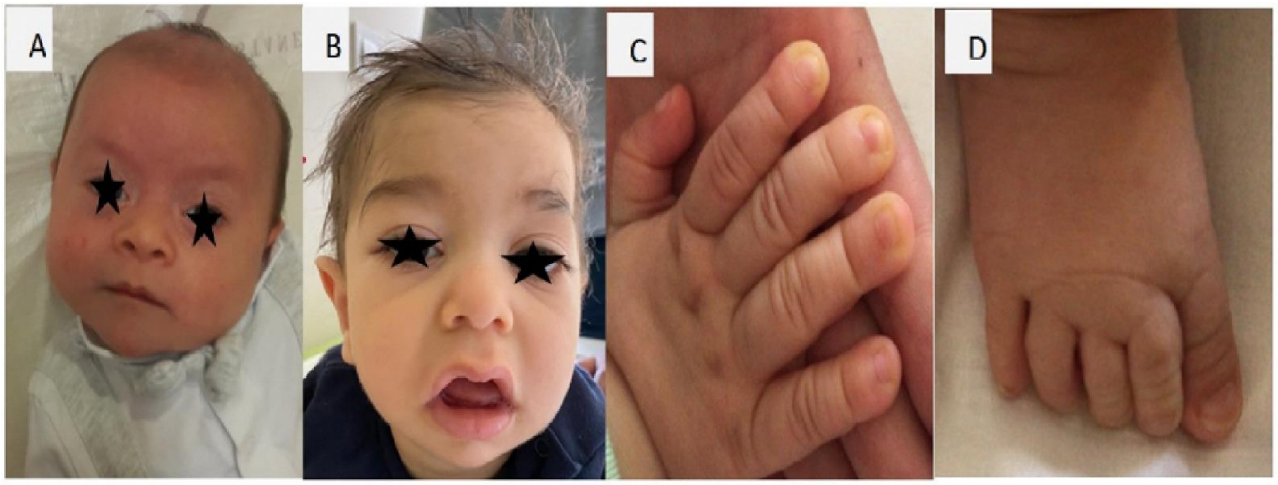

Fig. 1. The facial features of Coffin-Siris syndrome at age of 3 months (A) and 6 months (B), hypoplastic terminal phalanges of fifth finger(C) and dystrophic toenails (D)

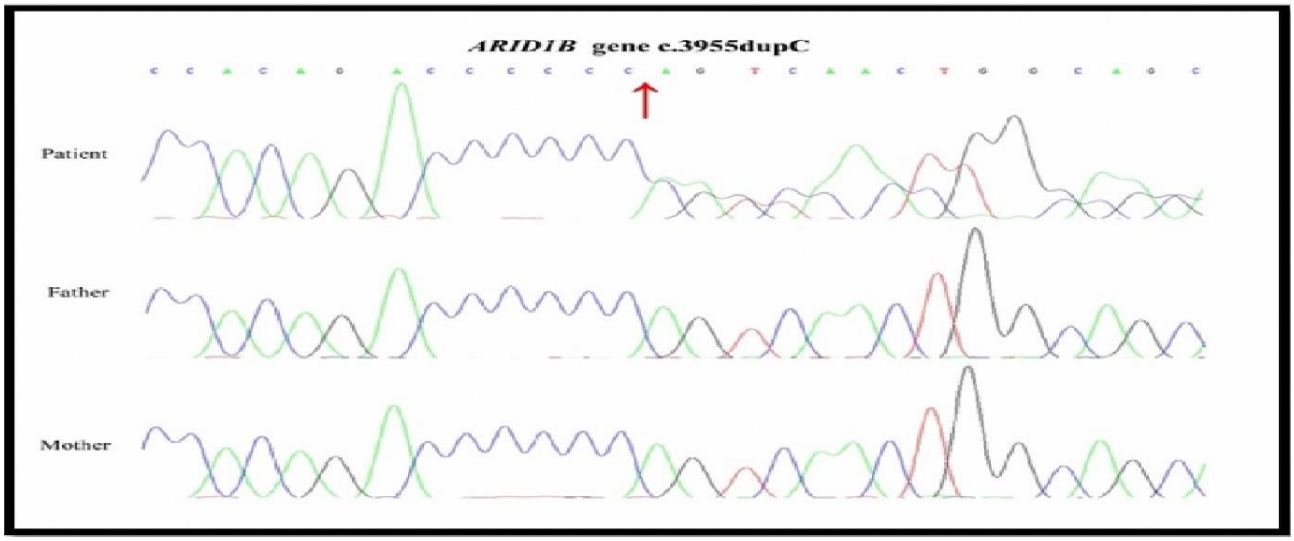

Fig. 2. Sanger sequence analysis of patient and his parents. The heterozygous mutation of ARID1B (NM_001374828.1) gene with c.3955dupC (p.Gln1319ProfsTer14) of patient pointed with red arrow

There was no abnormality detected in his basal metabolic screening. Brain magnetic resonance imaging of the patient revealed neither callosal malformation nor any other malformation of cortical development. His basal electroencephalogram was unremarkable. Either visual or hearing impairment was not determined. His echocardiography, spine X-ray for detecting scoliosis, and abdominal ultrasound scans were resulted in normal.

Molecular Analysis: Conventional cytogenetic analysis and molecular cytogenetic analysis as well as SMN1-exone-7-8 deletion analysis for spinal muscular atrophy were all normal in the patient. Whole Exome Sequencing (WES) data of the patient were analyzed according to the American College of Medical Genetics and Genomics (ACMG) criteria (ACMG-2015) (6). Databases such as PubMed, "OMIM (Online Mendelian Inheritance in Man)", ORPHANET, "ExAC", 1000Genomes, "ESP" and "in silico" analysis programs such as "Mutation Taster, PolyPhen2, PROVEAN, SIFT, GERP, CADD, Phred" were used. We found a heterozygous frameshift mutation in the ARID1B (NM_001374828.1) c.3955dupC (p.Gln1319ProfsTer14) in patient. The incidence of this variant in the community is not reported in gnomAD_genome and gnomAD_exom.

This variant was investigated by Sanger sequence analysis in patient and the parents. The patient was heterozygous, and his parents were wild type in terms of this variant. Therefore, this mutation was considered de-novo (Figure 2). According to the ClinVar data base two cases with this mutation were reported. Clinical features of one case were

not been available (SCV001428686.1), but those of other were reported as following: EEG abnormality, cryptorchidism, behavioral abnormality, aplasia/hypoplasia of the corpus callosum, intellectual disability, and profound myopia (SCV000999332.1).

Discussion

We reported a 3 month old aged case of CSS who is diagnosed at a very early age, which is rarely described in the literature. He has developmental delay and hypotonia as well as unique facial features as bushy eyebrows, hypertrichosis, wide mouth with thick lips. Medical examinations for investigating an accompanying cardiac, genitourinary, gastrointestinal, and craniofacial abnormalities, audio-visual impairments, and nutrition difficulties was not detected. A novel frameshift mutation in ARID1B was identified. The mutation in the patient was regarded as de novo according to the gene analysis on the parental blood samples.

Hypotonia and delayed developmental milestones may indicate underlying diseases like endocrinopathies, nervous system abnormalities, muscular diseases, genetic disorders, and inborn errors of metabolism. Central hypotonia in infancy includes non-syndromic causes (hypoxic-ischemic encephalopathy, brain damage, and intracranial hemorrhage) and syndromic hypotonia (chromosomal disorders, congenital syndromes, some inborn diseases of metabolism, and several neurometabolic diseases) (7). In our patient, syndromic hypotonia was suspected because his examination was consistent with generalized hypotonia accompanied by preserved deep tendon reflexes, facial dysmorphic features, and lack of muscle weakness.

Coffin-Siris syndrome is a malformation syndrome with intellectual disability, developmental delay (100 %), hypoplastic fifth fingers/nails (81 %) and sparse hair as well as more possible hypertrichosis, associated malformation patterns in the head (broad nasal bridge, low set ears, cleft palate, choanal atresia, hearing loss) and the heart (ventricular septal defects , malposition of great arteries, and patent ductus arteriosus) (8,9).

Santen et al. advocated that there are clear phenotypic differences in the comparison of patients with the SMARCA2 mutation and patients with other mutations of the chromatin remodeling complexes. By phenotype-genotype correlation, they suggest that although patients with the SMARCB1 mutation have distinctive physical findings and severe growth retardation, the clinical picture of patients with ARID1B mutations varies considerably (10). The ARID1B mutations has been reported as having mild to severe phenotype amongst CSS spectrum in aspects of mental development (severe speech and motor delay), acquisition of feeding functions, development of seizures and association with malformed structure of brain such as hypoplasia of the corpus callosum (11,12). Although our patient did not show feeding difficulties and cortical malformative changes on MRI, literature has shown that approximately 30-40% of patients with CSS have brain anomalies including delayed myelination, white matter changes, colpocephaly, mega cisterna magna, enlarged Virchow-Robin spaces, and hypoplasia or aplasia of the corpus callosum(11).

The performed conventional and molecular cytogenetic analysis was unable to reveal any diagnosis for the patient. WES analysis of the patient revealed a novel de novo homozygote variant in the ARID1B, confirming the clinical diagnosis of Coffin Siris syndrome. Previously reported two cases were detected in the ClinVar database. But the clinical features of one had not been reported. The other case has reported to have cryptorchidism intellectual disability, maladaptive behavior, and myopia as well as abnormal features on EEG and aplasia/hypoplasia of the corpus callosum on MRI. Our patient didn't present with any EEG abnormalities nor callosal malformation on MRI, although careful follow-up studies are necessary for the final conclusive phenotype of the feature.

In pediatric practice, children with intellectual disability, hypotonia are frequently admitting outpatient clinics. Meticulous examination of those children for dysmorphic features should be encouraged. Under these cases, a comprehensive genomic analysis would be reasonable to help precise diagnosis. Early diagnosis would help to predict the comorbidities of other systems or to manage the treatable diseases.

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Declaration of interest: None

Ethical Statement: All the procedures followed by the authors were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and

with the Helsinki Declaration of 1975, as revised in 1983. The privacy rights of our patient was always observed. Informed consent was obtained from the parents of the patient.

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