

CLINICAL REPORT

De novo splice site variant of *ARID1B* associated with pathogenesis of Coffin–Siris syndrome

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Abstract

Background: Coffin–Siris syndrome is an extremely rare syndrome associated with developmental and congenital anomalies. It is caused by heterozygous pathogenic variants of *ARID1A*, *ARID1B*, *SMARCA4*, *SMARCB1*, *SMARCE1*, and *SOX11*.

Methods: This case study presents the whole exome sequencing of a patient with characteristic clinical features of Coffin–Siris syndrome. Analysis included Sanger sequencing of complementary DNA and bioinformatic analysis of the variant.

Results: Analysis of cDNA Sanger sequencing data revealed that the donor splice site variant led to skipping of exon 19. Further, bioinformatic analysis predicted abnormal splicing in a translational frameshift of 11 amino acids and the creation of a premature termination codon. Results found a novel de novo splice site variant c.5025+2T>C in the *ARID1B* and truncated 1 633 amino acid protein NP_065783.3:p.(Thr1633Valfs*11).

Conclusion: Truncated *ARID1B* resulted in loss of the BAF250 domain, which is part of SWI/SNF-like ATP-dependent chromatin remodeling complex. The severe clinical manifestation presented by the proband was attributed to the disappearance of the BAF250 domain in the *ARID1B* protein. Our finding provides strong evidence that this pathogenic variant of exon 19 caused a frameshift mutation in the *ARID1B* at the terminal exon, resulting in the expression of a severe phenotype of CSS.

KEYWORDS

ARID1B, cDNA functional analysis, Coffin–Siris syndrome, de novo splice site variant, intellectual disability, skipping of exon 19, WES

1 | INTRODUCTION

Intellectual disability (ID) affects about 1–3% of the general population worldwide and is the most prevalent type of severe brain disorder. Evaluation of the genetic causes of ID remains challenging as the condition is clinically and genetically heterogeneous. ID can occur as an isolated condition, a variety of congenital anomalies, or other clinical symptoms

as part of a syndrome. More than 60 structural variants and over 700 genes have been proposed to cause ID; however, many of the genes associated with ID remain unidentified.

One of the genes associated with ID is *ARID1B* (MIM #614556) (Hoyer et al., 2012; Santen et al., 2012). In 2012, Hoyer et al. discovered that the *ARID1B* was directly involved in the pathogenesis of unexplained ID cases, based on their finding of a heterozygous 2.5 Mb deletion (Hoyer et al.,

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2012). Furthermore, in 2018, Bögershausen et al. conducted a candidate gene study on 887 patients with unexplained ID and isolated eight *ARID1B* variants (Bögershausen & Wollnik, 2018). Since this study, *ARID1B* has been found to be the most frequently mutated gene in patients with ID. The *ARID1B* associated phenotypes range from nonsyndromic ID to Coffin–Siris syndrome (MIM #135900, CSS). According to a recent study of 143 patients with pathogenic variants of the *ARID1B*, *ARID1B*-related disorders encompass a spectrum of features, including feeding difficulties, laryngomalacia, speech delay, motor delay, hypertrichosis, and cryptorchidism [PMID:30696996] (van der Sluijs et al., 2018).

1.1 | Case study

Here, we report a case of a patient with the clinical features of CSS caused by a previously undescribed de novo splice site variant detected by whole exome sequencing (WES) in the *ARID1B* and provided a functional evaluation of its effect on pre-mRNA splicing.

The patient was a 13-year-old female born to non-consanguineous Lithuanian parents. She was born following an uncomplicated pregnancy at 37 weeks of gestation via spontaneous vaginal delivery. Her birth weight was 2,200 g (3–10 centile) and Apgar scores at 1 and 5 min were 7 and 7, respectively. The newborn was sluggish, with low muscle tone and remained in the neonatal intensive care unit a few days after birth. Psychomotor delay was noted from infancy. When the infant was 16 months old, she was assessed according to the DISC scale, and her psychomotor development was evaluated at the range of 4 (gross motor) to 9 (auditory attention and memory) months. She could sit independently at 2 years and walk unassisted at 3 years. Brain CT at age 6 revealed an abnormal configuration of the ventricles, agenesis of the corpus callosum, and hypoplasia of the superior part of the left cerebellar hemisphere. EEG was normal. The proband exhibited extreme myopia (−23 in OD and −22 in OS) and myopic macular degenerative changes. An echocardiogram at the age of 8 denoted aortic valve insufficiency and mitral valve prolapse. Additional testing such as abdominal ultrasound, hearing examination, and endocrinological evaluation appeared normal. However, the proband experienced frequent recurrent infections. During her final examination at the age of 13 years and 10 months, her head circumference was 54 cm (25–50 centile), height was 145 cm (<3rd centile), and weight was 50.5 kg (50th centile). She presented with coarse facial features, low forehead, wide and thick eyebrows, long eyelashes, prominent ears, opened mouth, thick lower lip, sialorrhea, limited extension of the elbows, hypermobile small joints, brachydactyly, clinodactyly of the fifth finger, small nails, flat feet, one café au lait spot,

sparse and rough scalp hair, hirsutism, as well as obesity (Figure 1a–f). Her gait was unstable, she was recently toilet-trained, mute, and her ID was severe (IQ 23).

As no cytogenetic alterations were identified, WES of the proband and her healthy parents was performed.

2 | METHODS

2.1 | Whole exome sequencing

Genomic DNA (gDNA) was extracted from the peripheral blood lymphocytes using a phenol–chloroform extraction method. The WES was performed using a protocol that we have previously utilized successfully to identify the potential cause of this Mendelian trait disease (Alfaiz et al., 2014; Borck et al., 2015; Gueneau et al., 2018; Lodder et al., 2016; Tumienė et al., 2017). Briefly, exomes were captured using the Agilent SureSelect Human All Exon V5 enrichment kit (Agilent), and multiplex sequenced (6-plex) on an Illumina HiSeq 2,500 (Illumina, Inc.) platform to reach about 100-fold coverage. Resultant reads were mapped to the human reference genome UCSC genome browser build 38. Variants and small indels (up to 20 bp) were called using GATK v.3 analysis pipeline (Van der Auwera et al., 2013). BAM-formatted files of the mother, father, and child were combined using Samtools software. De novo variants were identified by VarScan software. A potential variant was deemed to be de novo if it was identified in the offspring but not present in either parent at the same position. Parameters used for the filtration of false-positive variants were described previously by Pranckėnienė et al. (Pranckėnienė, Jakaitienė, Ambrozaitė, Kavaliauskienė, & Kučinskis, 2018). All filtered and manually reviewed, de novo variants were annotated using ANNOVAR. Sanger sequencing of *ARID1B* coding region was amplified via polymerase chain reaction (PCR) with primer sets listed in Table S1. The resulting PCR product was purified and sequenced using BigDye Terminator kit v3.1 (Applied Biosystems) and ABI PRISM 3130xl Genetic Analyzer (Applied Biosystems). The resulting sequence was aligned with the *ARID1B* reference sequence (GenBank NCBI: NM_020732.3) using Nucleotide Blast toolkit, Mutation Taster (<http://www.mutationtaster.org/>), and Human Splicing Finder (<http://www.umd.be/HSF3/>) databases were used for predicting splice site alterations. Potential variants in the *ARID1B* protein (UniProtKB: Q8NFD5) were predicted using ExPASy Bioinformatics Resource Portal (<https://www.expasy.org/>) and Pfam 32.0 database (<https://pfam.xfam.org/>).

2.2 | Functional analysis of cDNA

Total RNA of the proband was isolated from whole blood using a Tempus™ Blood RNA Tube and Tempus™ Spin RNA



FIGURE 1 (a–b) Front and side facial views of the patient at 7 years of age. (c–f) Front and side facial views as well as the hands of the patient at the age of 13 years

Isolation Kit (Thermo Fisher Scientific). Complementary DNA (cDNA) was synthesized from total RNA using a High-Capacity RNA-to-cDNA Kit (Thermo Fisher Scientific). PCR of cDNA sequence flanking donor splice site variant of *ARID1B* was performed using specific primers designed with Primer Blast (<https://www.ncbi.nlm.nih.gov/tools/primer-blast/>) software. The designed primer pairs are listed in Table S1. In order to elucidate the pathogenicity of the detected variant, functional analysis using the proband's cDNA amplicon was performed. PCR products were sequenced using standard Sanger sequencing technique as indicated above. The resulting partially overlapping sequence was manually aligned with the reference sequence of the *ARID1B* (NCBI: NM_020732.3).

3 | RESULTS

A de novo 5' splice site NC_000006.12 (NM_020732.3): c.5025+2T>C variant in intron 19 of *ARID1B* was identified. However, data on the frequency of this variant are currently unavailable in the ExAC database. The donor splice site variant was confirmed by Sanger sequencing (Figure 2a). Segregation analysis of gDNA in the samples of the proband and her parents confirmed a de novo origin of the variant (Figure 2a). Moreover, all of the unique de novo variants for this proband are listed in Table S1.

The identified 5' splice site variant was predicted to be “probably pathogenic” utilizing bioinformatics tools. Sanger sequencing of the proband's cDNA sample was performed in order to validate these findings. The analysis of the *ARID1B* coding sequence revealed that the donor splice site variant led to skipping of exon 19 (131 bp in length). In further bioinformatic analysis, the abnormal splicing was predicted to result in a translational frameshift of 11 amino acids and the formation of a premature termination codon, thereby resulting in truncated 1,633 amino acid protein NP_065783.3:p.(Thr1633Valfs*11) (Figure 2).

4 | DISCUSSION

The main clinical signs presented by our patient were characteristic of Coffin–Siris syndrome, including ID, severe speech impairment, corpus callosum agenesis, growth deficiency, coarse facial features, *myopia*, and hypertrichosis. Heterozygous pathogenic variants in one or more genes among *ARID1A*, *ARID1B*, *SMARCA4*, *SMARCB1*, *SMARCE1*, and *SOX11* could be the cause of this syndrome. Due to the genetic heterogeneity of this disorder next generation sequencing has become the preferred method to identify underlying genetic causes in patients with ID. WES analysis of our patient revealed a novel de novo splice site variant in the *ARID1B*, confirming the clinical diagnosis of Coffin–Siris syndrome.



FIGURE 2 (a) Electropherogram of the gDNA sequence of the patient showed a de novo substitution in *ARID1B*: 5025+2T>C. (b) Schematic representation of *ARID1B* reference and mutant sequence with NM_020732.3: c.5025+2T>C variant, denoted skipping of exon 19. (c) Sanger sequencing of proband's cDNA sample reverse strand. (d) Schematic view of truncated ARID1B protein according to the Pfam protein domain database. ARID domain is indicated with a green square, while BAF250_C, which is lost due to the splice site variant in *ARID1B*, is represented with a red square

Recent studies of previously identified variants found human Brahma-associated factor (BAF) chromatin remodeling components in individuals with autism spectrum disorder (ASD) and ID. This finding provided strong evidence that the *ARID1B* created a link between chromatin remodeling and neurodevelopmental disorders. BAF is an ATP-dependent chromatin remodeling complex that controls gene expression by facilitating DNA access for transcription factors (Jung et al., 2017). ARID1, which is the largest subunit of the BAF complex, is expressed as two isoforms: ARID1A and ARID1B (Vasileiou et al., 2015). According to the GTEx portal, *ARID1B* is widely expressed in the skin, thyroid, ovaries, bladder, and whole blood. Elevated expression of this gene has also been detected in the human brain and mammalian embryonic stem cells. Thus, the heterogeneous nature of this gene could explain the vast array of phenotypic variability found in ID patients with mutations of the BAF complex (Santen et al., 2013; Wiczorek et al., 2013).

To date LOVD *ARID1B* database (<https://databases.lovd.nl/shared/variants/ARID1B>; accessed 10 December 2018) contained 153 pathogenic or likely pathogenic variants, 19 of which were in noncoding regions. The majority of variants in the *ARID* family genes were dominantly inherited with heterozygous loss-of-function variants, intragenic or whole gene deletions with the exception of very few de novo missense variants in the *ARID1B* (Bögershausen & Wollnik,

2018). The NC_000006.12 (NM_020732.3): c.5025+2T>C variant of *ARID1B* detected in our patient was predicted to be probably pathogenic by Mutation Taster and the Human Splicing Finder. Sanger sequencing of the patient's cDNA revealed that this variant disrupts the original 5' splice site in intron 19, thus leading to skipping of exon 19 (Figure 2b). Single exon skipping is a common outcome of the pathogenic pre-mRNA splicing variant, resulting in a shift of the open reading frame, formation of a premature termination codon, and, consequently, the synthesis of shorter proteins (Anna & Monika, 2018). The presence of both wild type and abnormal transcript resulting from the c.5025+2T>C variant indicated that the abnormal transcript does not undergo full nonsense-mediated decay, but instead resulted in the production of the truncated protein NP_065783.3:p.(Thr1633Valfs*11) (Figure 2c). The original ARID1B protein (UniProtKB: Q8NFD5) comprises 2,249 amino acids and contains two domains, the AT-rich interaction domain ARID and the C-terminal BAF250 domain. ARID1B truncation results in the loss of the BAF250 domain (Figure 2d), which is part of the SWI/SNF-like ATP-dependent chromatin remodeling complex, which regulates gene expression. Furthermore, BAF250 could act similarly to E3 ubiquitin ligase, which targets histone H2B (Li, Trojer, Matsumura, Treisman, & Tanese, 2010). Previous studies of BAF250b knockout mouse embryonic stem cells showed that the modified cells exhibited

defects in self-renewal capacity and increased differentiation. These findings suggest that BAF250 plays an important role in the early development of an embryo (Yan et al., 2008). ARID1B-associated BAF complexes are involved in the neuronal differentiation and maturation processes within mammalian brains, specifically developing pyramidal neurons to generate a complex dendritic architecture (Boyer et al., 2005; Flores-Alcantar, Gonzalez-Sandoval, Escalante-Alcalde, & Lomelí, 2011; Yan et al., 2008). It is known that haploinsufficiency of *ARID1B* leads to the reduction of GABAergic interneurons in the cerebral cortex, thereby affecting excitatory and inhibitory neurotransmission processes during brain development. Furthermore, it was suggested that haploinsufficiency might affect epigenetic regulation by disrupting normal histone modification processes. Studies in an *Arid1b* heterozygous mouse model revealed aberrant cognitive functioning and impaired social interaction, reflecting clinical features of ASD and ID (Jung et al., 2017). In 2016, Ka et al. explained the mechanism of pathogenesis of both. The authors demonstrated that *ARID1B* deficiency is critical to the expression of genes that are essential for neurite growth and resulted in aberrant dendritic branching, spine formation, and synaptic transmission (Halgren et al., 2012). Therefore, the defective differentiation of pyramidal neurons induced by ARID1B deficiency may cause ID via insufficient reception of inputs and the subsequent generation of abnormal outputs.

5 | CONCLUSIONS

In summary, a truncated 5' splice site c.5025+2T>C variant in *ARID1B* resulted in the presence of an aberrant transcript, indicating nonsense-mediated decay avoidance and predicting the production of a truncated protein. However, further proteomic analysis to validate the presence of a truncated protein would be required. The severe clinical manifestation of our proband and loss of BAF250 domain in the ARID1B protein provided clear evidence that this pathogenic variant in exon 19 caused a frameshift in the final exon, resulting in the expression of a severe phenotype of CSS.

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CONFLICT OF INTEREST

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTION

LP and ES performed data analysis and prepared the manuscript. LG performed WES and in silico analysis of de novo variant. ES performed functional assay and analysis of patient's cDNA sample. EP, VM, and AR contributed to conception and design of the whole experiment, and critically revised the manuscript. VK was the principal investigator.

ETHICAL APPROVAL

The patient's parents provided written informed consent to publish all clinical information, including photographs of the patient in accordance with the Declaration of Helsinki.

ACCESSION CODES

Sequence data have been deposited at the European Nucleotide Archive (ENA), under accession number PRJEB30505 (ERP112968).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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