Phenotypic and Molecular Spectrum of Patients With Switch/sucrose Nonfermenting Complex-related Intellectual Disabilities in Korea

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Research Article

Keywords: Intellectual disability, Chromatin Assembly and Disassembly, Language Development Disorders, Corpus Callosum, Whole Exome Sequencing, Germ-Line Mutation, Phenotype

Posted Date: September 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-518573/v1

Abstract

Background: The switch/sucrose nonfermenting (SWI/SNF) complex is an adenosine triphosphate (ATP)-dependent chromatin-remodeling complex associated with the regulation of DNA accessibility. Germline mutations in the components of the SWI/SNF complex are related to human developmental disorder, including the Coffin–Siris syndrome (CSS), Nicolaides–Baraitser syndrome (NCBRS), and nonsyndromic intellectual disability. These disorders are collectively referred to as SWI/SNF-related intellectual disability (SSRIDD).

Methods: Whole exome sequencing was performed in 564 Korean patients with neurodevelopmental disorders. Twelve patients with SSRIDDs (2.1%) were included, and their medical records were retrospectively analyzed.

Results: *ARID1B*, found in eight patients, were the most frequently-altered gene. Four patients harbored mutations in *SMARCA4*, *SMARCB1*, *ARID2*, and *SMARCA2*. Ten patients were diagnosed with CSS, and one patient without typical phenotypes was classified as *ARID1B*-related intellectual disability. Another patient harboring the *SMARCA2* mutation was diagnosed with NCBRS. All pathogenic variants in *ARID1B* were truncating, whereas variants in *SMARCA2*, *SMARCB1*, and *SMARCA4* were nontruncating (missense) mutations. Frequently-observed phenotypes were thick eyebrows (10/12), hypertrichosis (8/12), coarse face (8/12), thick lips (8/12), and long eyelashes (8/12). Developmental delay was observed in all patients, and profound speech delay was also characteristic. Agenesis or hypoplasia of the corpus callosum was found in half of the patients (6/12).

Conclusions: SSRIDD holds a broad disease spectrum, including NCBRS, CSS, and *ARID1B*-related intellectual disability. Thus, the SSRIDD should be considered as a small but important cause of human developmental disorder.

Background

The switch/sucrose nonfermenting (SWI/SNF) complex, first purified in yeast, is an adenosine triphosphate (ATP)-dependent chromatin-remodeling complex, which regulates DNA accessibility by mobilizing nucleosome in an ATP-dependent manner [1]. The components of the SWI/SNF complex were first recognized as tumor-suppressor genes implicated in oncogenesis [2]. The association between the chromatin-remodeling complex and human developmental syndromes has been discovered with remarkable progress in the next-generation sequencing technique [3–5].

Coffin–Siris syndrome (CSS, MIM #135900) is recognizable and characterized by mental retardation associated with a coarse face, hypertrichosis, sparse scalp hair, and hypoplasia or aplasia of the distal phalanx or nail of the fifth digits. After the discovery of *ARID1B*, several other genes (e.g., *ARID1A*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SOX11*, *ARID2*, and *DPF2*) were identified as the causative genes for CSS as well [6–11].

The Nicolaides–Baraitser syndrome (NCBRS, MIM #601358) overlaps with the CSS syndrome, with more severe intellectual disability (ID) associated with a dysmorphic coarse face, microcephaly, seizure, and prominence of the interphalangeal joints. This syndrome is caused by *SMARCA2*, which is also one component of the SWI/SNF complex [12].

As mutations in the SWI/SNF complex gene are continuously detected in more patients with ID, these conditions are being considered as manifestations of one clinical continuum, with *ARID1B*-related ID and mild CSS at one end, more severe forms of CSS in the middle, and NCBRS at the other end of the spectrum [13]. Therefore, the concept of SWI/SNF-related intellectual disability disorders (SSRIDDs) was introduced to explain this clinical spectrum [13, 14].

This study analyzed 12 unrelated Korean patients, with SSRIDDs confirmed by genetic testing while evaluating the cause of the neurodevelopmental disorder. Clinical information and the result of molecular analysis were analyzed to make a better characterization of the phenotypic spectrum of SSRIDDs among Asian populations.

Methods

Subjects and clinical assessment

Whole exome sequencing (WES) was used to evaluate 564 patients with neurodevelopmental problems, such as developmental delay (DD), ID, epilepsy, neuromuscular disease, or central nervous system (CNS) anomaly, at the Medical Genetic Center of Asan Medical Children's Hospital, Seoul, Korea, from March 2018 to October 2020. Patients who identified mutations or microdeletion in the components of the SWI/SNF complex were included in this study.

Clinical data were retrospectively collected to describe detailed phenotypes of SSRIDDs. Standard deviation scores (SDSs) of the height and body weight were calculated based on the Korean National Growth Charts for children and adolescents [15]. Short stature was defined as the height SDS below − 2.0 SDS for age- and gender-matched normative data [15]. The degree of cognitive impairment was evaluated by the intelligence quotient test or the disability rating system, which was issued by the Korean government.

All subjects were born from nonconsanguineous Korean parents. Blood or buccal smear samples were obtained with the informed consent of the patients' parents. This study was approved by the Institutional Review Board for Human Research of the Asan Medical Center (2021 − 0347).

Molecular analysis

WES was performed using genomic DNA isolated from either whole blood or buccal epithelial cells. Exons of human genes (approximately 22,000) were captured using a SureSelect kit (version C2; Agilent Technologies, Inc., Santa Clara, CA, USA). The captured genomic regions were sequenced using a NovaSeq platform (Illumina, San Diego, CA, USA). Raw genome-sequencing data analyses included alignment to the reference sequence (National Center for

Biotechnology Information(NCBI) genome assembly GRCh37; accessed in February 2009). Mean read depth was 100-fold, with 99.2% coverage higher than tenfold. Variant calling, annotation, and prioritization were performed as previously described [16].

Allele frequency of the general population was assessed by Genome Aggregation Database (gnomAD; http://gnomad.broad institute.org/). The pathogenicity of the variants was evaluated following the guidelines of the American College of Medical Genetics and Genomics (ACMG) [17]. In silico analysis was performed by using a prediction software, such as Polyphen-2 (http://genetics. bwh.harvard.edu/pph2/), MutationTaster (http:// www.mutationtaster.org/), SIFT (https:// sift.bii.a-star.edu.sg/), and PROVEAN (http://provean.jcvi.org/index.php).

Chromosomal microarray (CMA) was performed using the CytoScan 750K assay platform (Thermo Fisher Scientific, Waltham, MA, USA). The genomic DNA (250 ng) extracted from the peripheral blood was digested by NspI and amplified using ligation-mediated polymerase chain reaction (PCR). The PCR product was purified, quantitated, fragmented using DNase I, labeled with biotin, and hybridized overnight (16–18h) in a CytoScan 750K array. After hybridization, the sample was washed and stained with streptavidin using GeneChip Fulidics Station 450. Moreover, the array was scanned using GeneChip Scanner 3000 to generate a CEL file. The CEL file was analyzed using Chromosome Analysis Suite (Thermo Fisher Scientific) and converted to a CYCHP file to visualize the status of genomic copy number and absence of heterozygosity.

Results

Twelve patients with SSRIDDs were found among the 564 patients with neurologic disorders (12/564 patients; 2.13%).

Clinical Features Of Patients With Ssridds

The clinical features of the 12 patients (seven females and five males) are described in Tables 1 and 2.

Table 1
Baseline characteristics of patients with SSRIDDs

Case ID	1	2	3	4	5	6	7	8	9	10	11	12
Diagnosis	CSS	CSS	A-ID	CSS	CSS	CSS	CSS	CSS	CSS	CSS	CSS	NCBRS
Gender	F	F	M	F	M	M	F	F	F	M	F	M
Age at initial visit	18 months	11 months	6 months	At birth	8 months	At birth	2 years	19 days	78 days	4 months	1 months	22 months
Reason of genetic testing	DD	DD	DD	DD	DD	DD, CNS anomaly	DD	DD	DD, epilepsy	DD	DD, short stature	DD, epilepsy
Age at diagnosis (year)	3	3	2	3	5	3	2	5	7	11 months	5	3
Current age (year)	3	6	3	4	6	3	3	6	8	1	15	3
GA at birth (weeks)	38	39	41	38	38	38	37	39	37	37	41	37
Birth weight (kg)	2.7	2.92	2.73	2.13	2.2	2.48	2.9	2.61	2.11	2.28	2.5	2.9
SGA	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No
Perinatal event	OH	No	No	OH	TTN	No	No	No	Seizure	TTN	No	No
Current height (SDS)	−1.33	0.37	−1.13	−2.8	−3.02	−3.51	0.21	−2.72	−2.17	−3.57	−1.97	−0.01
Current Body weight (SDS)	−0.16	−0.27	−0.62	−2.49	−2.19	−2.96	−0.45	−2.32	−3.1	−4.06	−1.59	0.24
Short stature	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes (GH)	No

SSRIDDs, switch/sucrose nonfermenting-related intellectual disabilities; CSS, Coffin–Siris syndrome; A-ID, *ARID1B*-related intellectual disability; NCBRS, Nicolaides–Baraitser syndrome; F, female; M, male; DD, developmental delay; CNS, central nervous system; GA, gestational age; SGA, small for gestational age; OH, oligohydramnios; TTN, transient tachypnea of the newborn; SDS, standard deviation score, GH, growth hormone.

Table 2
Clinical features of patients with SSRIDDs

Case ID	1	2	3	4	5	6	7	8	9	10	11	12
Diagnosis	CSS	CSS	A-ID	CSS	CSS	CSS	CSS	CSS	CSS	CSS	CSS	NCBRS
Gender	F	F	M	F	M	M	F	F	F	M	F	M
Dysmorphic features												
Microcephaly	No	No	No	No	Yes	No	No	No	Yes	Yes	Yes	No
Coarse face	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes
Sparse hair	No	No	No	No	No	Yes	Yes	No	No	Yes	Yes	No
Hypertrichosis	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
Narrow forehead	No	Yes	No	No	No	No	No	No	No	Yes	No	No
Thick eyebrow	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Long eyelashes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes
Eyes	Prominent	–	–	Long PF	–	Prominent	–	Puffy eyes	EF Down slanting PF	Short PF	EF, HT	HT
Flat & broad nasal bridge	No	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No
Low-set ears	Yes	No	No	Yes	No	No	Yes	No	Yes	Yes	Yes	No
Philtrum	–	–	–	Short	–	–	Short	–	Short	–	Long	–
Large mouth	No	No	No	Yes	No	No	No	No	Yes	No	Yes	No
Thick lips	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Micrognathia	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No
Hypoplastic 5th finger	No	No	No	No	No	Yes	Yes	No	Yes	No	No	No
Hypoplastic nail	No	No	No	Yes	No	Yes	Yes	No	No	Yes	No	Yes
Clinodactyly	No	No	No	Yes	Yes	No	No	No	No	No	No	No
Congenital anomalies												
CHD	PFO	PFO	Normal	ASD	Normal	Normal	Normal	Normal	Normal	Normal	VSD	Normal
GI system	–	CP	–	FD	FD	FD	–	CP	IH	IH, FD	IH, FD	–
Cryptorchidism	–	–	No	–	No	No	–	–	–	Yes	–	Yes
Laryngomalacia	No	Yes	No	Yes	No	No	No	No	Yes	Yes	No	No
Frequent infection	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Agenesis /hypoplasia of CC	No	No	ND	Yes	No	Yes	Yes	Yes	Yes	Yes	ND	No
Other CNS anomaly	Small pons, ARC	Normal	ND	Hypoplasia of OB	Normal	Mega cisterna magna	No	No	No	No	ND	Normal
Hearing loss	No	No	No	No	Yes	No	No	No	No	Yes	No	No

SSRIDDs, switch/sucrose nonfermenting-related intellectual disabilities; CSS, Coffin–Siris syndrome; A-ID, *ARID1B*-related intellectual disability; NCBRS, Nicol
Baraitser syndrome; F, female; M, male; PF, palpebral fissure; EF, epicanthal folds; HT, hypertelorism; CHD, congenital heart defect; PFO, patent foramen ovale;
atrial septal defect; VSD, ventricular septal defect; GI, gastrointestinal; CP, constipation; FD, feeding difficulty; IH, inguinal hernia; CC, corpus callosum; ND, no
CNS, central nervous system; ARC, arachnoid cyst; OB, olfactory bulb

Ten patients were clinically diagnosed with CSS, and one patient with subtle dysmorphic features and mild ID was classified as *ARID1B*-related ID. Moreover, 1 patient harboring *SMARCA2* mutation was diagnosed with NCBRS.

The mean age at diagnosis was 39.4 ± 18.9 months old. All patients performed genetic analysis to evaluate DD (12/12 patients, 100%), which was combined with epilepsy (2/12 patients, 16.7%), short stature (1/12 patients, 8.3%), or CNS anomaly (1/12 patients, 8.3%).

Six patients (6/12 patients, 50%) were born small for gestational age. In addition, abnormal perinatal history was observed in five patients, including oligohydramnios (2/12 patients, 16.7%), transient tachypnea of the newborn (2/12 patients, 16.7%), and neonatal seizure (1/12 patients, 8.3%). The mean height at the latest evaluation (age, 5.1 ± 3.5 years) was − 1.80 ± 1.36 SDS, and the mean body weight was − 1.66 ± 1.33 SDS. Seven patients (7/12 patients, 58.3%) were described as short stature patients.

Frequently found dysmorphic features were thick eyebrows (10/12 patients, 83.3%), hypertrichosis (8/12 patients, 66.7%), coarse face (8/12 patients, 66.7%), thick lips (8/12 patients, 66.7%), and long eyelashes (8/12 patients, 66.7%). Broad nasal bridge and low-set ears were found in six patients (6/12 patients, 50%). Hypoplasia of the fifth digital nail (5/12 patients, 41.7%) or the phalanx (3/12 patients, 25%), which is a characteristic feature of CSS, was not frequently observed in the subjects of this study. A congenital heart defect was identified in four patients (4/12 patients, 33.3%). Moreover, several patients had gastrointestinal problems, including feeding difficulties in infancy (5/12 patients, 41.7%), inguinal hernia (3/12 patients, 25%), and constipation (2/12 patients, 16.7%). Frequent infection was noted in seven patients (7/12 patients, 58.3%). Two of the five male patients had cryptorchidism (2/5 patients, 40%). Agenesis or hypoplasia of the corpus callosum was found in half of the patients (6/12 patients, 50%).

DD/ID was a cardinal feature (Table 3). Hypotonia in infancy associated with gross motor delay was noted in all patients (12/12 patients, 100%). The mean age at walking alone was 20.4 ± 3.7 months old. All patients had a delay in language development, including four patients with no meaningful speech at all (4/12 patients, 33.3%). The degree of ID was assessed in patients > 5 years old. Two patients had mild ID (2/12 patients, 16.7%), whereas three showed moderate ID (3/12 patients, 25%). Seizure and hyperactivity were documented in five (5/12 patients, 41.7%) and four patients (4/12 patients, 33.3%), respectively.

Table 3
Degree of developmental delay and intellectual disability in patients with SSRIDDs

Case ID	1	2	3	4	5	6	7	8	9	10	11	12	Total
Diagnosis	CSS	CSS	A-ID	CSS	CSS	CSS	CSS	CSS	CSS	CSS	CSS	NCBRS	
Current age	3	6	3	4	6	3	3	6	8	1	15	3	
Degree of ID	–	Mild	–	–	Moderate	–	–	Moderate	Moderate	–	Mild (IQ 69)	–	
Age of walking alone (months)	18	20	19	23	24	24	24	20	ND	ND	ND	12	
Language delay	No speech	No speech	Yes	Yes	Yes	No speech	Yes	Yes	Yes	Yes	Yes	No speech	12/12
Hyperactivity	No	Yes	No	No	Yes	Yes	No	Yes	No	No	No	No	4/12
Autistic features	No	Yes	No	No	No	No	No	No	No	No	No	No	1/12
Seizure	No	No	No	No	Yes	No	No	Yes	Yes	Yes	No	Yes	5/12
Results of development test (months)													
Age at test (months)	23	53	29	32	9	29	38	55	64	No data	No data	36	
Cognition	13	–	24	22	6	21	22	24	17			12	
Language	8	11	22	17	5	12	16	21	–			6	
Social	11	18	22	20	5	15	18	22	–			6	
Fine motor	16	31	22	24	4	20	22	22	–			15	
Gross motor	15	20	20	22	4	17	20	21	27			24	

SSRIDDs, switch/sucrose nonfermenting-related intellectual disabilities; ID, intellectual disability; CSS, Coffin–Siris syndrome; A-ID, *ARID1B*-related intellectual disability, NCBRS, Nicolaides–Baraitser syndrome; ND, no data

Molecular Analysis Of Patients With Ssridds

WES identified 10 pathogenic mutations from 10 patients, which either parent did not carry. All patients confirmed de novo mutation origin. WES did not find a point mutation in the remaining two patients (subjects 5 and 11), whereas chromosomal microarray revealed microdeletion at regions encompassing the genes of the SWI/SNF complex (Table 4).

Table 4
Genotypes of patients with SSRIDDs (*ARID1B*: NM_001374820.1, *SMARCA4*: NM_001128845.1, *SMARCB1*: NM_001007468.2, *SMARCA2*: NM_003070.5)

ID	Gene	Diagnosis	Nucleotide change	Amino acid change	Exon	Inheritance	Known mutation	Interpretation
1	*ARID1B*	CSS	c.1311C > G	p.Tyr437*	1	*De novo*	Novel	Pathogenic
2	*ARID1B*	CSS	c.1612C > T	p.Gln538*	2	*De novo*	Known	Pathogenic
3	*ARID1B*	A-ID	c.2362C > T	p.Gln788*	7	*De novo*	Known	Pathogenic
4	*ARID1B*	CSS	c.2692C > T	p.Arg898*	9	*De novo*	Known [8]	Pathogenic
5	*ARID1B*	CSS	arr 6q25.3 (157,482,390_157,561,632)x1, 34 kb deletion		10–18 deletion [a]	*De novo*	Novel	Pathogenic
6	*ARID1B*	CSS	c.3345 + 1G > A	–	Intron 12	*De novo*	Novel	Pathogenic
7	*ARID1B*	CSS	c.4849C > T	p.Gln1617*	18	*De novo*	Novel	Pathogenic
8	*ARID1B*	CSS	c.5725del	p.Gln1909Lysfs*65	20	*De novo*	Novel	Pathogenic
9	*SMARCA4*	CSS	c.3128G > T	p.Arg1043Leu	22	*De novo*	Novel	Likely pathogenic
10	*SMARCB1*	CSS	c.1087A > G	p.Lys363Glu	8	*De novo*	Known	Pathogenic
11	*ARID2*	CSS	arr 12q12-13.11 (43,005,992_46,669,000) × 1, 3.7 Mb deletion		Entire deletion	*De novo*	Known [18]	Pathogenic
12	*SMARCA2*	NCBRS	c.3479C > G	p.Ala1160Gly	25	*De novo*	Novel	Pathogenic

SSRIDDs, switch/sucrose nonfermenting-related intellectual disabilities; CSS, Coffin–Siris syndrome; A-ID, *ARID1B*-related intellectual disability, NCBRS, Nicolaides–Baraitser syndrome; ND, No data.

[a] : Multiplex ligation-dependent probe amplification (MLPA) confirmed exons 10–18 deletion of *ARID1B*

Ten patients harbored missense, nonsense, or frameshift mutations in the SWI/SNF complex. *ARID1B* was the most common causative gene (8/12 patients, 66.7%). Four mutations (p.Tyr437*, c.3345 + 1G > A, p.Gln1617*, and p.Gln1909Lysfs*65) were not previously reported, and the other three mutations (p.Gln538*, p.Gln788*, and p.Arg898*) were reported (https://www.ncbi.nlm.nih.gov/clinvar/variation/374179/, https://www.ncbi.nlm.nih.gov/clinvar/variation/450773/, and [8]). *ARD1B* mutations were either nonsense, frameshift, or splicing site mutations. All *ARID1B* mutations were distributed throughout the entire exon, and mutational hotspots were not noticeable. All variants in *ARID1B* were interpreted as pathogenic mutations according to the ACMG guidelines [17]. In subject 5, CMA revealed a 34-kb deletion at 6q25.3 (chr6: 157,482,390 – 157,561,632 [hg19]). Further evaluation using multiplex ligation-dependent probe amplification confirmed microdeletion from exons 10 to 18 of *ARID1B*.

The remaining three patients harbored mutations in the other components of the SWI/SNF complex (i.e., *SMARCA4*, *SMARCA2*, and *SMARCB1*).

SMARCA4 p.Arg1043Leu from subject 9 is a novel mutation that was absent from the general population database (gnomAD). This variant was predicted to be causing disease in MutationTaster, damaging in SIFT, and deleterious in PROVEAN. Moreover, missense change at this amino acid residue, *SMARCA4* p.Arg1043Trp, was previously reported as a likely pathogenic variant in ClinVar. Therefore, *SMARCA4* p.Arg1043Leu was interpreted as a likely pathogenic variant with the evidence of PS2, PM2, PM5, and PP3.

SMARCB1 p.Lys363Glu from subject 10 is a known mutation (https://www.ncbi.nlm.nih.gov/clinvar/variation/212263/). Consequently, it was adjusted to as a pathogenic variant by adding PS2 (PS2, PM2, PP2, PP3, and PP5) after confirming de novo mutation origin.

SMARCA2 p.Ala1160Gly from subject 12, with NCBRS, is located in the mutational hotspot (C-terminal helicase domain) and absent from the general population database. As a novel mutation, *in silico* analysis predicted this variant to be probably damaging in PolyPhen-2, causing disease in MutationTaster, and damaging in SIFT. Thus, *SMARCA2* p.Ala1160Gly was classified as a pathogenic variant (PS2, PM1, PM2, PP2, and PP3).

Subject 11 discovered de novo 3.7-Mb deletion at the chromosomal region 12q12-13.11, where *ARID2* is located by CMA (chr12:43005992–46669000 [hg19]) [18].

Discussion

This study has provided the clinical and molecular information of 12 Korean patients with SSRIDDs. These 12 patients were recruited from the neurodevelopmental disease cohort who underwent WES or CMA to decipher a causative gene for their condition. *ARID1B*, identified in eight patients, was the most frequently altered gene in this study. The remaining four patients harbored mutations or microdeletion in *SMARCA4*, *SMARCB1*, *SMARCA2*, and *ARID2*. The clinical diagnoses were CSS for 10 patients, *ARID1B*-related ID for one patient, and NCBRS for one patient.

The SSRIDDs proportion in the current cohort was 2.13% of the neurodevelopmental disorder (12/564, 2.13%). Unexplained ID due to the SWI/SNF complex mutations was estimated to be up to 3%, and the data (2.13%) of this study supports this idea [19]. Hoyer et al. [3] reported that *ARID1B* mutations were identified in 0.9% of unexplained ID.

Accurate genotype–phenotype correlation was not possible due to the small number of patients. However, several phenotypic differences were found between genotypes.

ARID1B mutations are considered the leading cause of CSS (68–83%) [7, 8, 20]. In this study, the *ARID1B* mutation was 66.7% (8/12 patients). Clinical phenotypes associated with *ARID1B* mutations are highly variable and reported not to be severe compared with other genotypes [21]. As broad genetic tests such as WES are becoming more widely used, individuals who may not fit the diagnosis of classic CSS but rather presented with more inconclusive phenotypes are now being discovered. These *ARID1B*-associated patients with ID are expanding the phenotypic spectrum of the *ARID1B*-related disorder. The major differences between *ARID1B*-ID and *ARID1B*-CSS are the presence of typical dysmorphic features including thick eyebrows, long eyelashes, small nails or absent fifth distal phalanx, and hypertrichosis [22].

For example, subject 3 was incidentally found to have an *ARID1B* mutation while evaluating his mild DD. At first, the patient was described as phenotypically normal without having any congenital anomaly with mild DD. The patient was reevaluated after identifying the nonsense mutation in *ARID1B*, and thick eyebrows and long eyelashes were noted. However, his phenotype was not sufficient to make a clinical diagnosis of CSS.

The *ARID1B*-CSS patients in this study are likely to have a coarse face (6/7 patients, 85.7%), hypertrichosis (6/7 patients, 85.7%), thick eyebrows (5/7 patients, 71.4%), large mouths (5/7 patients, 71.4%), thick lips (5/7 patients, 71.4%), long eyelashes (4/7 patients, 57.1%), and micrognathia (4/7 patients, 57.1%). Nail hypoplasia and short fifth finger are known as cardinal CSS features. However, only two patients (2/8 patients, 25%) with the *ARID1B* mutation showed hypoplasia of the fifth finger and nail hypoplasia was noted in three patients (3/8 patients, 37.5%).

Previous studies [7, 8, 20] reported that the fifth finger and nail anomalies are present in 50–68% of patients. According to a web-based survey (www.arid1bgene.com), which is an open collection of clinical information of patients with *ARID1B* mutations, the frequency of a hypoplastic fifth fingernail and short distal phalanx of the fifth finger was estimated as 24.6% (42/171 patients) and 22.0% (37/168 patients), respectively. Previous high frequency of the fifth finger and nail abnormalities may reflect ascertainment bias because *ARID1B* mutations were preferentially sought in the clinically diagnosed CSS group [7, 8, 20]. Moreover, Mannino et al. [21] also reported the short fifth digital phalanges and/or nail hypoplasia in only 48% of the subjects.

The position of the mutation in *ARID1B* may not influence the severity of the clinical phenotypes. Santen et al. [23] found no relationship between the mutation position on cDNA and clinical severity. For example, patients who had mutations in exon 20, the 3' terminal region of the gene, showed severe ID [23]. In the current cases, subject 8, having mutation in exon 20, also showed a short stature, moderate ID, and a classical feature of CSS.

Almost all patients with *SMARCA4* were reported as having hirsutism, thick eyebrows, long eyelashes, and a less coarse face [24]. Subject 9, with a *SMARCA4* mutation, also exhibited these typical features.

SMARCB1 mutation leads to a severe form of CSS with various CNS anomalies and severe growth retardation [7, 8]. Subject 10 harbored a *SMARCB1* mutation in exon 8, which is a highly-conserved region and well-established causative CSS domain [7, 8]. Born small for gestational age, the patient had gastrostomy due to severe feeding difficulties. Microcephaly and low body weight were observed as well. Partial agenesis of the corpus callosum was demonstrated by the brain magnetic resonance imaging at 6 months old.

Subject 11 had mild mental retardation with a profound short stature. As previously described [18], the patient had overlapping phenotypes including RASopathy-associated features (e.g., profound short stature, epicanthal folds, down slanting palpebral fissures, and webbed neck) and CSS-like features (e.g., thick eyebrows, thick upper lips, and large mouths). Chromosomal microarray revealed 3.7-Mb deletion at chromosome 12q12-13.11 encompassing *ARID2*. As one component of the SWI/SNF complex, *ARID2* haploinsufficiency is associated with CSS-like phenotypes [10]. In a previous study, an increased extracellular signal-regulated kinase (ERK) activation in ARID2 haploinsufficiency was demonstrated, suggesting the association between the SWI/SNF complex and RAS–MAPK pathway [18].

Subject 12, with the *SMARCA2* mutation, showed the typical features of NCBRS (e.g., coarse face with hypertrichosis, thick eyebrows, thick lips, long eyelashes, nail hypoplasia, and microcephaly) but did not have prominent interphalangeal joints. Cognitive dysfunction was more severe than those with other types of SSRIDDs. Differential diagnosis is sometimes confusing because CSS and NCBRS are overlapping syndromes that share similar phenotypes. Moreover, changes in clinical diagnosis exist according to molecular results [8, 13]. Molecular confirmation is required to make an accurate diagnosis between these two overlapping syndromes.

Similar to previous studies [13, 20], *ARID1B* mutations in this study were truncating mutations (nonsense or splicing site mutations), whereas those in *SMARCA4*, *SMARCB1*, and *SMARCA2* were nontruncating mutations (missense mutation). The *ARID1B* haploinsufficiency is a pathogenic mechanism leading to CSS or *ARID1B*-related ID because subject 5 with exons 10–18 deletion in *ARID1B* also showed CSS phenotypes. *AIRD2* haploinsufficiency seems to cause CSS-like phenotypes as well as ID in subject 12. All variants of *SMARCA4*, *SMARCB1*, and *SMARCA2* were missense mutations, implying that they may exert gain of function or dominant negative mechanism of pathogenicity [13, 20].

The SWI/SNF complex components were initially recognized as tumor-suppressor genes associated with oncogenesis. Inactivating mutations in several SWI/SNF components have recently been identified in a wide variety of tumors, including rhabdoid and lung cancer tumors [25]. Furthermore, truncating and missense germline mutations in *SMARCB1* and truncating germline mutations in *SMARCA4* have been shown to lead to a cancer predisposition syndrome [26, 27]. Several cases with tumor formation exist in patients with SSRIDDs. Papillary thyroid cancer was reported in a patient with interstitial 6q25 deletion, including *ARID1B* [28]. Moreover, a patient carrying an *ARID1A* mutation presented with hepatoblastoma in previous literature [6]. van der Sluijs et al. [22] reported a boy with *ARID1B* mutation diagnosed with a Sertoli–Leydig cell tumor and a temporal glioneuronal tumor at 3 and 12 years, respectively. Longer observations are needed to conclude the association of SSRIDDs and cancer predisposition.

The limitation of this study should be noted. As a retrospective study, clinical information was not available in some patients. The phenotypes among the patients were variable because of the varying ages. Thus, longer observation and larger number of patients are needed to determine the whole clinical features and courses of these patients.

Conclusions

SSRIDDs can be found in a small but considerable proportion of the neurodevelopmental disorder patient cohort. Some common clinical features (e.g., hypertrichosis, coarse face, thick eyebrows, long eyelashes, and thick lips) and agenesis or hypoplasia of corpus callosum can be clues suggesting SSRIDDs. Moreover, SSRIDD seems to be a disorder spectrum with *ARID1B*-related ID in one end, classic CSS in the middle, and NCBRS on the other side [21]. The phenotypic spectrum of SSRIDDs will be more clearly documented as more individuals with SSRIDDs are identified by large-scale genomic analysis of unselected patient cohorts and followed up in a longer term.

Abbreviations

ACMG American College of Medical Genetics and Genomics

ATP Adenosine triphosphate

CMA Chromosomal microarray

CNS Central nervous system

CSS Coffin-Siris syndrome

DD Developmental delay

ID Intellectual disability

IITP Institute for Information & Communications Technology Promotion

NCBRS Nicolaides–Baraitser syndrome

NGS Next-generation sequencing

NRF National Research Foundation

PCR Polymerase chain reaction

SDS Standard deviation scores

SSRIDD Switch/sucrose nonfermenting-related intellectual disability

SWI/SNF Switch/sucrose nonfermenting

WES Whole exome sequencing

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board for Human Research of the Asan Medical Center (2021-0347). Blood or buccal smear samples were obtained with the informed consent of the patients' parents.

Consent for publication

Written informed consent for publication of the information regarding clinical details, pedigree was obtained from the participants or their parents or legal guardians.

Availability of data and materials

All data supporting our results are included in this published article. The raw data of whole-exome sequencing of the patient in this study are not publicly available in order to protect participant confidentiality, but are available from the corresponding author on reasonable request. If you want to request access to the data, please contact professor BH Lee at the Department of Medical Genetics in Asan Medical Center Children's hospital.

Reference sequences for *ARID1B* (NC_000006.12), *SMARCA4* (NC_000019.10), *SMARCB1* (NC_000022.11), *SMARCA2* (NC_000009.12) and *ARID2* (NC_000012.12) are available in the Genbank repository. The links to the Genbank repositories are as follows;
ARID1B(https://www.ncbi.nlm.nih.gov/nuccore/NC_000006.12?from=156776026&to=157210779&report=genbank),
SMARCA4(https://www.ncbi.nlm.nih.gov/nuccore/NC_000019.10?from=10960999&to=11062277&report=genbank),

SMARCB1(https://www.ncbi.nlm.nih.gov/nuccore/NC_000022.11?from=23786966&to=23838009&report=genbank), *SMARCA2*(https://www.ncbi.nlm.nih.gov/nuccore/NC_000009.12?from=2015347&to=2193624&report=genbank), and *ARID2*(https://www.ncbi.nlm.nih.gov/nuccore/NC_000012.12?from=45729706&to=45908037&report=genbank). Databases used in this study were Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk), ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar), gnomAD Browser (https://gnomad.broadinstitute.org/), SIFT (http://provean.jcvi.org/index.php), PROVEAN (http://provean.jcvi.org/index.php), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), and Mutation Taster (http://www.mutationtaster.org/).

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Institute for Information & Communications Technology Promotion (IITP) and by a grant from the government of South Korea (MSIT) (grant number 2018-0-00861; Intelligent SW Technology Development for Medical Data Analysis) and the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (NRF-2018M3A9H1078335).

Authors' contributions

BH Lee designed the research. Y Lee and BH Lee wrote the manuscript. Y Choi, GH Seo, GH Kim, C Keum, YM Kim, HS Do, J Choi, IH Choi, HW Yoo collected the data. All authors contributed to the article and approved the submitted version.

Acknowledgements

The authors are deeply grateful to the patients and their families for providing their clinical information.

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