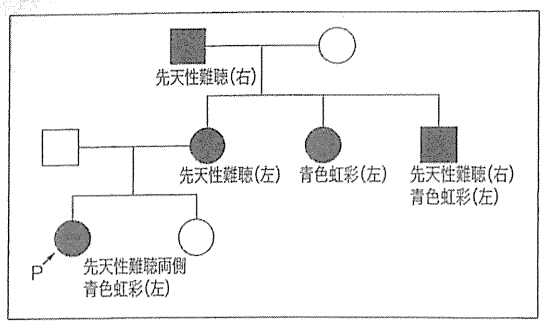

図 1　本症例の家系図
母方の血縁者にWaardenburg症候群の所見がみられる.

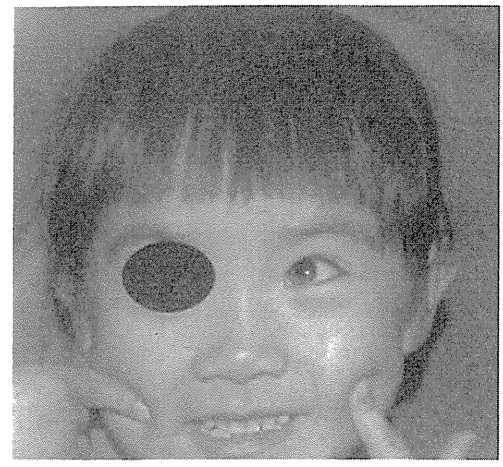

図 2　本症例の身体的特徴
左虹彩の一部が青色である．内眼角の乖離は認めない.

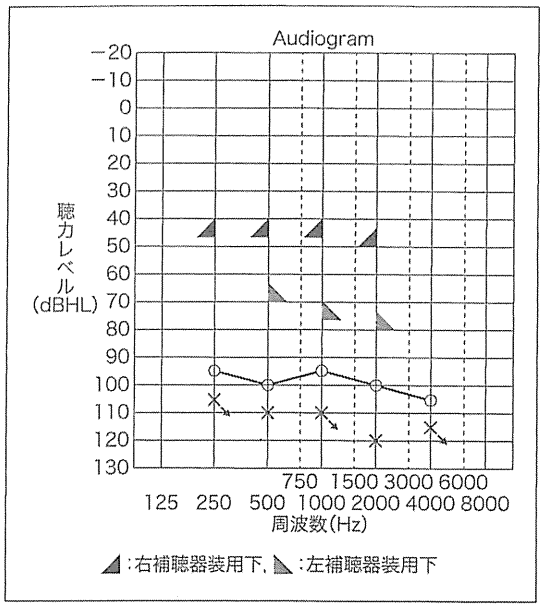

図 3　術前の視覚強化聴力検査（VRA）
裸耳で両側とも重度難聴，補聴器装用でも聴力改善が乏しかった.

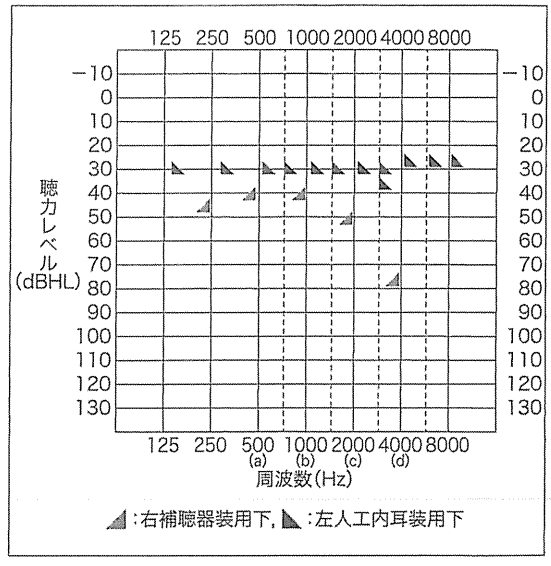

図 4　人工内耳装用下条件詮索反射聴力検査（COR）
補聴器装用時と比べて聴力の改善を認めた.

開始したが，1歳6か月になっても有意語が認められなかった。

身体所見：左虹彩の一部が青色（図2）。内眼角乖離なし。毛髪・皮膚に白斑なし。四肢奇形なし。便秘なし。

術前検査：CTにて中耳・内耳に明らかな奇形なし。MRIにて中耳・内耳に明らかな奇形なし，蝸牛神経は同定可能であり，明らかな萎縮は認めなかった。聴力は裸耳で両側とも90dBHL以上の重度難聴，補聴器装用で右40〜50dBHL，左70〜80dBHLであった（図3）。

遺伝子検査：遺伝子検査ではMITF遺伝子変異を認め，母にもMITF遺伝子変異を認めた。

経過：当科初診時の視覚強化聴力検査(VRA)で，裸耳で右は平均98 dBHL，左は平均113 dBHL，補聴器装用下で右は40〜50dBHL，左は70〜80dBHLの反応は閾値を示した。しかし，言語発達がきわめて不十分であったため，両親の希望および手術適応の条件を検討し，人工内耳埋め込み術を行う方針となった。2歳3か月に聴力検査で閾値の高い左耳に人工内耳埋め込み術を行った。術後は聴覚口話法による教育を受け，2年6か月

が経過した現在は人工内耳装用下のCORで閾値が約30dBHL（図4），聴覚を使った絵カードの指さし検査はすべて正答できる。しかし，絵画語彙検査（PVT）は生活年齢4歳9か月に対して2歳4か月相当と抽象概念の獲得は不十分である。か行，さ行，た行に構音の一部不明瞭さはあるが発声発語活動は良好である。

考察

Waardenburg症候群は1型が最も多く，わが国では，約30,000人に1人と報告されている。聴力障害者の0.5～3.5%を占め，性差はない[2]。Waardenburg症候群は人工内耳装用により，聴覚・言語発達に効果が得られている。そのうち，2型に関する報告は2編あり，いずれにおいても人工内耳装用により聴覚・言語発達への効果が報告されている[7,8]。また，先天性難聴児に対する人工内耳については，早期に人工内耳装用を開始することで良好な言語発達が期待でき，聴覚活用の適期である2歳ごろまでの装用が最も効果的といわれている[9]。人工内耳装用開始年齢（0歳群，1歳群，2歳群）と6歳時点でのWPPSI検査言語性IQの関係を調べた報告では，いずれも早期に装用・療育を開始したほどよい成果を挙げている。さらに2歳群において，言語性IQ120～75とばらつきはあるが，平均言語性IQ95であることから，健聴児に劣らない結果であった[10]。本症例においても，2歳3か月で人工内耳を装用開始し，2年6か月が経過した現在は構音に一部不明瞭さは残るが，装用前と比べると聴覚・言語発達は良好である。そして，就学期である6歳時点での言語性IQは健聴児と同等まで発達がみられるのではないかと期待している。

まとめ

今回われわれは，Waardenburg症候群2型と診断された女児に対して，2歳3か月で左人工内耳埋め込み術を行った。術後，聴覚口話法による教育を受け，良好な聴力を得ている。絵画語彙発達検査では生活年齢4歳9か月に対して2歳4か月相当であったが，発声発語活動は良好である。

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ARTICLE

Genotype-Phenotype Correlation of Coffin-Siris Syndrome Caused by Mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, and *ARID1A*

TOMOKI KOSHO*, NOBUHIKO OKAMOTO, AND COFFIN-SIRIS SYNDROME INTERNATIONAL COLLABORATORS

Coffin–Siris syndrome (CSS) is a rare congenital malformation syndrome, recently found to be caused by mutations in several genes encoding components of the BAF complex. To date, 109 patients have been reported with their mutations: *SMARCB1* (12%), *SMARCA4* (11%), *SMARCE1* (2%), *ARID1A* (7%), *ARID1B* (65%), and *PHF6* (2%). We review genotype-phenotype correlation of all previously reported patients with mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, and *ARID1A* through reassessment of their clinical and molecular findings. Cardinal features of CSS included variable degrees of intellectual disability (ID) predominantly affecting speech, sucking/feeding difficulty, and craniofacial (thick eyebrows, long eyelashes), digital (hypoplastic 5th fingers or toes, hypoplastic 5th fingernails or toenails), and other characteristics (hypertrichosis). In addition, patients with *SMARCB1* mutations had severe neurodevelopmental deficits including severe ID, seizures, CNS structural abnormalities, and no expressive words as well as scoliosis. Especially, those with a recurrent mutation "p.Lys364del" represented strikingly similar phenotypes including characteristic facial coarseness. Patients with *SMARCA4* mutations had less coarse craniofacial appearances and behavioral abnormalities. Patients with *SMARCE1* mutations had a wide spectrum of manifestations from severe to moderate ID. Patients with *ARID1A* also had a wide spectrum of manifestations from severe ID and serous internal complications that could result in early death to mild ID. Mutations in *SMARCB1*, *SMARCA4*, and *SMARCE1* are expected to exert dominant-negative or gain-of-function effects, whereas those in *ARID1A* are expected to exert loss-of-function effects.

KEY WORDS: Coffin–Siris syndrome; BAF (mSWI/SNF) complex; *SMARCB1*; *SMARCA4*; *SMARCE1*; *ARID1A*; intellectual disability (ID)

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INTRODUCTION

Coffin–Siris syndrome (CSS) (OMIM# 135900) is a rare congenital malformation syndrome characterized by developmental delay or intellectual disability (ID), coarse facial appearance, feeding difficulties, frequent infections, and hypoplastic-to-absent fifth fingernails and fifth distal phalanges [Levy and Baraitser, 1991; Fleck et al., 2001; Schrier et al., 2012]. In 2012, 42 years after the first description by Coffin and Siris in 1970, the syndrome was found to be caused by mutations in several genes encoding components of the BRG1- and BRM-associated factor (BAF) complex, originally called as the mammalian SWItch/sucrose nonfermentable (mSWI/SNF)-like complex [Santen et al., 2012a; Tsurusaki et al., 2012]. To date, three research groups (Department of Human Genetics, Yokohama City University Graduate School of Medicine; Center for Human and Clinical Genetics, Leiden University Medical Center; Institut für Humangenetik, Universitätsklinikum Essen, Universität Duisburg-Essen) have published large series describing cohorts of CSS patients with germline heterozygous mutations in BAF complex-related genes: *SMARCB1* mutations in 13 patients (12% of all mutated patients), *SMARCA4* mutations in 12 (11%), *SMARCE1* mutations in three (2%),

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ARID1A mutations in eight (7%), *ARID1B* mutations in 71 (65%), and *PHF6* mutations in two (2%) [Santen et al., 2012a, 2013; Tsurusaki et al., 2012, 2014; Kosho et al., 2013; Wieczorek et al., 2013].

In 2012, 42 years after the first description by Coffin and Siris in 1970 the syndrome was found to be caused by mutations in several genes encoding components of the BRG1- and BRM-associated factor (BAF) complex, originally called as the mammalian SWItch/sucrose nonfermentable (mSWI/SNF)-like complex.

In this review, we describe genotype-phenotype correlation of patients with CSS caused by mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, and *ARID1A*, based on reassessment of clinical and molecular findings of all previously reported patients. Genotype-phenotype correlation of patients with CSS caused by mutations in *ARID1B* and *PHF6* is described in other articles in this issue [Santen and Coffin-Siris SIC, 2014; Wieczorek et al., 2014].

PATIENTS

All previously reported patients with mutations in *SMARCB1* (n = 13), *SMARCA4* (n = 12), *SMARCE1* (n = 3), and *ARID1A* (n = 8) were enrolled (Tables I and II) [Tsurusaki et al., 2012, 2014; Kosho et al., 2013; Santen et al., 2013; Wieczorek et al., 2013]. Clinical information of all the patient, except for two (Y37 and Y48), have been collected again from coordinating researchers (Dr. Miyake, Dr. Santen, and Dr. Wieczorek) or directly from related physicians, according to the common format used throughout this issue, as well as from previously published articles [Santen et al., 2013; Wieczorek et al., 2013]. Overall male ratio was 20/34 (59%): 5/11 (45%) in patients with *SMARCB1* mutations, 9/12 (75%) in those with *SMARCA4* mutations, 1/3 (33%) in those with *SMARCE1* mutations, and 5/8 (63%) in those with *ARID1A* mutations. Overall median age at the last observation was 9 years (range, 6 months–40 years): 9 years in patients with *SMARCB1* mutations, 10 years in those with *SMARCA4* mutations, 17 years in those with *SMARCE1* mutations, and 5.5 years in those with *ARID1A* mutations.

Genotypes

Mutations were confirmed to have occurred de novo in all the patients whose parental samples were available, except L72 whose *SMARCE1* mutation was inherited from his affected mother.

SMARCB1 mutations were all localized within exons 8 and 9 at the C-terminus of the protein, around the highly conserved sucrose/non-fermenting domain 5 (SNF5) (Fig. 1) [Tsurusaki et al., 2012, 2014; Santen et al., 2013; Wieczorek et al., 2013]. The mutation "p.Lys364del" was the only recurrent mutation, which was found in nine patients from various ethnic backgrounds. These patients had strikingly similar manifestations as shown in the following sections. The mutation "p.Lys364del" as well as other described missense mutations were non-truncating, implying that these mutations are expected to exert dominant-negative or gain-of-function effects (excluding haploinsufficiency as a cause) [Tsurusaki et al., 2012, 2014]. A heterozygous missense mutation (c.110G > A; p.Arg37His) was found in a patient with severe ID, childhood hypotonia, hydrocephalus, and characteristic craniofacial features (brachycephaly, midface hypoplasia, coarseness, hypertelorism, synophrys, short nose with anteverted nostrils), whose clinical diagnosis was Kleefstra syndrome (OMIM#610253) [Kleefstra et al., 2012]. Fibroblast study by Kleefstra et al. [2012] showed equal expression of *SMARCB1* from wild-type and mutant alleles, suggesting that altered protein function might cause the phenotype similar to *SMARCB1*-related CSS patients [Kleefstra et al., 2012]. Clinical difference between *SMARCB1*-related CSS patients and the patient with Kleefstra syndrome might be related to the mutation site: at the C-terminus in the former and close to the N-terminus [Kleefstra et al., 2012].

SMARCB1 mutations were all localized within exons 8 and 9 at the C-terminus of the protein, around the highly conserved sucrose/non-fermenting domain 5 (SNF5). The mutation "p.Lys364del" was the only recurrent mutation, which was found in nine patients from various ethnic backgrounds. These patients had strikingly similar manifestations as shown in the following sections.

SMARCA4 mutations were localized widely in the middle of the gene including a helicase/SANT-associated domain (HAS), a DEAD-like helicases superfamily domain (DEXDc), and a helicase superfamily c-terminal domain (HELICc) (Fig. 1). The mutations were all non-truncating (missense or in-frame deletion), implying that they are expected to exert dominant-negative or gain-of-function effects [Tsurusaki et al., 2012, 2014; Santen et al., 2013].

SMARCE1 mutations were all localized within a high-mobility group domain (HMG) (Fig. 1). The mutations were all non-truncating (missense), implying that they are expected to exert dominant–negative or gain-of-function effects [Tsurusaki et al., 2012, 2014;

TABLE I. Clinical Features of Patients with Mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, and *ARID1A* Genes (Mutation, Growth, Craniofacial Features, and Skeletal-limb Features)

	Mutation				Growth			Craniofacial features							Skeletal-limb features				
Patient ID[#]	Nucleotide change	Amino acid change	Sex	Age[§] (years)	Prenatal (SD) Weight/ Length/ OFC	Postnatal (SD) Weight/ Height/ OFC	Sucking/ feeding difficulty (tube/GS)	Sparse scalp hair/ hypertrichosis	Thick Eyeborws/ long eyelashes/ ptosis	Nasal bridge	Philtrum	Upper lip vermilion	Lower lip vermilion	Palatal abnormalities	Hypoplastic or absent 5th finger/ toe	Hypoplastic or absent nail (5th finger/toe)	Hypoplastic or absent nail (other fingers/toes)	Prominent interphalangeal joints /prominent distal phalanges	Scoliosis
SMARCB1 mutations																			
L43	c.1089G>T	p.Lys363Asn	F	13	−1.3/NA/NA	−2.3/−4.5/−3.0	Yes (NA)	Yes/Yes	Yes/Yes/No	Narrow	Normal	Thin	Normal	HP	Yes/NA	Yes	No	Yes/Yes	Yes
L5	c.1091_1093del	p.Lys364del	F	6	−1.8/NA/NA	0.7/−4.8/−2.5	Yes (tube O)	No/Yes	Yes/Yes/No	Wide	Long	Thin	Normal	No	Yes/NA	Yes	No	No/NA	NA
L18	c.1091_1093del	p.Lys364del	F	9	−2.5/NA/NA	−2.6/−4.6/−3.0	Yes (tube O)	Yes/Yes	Yes/Yes/Yes	Normal	Broad, long	Normal	Thick	NA	Yes/NA	Yes	Yes	Yes/Yes	NA
L37	c.1091_1093del	p.Lys364del	M	10	−3.0/NA/NA	−2.0/−3.0/−3.8	Yes (GS O)	yes/Yes	Yes/Yes/Yes	Wide	Broad	Thick	Thick	HP	No/NA	Yes	Yes	No/Yes	Severe
Y4	c.1091_1093del	p.Lys364del	F	21	−0.5/−0.2/0	−3.4/−8.4/−2.9	Yes (no)	Yes/Yes	Yes/Yes/No	Wide	Broad	Thin	Thick	CP	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Severe
Y21	c.1091_1093del	p.Lys364del	F	9	−3.0/−2.4/−1.9	−3.0/−4.1/−4.3	Yes (GS O)	Yes/Yes	Yes/Yes/No	Wide	Long	Thin	Thick	HP	Yes/Yes	Yes/Yes	Yes/Yes	No/Yes	Yes
Y22	c.1091_1093del	p.Lys364del	M	3	+0.2/NA/NA	−2.3/−2.2/−3.4	Yes (tube W)	Yes/Yes	Yes/Yes/Yes	Wide	Long	Thin	Thick	HP	Yes/Yes	Yes/Yes	Yes/Yes	No/NA	No
Y29	c.1091_1093del	p.Lys364del	M	9	−0.9/−2.2/−1.3	−3.3/−5.1/−3.1	Yes (GS O)	Yes/No	Yes/Yes/Yes	Normal	Broad, short	Thin	Normal	No	No/NA	Yes/Yes	Yes/Yes	Yes/Yes	Yes
Y37	c.1091_1093del	p.Lys364del	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Y48	c.1091_1093del	p.Lys364del	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
K2588	*c.1096C>T*	p.Arg366Cys	M	11m	−0.6/−0.2/−1.0	NA/−2.6/−1.5	Yes (NA)	Yes/No	Yes/Yes/No	Flat	Long	Thin	Thick	No CP	No	Yes/Yes	No/No	No/No	No
K2426	c.1121G > A	p.Arg374Gln	M	4	−0.9/−0.9/−0.4	NA/−3.4/−3.2	Yes (NA)	Yes/Yes	Yes/Yes/Yes	Flat	Normal	Thin	Thick	No CP	Yes	Yes/Yes	Yes	NA/No	Yes
Y11	c.1130G > A	p.Arg377His	F	7	−1.8/−2.9/0	−3.1/−2.7/NA	Yes (NA)	Yes/No	Yes/Yes/Yes	Wide	NA	NA	Thick	CP	Yes/Yes	Yes	NA	NA/NA	Yes
SMARCA4 mutations																			
L46	c.1349C>A	p.Ala450Asp	M	4	−1.3/NA/NA	−1.3/−2.0/−2.5	Yes (tube O)	No/Yes	No/Yes/Yes	NA	Long	Normal	Thick	No	Yes/NA	Yes	No	No/No	NA
Y32	c.1372_1395del	p.Lys458 Glu465del	M	6m	−2.1/−2.1/+0.2	−3.7/−3.3/−2.2	Yes (NA)	Yes/Yes	Yes/Yes/No	Flat	Normal	NA	Thick	CP	Yes/Yes	Yes	NA	NA	No
Y9	c.1636_1638del	p.Lys546del	M	18	NA	−1.8/−2.3/NA	No	No/Yes	Yes/Yes/Yes	Narrow	Long	Everted	Normal	SMCP	Yes/NA	Yes/NA	NA	No/Yes	No
Y7	c.2576C > T	p.Thr859Met	M	20	−2.2/NA/NA	−0.2/−2.6/−3.8	Yes (GS)	Yes/Yes	Yes/Yes/Yes	Narrow	Short	Everted	Thick	HP	Yes/Yes	Yes/Yes	Yes/No	Yes/Yes	NA
Y5	c.2653C > T	p.Arg885Cys	M	9	−1.2/−0.9/−0.9	−1.5/−3.2/−3.6	Yes (tube W)	No/Yes	Yes/Yes/Yes	Normal	Short	Everted	Thick	CP	No/Yes	No/yes	No/Yes	No/Yes	No
Y14	c.2654G > A	p.Arg885His	F	8	−2.6/−2.7/−3.9	−1.9/−1.8/−3.0	Yes (NA)	No/Yes	Yes/Yes/Yes	Flat	Short	Normal	Thick	HP	No/Yes	No/Yes	No/No	No/NA	No
Y16	c.2761C > T	p.Leu921Phe	M	11	−1.7/−1.6/−0.6	−1.8/−3.1/−2.9	Yes (tube W)	Yes/Yes	Yes/Yes/Yes	Flat	NA	Thin	Thick	HP	Yes/Yes	Yes/Yes	Yes/Yes	No/Yes	No
Y25	c.3032T > C	p.Met1011Thr	F	16	−1.0/−1.9/+0.1	−1.9/−1.9/−2.3	Yes (NA)	No/Yes	Yes/Yes/No	Flat	Short	Everted	Thick	HP	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	No
L70	c.3127C > T	p.Arg1043Trp	M	4	0.2/NA/NA	−0.7/0.7/−1.1	Yes (NA)	Yes/Yes	No/Yes/No	Normal	Long	Normal	Thick	No	Yes/NA	Yes	No	Yes/No	No
L42	c.3380A > G	p.Asp1127Gly	F	12	−1.0/NA/NA	−2.3/−3.0/−3.7	Yes (NA)	No/Yes	Yes/No/Yes	Normal	Broad, long	Thin	Normal	HP	Yes/NA	Yes	No	No/No	Yes
Y17	c.3469C > G	p.Arg1157Gly	M	4	−1.1/−2.3/−1.3	−3.0/−3.4/−2.7	Yes (GS O)	Yes/Yes	Yes/Yes/Yes	Flat	Normal	Normal	Thick	CP	Yes/Yes	Yes/Yes	Yes/Yes	No/No	No
L2	c.3608G > A	p.Arg1203His	M	40	0.5/NA/NA	−2.3/−3.0/−3.7	Yes (NA)	No/Yes	No/No/Yes	Normal	Short	Thin	Thick	CP	Yes/NA	Yes	No	No/No	No
SMARCE1 mutations																			
K2442	c.218A > C	p.Tyr73Ser	F	3	−2.3/−2.8/NA	NA/−3.7/−4.6	Yes (NA)	Yes/NA	Yes/Yes/Yes	Flat	Short	Thin	Thick	NA	Yes	Yes/Yes	Yes	NA/No	No
Y24	c.218A > G	p.Tyr73Cys	F	17	−2.4/−3.0/−4.2	−4.5/−5.8/NA	Yes (GS W)	Yes/Yes	No/No/No	Narrow	Long	Thin	Thick	CP	Yes/Yes	Yes/Yes	Yes/Yes	No/No	Severe
L72	c.314G > A	p.Arg105Gln	M	19	−0.8/−0.5/0	−2.0/−2.0/NA	Yes (tube W)	No/Yes	Yes/NA/No	Normal	NA	Normal	Thick	No	Yes/NA	Yes	No	Yes/Yes	NA
ARID1A mutations																			
Y3	c.31_56del	p.Ser11Alafs*91	M	2[¶]	−1.0/−1.4/NA	−6.2/−8.9/−3.7	Yes (GS O)	Yes/Yes	Yes/Yes/No	Wide	Short	NA	Thick	CP	NA	Yes	Yes/Yes	NA/NA	NA
L48	c.1113del	p.Gln372Serfs*19	F	1	−3.0/NA/NA	−2.6/−1.7/−0.5	Yes (NA)	NA/Yes	Yes/Yes/Yes	NA	Broad, long	Normal	Thick	No	Yes	Yes	No	No/No	No
Y6	c.2758C > T	p.Gln920*	M	1[¶]	−0.6/−1.1/2.2	−5.5/−8.2/−3.1	Yes (tube O)	Yes/Yes	Yes/Yes/No	Wide	Broad, long	Thin	Thick	CP	Yes/Yes	Yes/Yes	Yes/Yes	No/No	No
L26	c.3679G > T	p.Glu1227*	F	8	−0.2/NA/NA	0/−2.0/0	Yes (tube W)	NA/Yes	No/Yes/Yes	Wide	Broad, long	Thin	Thick	NA	Yes	Yes	No	No/No	No
Y8	c.4003C > T	p.Arg1335*	M	10	NA	50th/3rd/50th	Yes (GS O)	Yes/Yes	Yes/Yes/No	Wide	Long	Normal	Thick	HP	Yes/Yes	Yes/Yes	Yes/Yes	No/Yes	Kyphoscoliosis
K2435	c.5965C > T	p.Arg1989*	M	9	NA	NA/−1.6/−0.3	NA	No/Yes	Yes/Yes/Yes	Flat	Short	Normal	Thick	No CP	No	No/No	Yes	Yes/No	No
L33	c.6493G > T	p.2165*	M	10	0/NA/NA	NA/−0.6/NA	Yes (tube)	NA/NA	Yes/NA/NA	NA	NA	NA	NA	NA	Yes	NA/Yes?	NA/Yes?	NA/NA	Severe
L25	c.6532del	p.Asp2178Thrfs*22	F	3	0/NA/NA	−0.3/−0.3/0.5	Yes (tube O)	No/Yes	No/NA/No	NA	Normal	Thin	Normal	No	Yes	Yes/Yes	No/Yes	NA/NA	No

[#]"Y..." according to the article by Tsurusaki et al. [2014], "L..." according to the article by Santen et al. [2013], and "K..." according to the article by Wieczorek et al. [2013].

[§]age at the last observation.

[¶]died CP, cleft palate; F, female; GS, gastrostomy; H, high palate; M, male; Mo, moderate; NA, data not available; O, tube feeding ongoing; OFC, occipitofrontal circumference; S, severe; SD, standard deviation; SMCP, submucous cleft palate; W, tube feeding weaning off.

TABLE II. Clinical Features of Patients with Mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, and *ARID1A* Genes (Complications, Neurology, Development, and Behavior)

									Neurological features			Development/intelligence			
Patient ID#	Cardiovascular	Gastrointestinal	Genitourinary	Hernia	Hearing impairment	Visual impairment	Ophthalmological abnormalities	Frequent infection	Hypotonia	Seizures	CNS structural abnormalities	Developmental delay/intellectual disability	Age of independent sitting/walking	Speech	Behavioral abnormalities
SMARCB1 mutations															
L43	No	No	No	U	Mo	No	NA	Yes	Yes	No	NA	Mo-Se	11m/2y2m	Sen	Ta n
L5	Dex, PS	PyS	HK	NA	Yes	Yes	My, Sph	NA	No	Yes	ACC	Se	NA	NW	NA
L18	ASD	No	No	NA	NA	Yes	My	Yes	Yes	Yes	ACC	Se	3y/6y	NW	NA
L37	Dex	GER, PyS	Cr	H, I	NA	Yes	Am	Yes	Yes	Yes	ACC	Se	No/No	SW	HyAc
Y4	No	V	NA	No	Se	NA	NA	NA	Yes	Ye s	NA	Se	2y3m/7y	NW	Im, HyAc, SI
Y21	No	GER	No	I	Se	No	NA	Yes	Yes	Ye s	ACC	Se	No/No	NW	No
Y22	No	PyS	No	I	No	No	NA	Yes	Yes	No	ACC	Se	2y/No	NW	No
Y29	No	GER	VUR, HU, HN, VD	I, U	No	No	NA	Yes	Yes	Yes	ACC	Se	No/No	NW	No
Y37	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Y48	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
K2588	No	NA	No	U	NA	NA	NA	No	No	NA	ACC	Mi	7m/No	Yes	NA
K2426	ASD, VSD, PS	PyS	Cr	NA	Yes	Yes	NA	Yes	No	Yes	ACC	Mo	NA/2y6m	NW	HyAc
Y11	VSD	No	No	D	Mo	Yes	NA	Yes	Yes	Yes	CH, DW	Se	No/No	NW	No
SMARCA4 mutations															
L46	No	PyS, GER	CF, Cr	NA	No	No	NA	Yes	Yes	No	DW, ACC	Se	9m/2y9m	SW	SAS
Y32	No	No	No	No	Yes	No	NA	No	No	No	CH, DW, ACC	Ye s	NA	NA	NA
Y9	No	No	No	No	No	Ye s	My, As	No	Yes	Yes	NA	Mi	10m/NA	Sen	NA
Y7	No	GOS, Co	No	I	Yes	Yes	My	Yes	Yes	No	NA	Se	2y/6y	SW	HyAc, Im
Y5	No	Co	Cr	No	Mo	Yes	NA	No	Yes	No	CH, ACC	Se	1y3m/6y	NW	HyAc, HySe, SI, Ob
Y14	Yes	GER	No	I,U	No	No	NA	Yes	Yes	No	No	Mo	NA/2y6m	Sen	HyAc
Y16	VSD*, PDA*, PR	DU, Co	No	I	No	Yes	ODC	Yes	No	Yes	NA	Se	NA/6y	NW	No
Y25	No	Co	No	No	Yes	Yes	NA	Yes	Yes	No	ACC	Mo	1y6m/2y8m	Sen	ReMo
L70	VSD	No	No	No	No	No	NA	No	Yes	No	NA	Se	9m/1y6m	NW	HyAc, SAS
L42	No	Co	No	I	No	No	NA	Yes	Yes	No	ACC	Mo	1y/4y	Sen	Ob, SI
Y17	ASD, PDA, MA, PA, SRV,	GER	Cr	Om	No	No	NA	Yes	No	No	ACC	Se	No/No	NW	NA
L2	VSD, PS	No	No	Yes	No	NA	NA	Yes	NA	No	NA	Mo	5m/3y	Sen?	NA
SMARCE1 mutations															
K2442	Dex, ASD, PH	NA	NA	NA	NA	NA	NA	Yes	No	No	CH, DW, ACC	Mo	1y6m/4y6m	NW	No
Y24	AS, TS, MS, CAA	No	NA	No	Se	NA	ONA	No	Yes	Ye s	CH	Se	NA/NA	NW	NA
L72	No	PyS	No	No	No	Yes	My	Yes	No	Yes	NA	Mo	NA/3y	Sen?	HyAc
ARID1A mutations															
Y3	CoA, ASD, VSD	PyS	NA	No	No	No	NA	NA	Yes	No	ACC	Se	No/No	NW	NA
L48	No	No	No	No	No	Yes	ODC	No	Yes	No	ACC	Mo-Se	13m/No	NW?	No
Y6	CoA, VSD, AS, AVB,	AA, RUF	HSp, Cr	No	NA	NA	NA	NA	Yes	No	CH, DW, ACC	Se	No/No	NW	NA
L26	No	No	No	NA	Mi	Yes	My, St	Yes	Yes	No	No	Mi	NA	Sen	Anx, Cm
Y8	ASD*	IO, GER	No	I	Mi	NA	St	Yes	No	NA	ACC	Se	9m/No	NW	HyAc
K2435	No	NA	Cr	NA	No	NA	St	No	Yes	Yes	ACC	Mi	NA/>1y7m	Yes	HyAc
L33	No	HD	No	NA	NA	NA	NA	NA	Yes	No	ACC	Se	NA	NW	No
L25	No	No	No	NA	No	Yes	St	Yes	Yes	Yes	ACC	NA	NA	Yes	NA

#"Y..." according to the article by Tsurusaki et al. [2014], "L..." according to the article by Santen et al. [2013], and "K..." according to the article by Wieczorek et al. [2013].

*spontaneously closed; AA, anal atresia; ACC, abnormal corpus callosum; Am, amblyopia; Anx, anxiety; AS, aortic stenosis; As, astigmatism; ASD, atrial septal defect; AVB, AV block; CAA, cervical arterial anomaly; CF, calyceal fulness; CH, cerebellar hypoplasia; Cm, compulsive; CNS, central nervous system; Co, constipation; CoA, coarctation of aorta; Cr, cryptorchidism; D, diaphragmatic hernia; Dex, dextrocardia; DU, duodenal ulcer; DW, Dandy-Walker malformation; GER, gastroesophageal regurgitation; GOS, gastric outlet syndrome; H, Hiatus hernia; HD, Hirschsprung disease; HK, horseshoe kidney; HN, hydronephrosis; HSp, hypospadias; HU, hydroureter; HyAc, hyperactivity; HySe, hypersensitivity; I, inguinal hernia; Im, impulsiveness; IO, intestinal obstruction; MA, mitral atresia; Mi, mild; Mo, moderate; MS, mitral stenosis; My, myopia; NW, no word; Ob, obsession; ODC, optic disc coloboma; Om, omphalocele; ONA, optic nerve atrophy; PA, pulmonary atresia; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PR, pulmonary regurgitation; PS, pulmonarey stenosis; PyS, pyloric stenosis; ReMo, repetitive movement; RUF, retrourethral fistula; SAS, short attention span; Se, severe; Sen, sentence; SI, self-injury; Sph, spherophakia; SRV, single right ventricle; St, strabismus; SW, several words; Tan, tantrum; TS, tricuspid stenosis; U, umbilical hernia; VD, vesical diverticulum; VSD, ventricular septal defect; VUR, vesicoureteral reflux.

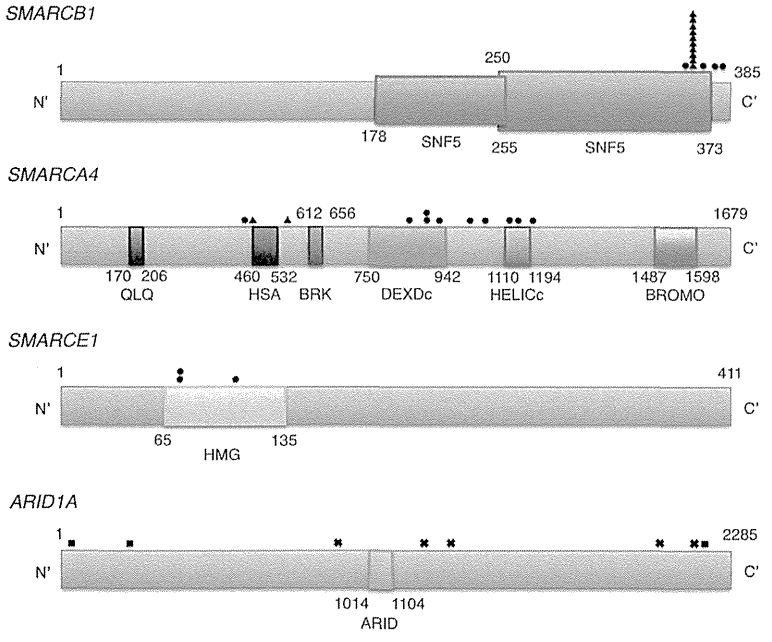

Figure 1. Previously reported mutations in each gene. A black circle indicates a missense mutation, a black triangle indicates a inframe deletion, a black square indicates a nonsense mutation, and a black X indicates a frameshift deletion. Specific domains are shown as follows: sucrose/non-fermenting domain 5 (SNF5); Gln, Leu, Gln motif (QLQ); helicase/SANT-associated domain (HAS); Brahma and Kismet domain (BRK); DEAD-like helicases superfamily domain (DEXDc); helicase superfamily c-terminal domain (HELICc); bromodomain (BROMO); highly-mobility group domain (HMG); and ARID/BRIGHT DNA-binding domain (ARID).

Santen et al., 2013; Wieczorek et al., 2013]. L72 was the only familial case in this series, whose mutation (Arg105Gln) was inherited from his mother with phenotypic similarities [Santen et al., 2013]. However, pathogenicity of this missense variant should be proved through detailed clinical evaluation of L72 and his mother as well as functional analysis.

ARID1A mutations were all truncating (nonsense, frameshift), implying that loss-of-function of the gene would cause the phenotype (Fig. 1) [Tsurusaki et al., 2012, 2014; Santen et al., 2013; Wieczorek et al., 2013]. The mutated transcripts from one of the nonsense mutations (p.Gln920*) were found to be subject to nonsense-mediated decay [Tsurusaki et al., 2012]. Sanger sequencing results of two nonsense mutations (L26 and L33) showed that they were mosaic (clearly lower peaks of the variant alleles than the normal alleles), and that two frameshift mutations (L25 and L48) were also suggested to be mosaic, though it was less obvious [Santen et al., 2013]. There have been only eight patients reported to have *ARID1A* mutations, significantly fewer than those with *ARID1B* mutations (71 patients) [Santen et al., 2012a, 2013; Tsurusaki et al., 2012, 2014; Kosho et al., 2013; Wieczorek et al., 2013], though the pathogenic variants in both genes lead to haploinsufficiency and size of the coding region is comparable (6,855 bp in *ARID1A* and 6,747 bp in *ARID1B*) [Santen et al., 2013]. Furthermore, heterozygous truncating variants in *ARID1A* have been shown to be embryonically lethal in mice, whereas no *ARIB1B*-knockout mice have been reported to date [Gao et al., 2008]. Therefore, truncating heterozygous germline variants in *ARID1A* would be embryonically lethal in human [Santen et al., 2013].

Growth and Feeding

Growth and feeding are listed in Table I and summarized in Table III. Growth was mildly impaired prenatally and more severely impaired postnatally. Sucking/feeding difficulty was observed in almost all the patients, and the majority of them whose data were available had tube feeding, which could be weaned off in approximately one-third of them.

Craniofacial Features

Craniofacial features are listed in Table I, illustrated in Figure 2, and summarized in Table III. The facial gestalt of patients with mutations in each gene could be described as follows: The facial gestalt of patients with the recurrent mutation "p.Lys364del" in *SMARCB1* represented characteristic coarseness (in early childhood, round face with thick and arched eyebrows, short nose with bulbous tip and anteverted nostrils, long philtrum, small mouth, and micro-retrognathia; later, broad nasal bridge without anteverted nostrils, broad philtrum, large tongue, and protruding jaw). The facial gestalt of patients with *SMARCA4* mutations appeared less coarse with characteristic patterns of the phitrum (short or long/broad) and upper lip vermilion (everted or thin) as well as pointed chin especially in older ages. The facial gestalt of patients with *ARID1A* mutations represented some coarseness with short nose and characteristic patterns of the phitrum (short or long/broad) and lower lip vermilion (thick, everted).

The facial gestalt of patients with SMARCA4 mutations appeared less coarse with characteristic patterns of the phitrum (short or long/broad) and upper lip vermilion (everted or thin) as well as pointed chin especially in older ages.

TABLE III. Comparison of Clinical Features of Patients Caused by Mutations in Each Gene (Growth, Craniofacial Features, and Skeletal Features)

Genes	*SMARCB1*	*SMARCA4*	*SMARCE1*	*ARID1A*	Total
Growth and feeding					
Prenatal growth					
Birth weight (mean SD score)	−1.5 (n = 11)	−1.2 (n = 11)	−1.8 (n = 3)	−0.8 (n = 6)	−1.3 (n = 31)
Birth length (mean SD score)	−1.5 (n = 6)	−1.9 (n = 6)	−2.1 (n = 3)	−1.3 (n = 2)	−1.7 (n = 17)
Birth OFC (mean SD score)	−0.8 (n = 6)	−1.1 (n = 6)	−2.1 (n = 2)	2.2 (n = 1)	−0.9 (n = 15)
Postnatal growth at the last observation					
Weight (mean SD score)	−2.4 (n = 9)	−1.9 (n = 12)	−3.3 (n = 2)	−2.9 (n = 5)	−2.3 (n = 28)
Height (mean SD score)	−4.1 (n = 11)	−2.4 (n = 12)	−3.8 (n = 3)	−3.3 (n = 7)	−3.3 (n = 33)
OFC (mean SD score)	−3.1 (n = 10)	−2.9 (n = 11)	−4.6 (n = 1)	−1.2 (n = 6)	−2.6 (n = 28)
Sucking/feeding difficulty	100% (11/11)	92% (11/12)	100% (3/3)	100% (7/7)	99% (32/33)
Tube feeding	86% (6/7)	100% (5/5)	100% (2/2)	100% (6/6)	95% (19/20)
Weaned off tube feeding	17% (1/6)	67% (2/3)	100% (2/2)	20% (1/5)	38% (6/16)
Craniofacial features					
Sparse sculp hair	91% (10/11)	42% (5/12)	67% (2/3)	60% (3/5)	65% (20/31)
Hypertrichosis	73% (8/11)	100% (12/12)	100% (2/2)	100% (7/7)	91% (29/32)
Thick eyebrows	100% (11/11)	75% (9/12)	67% (2/3)	75% (6/8)	82% (28/34)
Long eyelashes	100% (11/11)	83% (10/12)	50% (1/2)	100% (6/6)	90% (28/31)
Ptosis	55% (6/11)	75% (9/12)	33% (1/3)	43% (3/7)	58% (19/33)
Nasal bridge					
Wide	55% (6/11)	0% (0/11)	0% (0/3)	80% (4/5)	60% (18/30)
Flat	18% (2/11)	45% (5/11)	33% (1/3)	0% (0/5)	
Normal	18% (2/11)	36% (4/11)	33% (1/3)	20% (1/5)	27% (8/30)
Narrow	9% (1/11)	18% (2/11)	33% (1/3)	0% (0/5)	13% (4/30)
Philtrum					
Long	40% (4/10)	27% (3/11)	50% (1/2)	14% (1/7)	30% (9/30)
Short	0% (0/10)	45% (5/11)	50% (1/2)	29% (2/7)	27% (8/30)
Normal	20% (2/10)	18% (2/11)	0% (0/2)	14% (1/7)	17% (5/30)
Broad/long	10% (1/10)	9% (1/11)	0% (0/2)	43% (3/7)	17% (5/30)
Broad	20% (2/10)	0% (0/11)	0% (0/2)	0% (0/7)	7% (2/30)
Broad/short	10% (1/10)	0% (0/11)	0% (0/2)	0% (0/7)	3% (1/30)
Upper lip vermilion					
Thin	80% (8/10)	27% (3/11)	67% (2/3)	50% (3/6)	53% (16/30)
Normal	10% (1/10)	36% (4/11)	33% (1/3)	50% (3/6)	30% (9/30)
Everted	0% (0/10)	36% (4/11)	0% (0/3)	0% (0/6)	13% (4/30)
Thick	10% (1/10)	0% (0/11)	0% (0/3)	0% (0/6)	3% (1/30)
Lower lip vermilion					
Thick	73% (8/11)	83% (10/12)	100% (3/3)	86% (6/7)	82% (27/33)
Normal	27% (3/11)	17% (2/12)	0% (0/3)	14% (1/7)	18% (6/33)
Palatal abnormalities					
Cleft palate	20% (2/10)	33% (4/12)[a]	50% (1/2)	33% (2/6)	30% (9/30)
Skeletal-limb features					
Hypoplastic 5th fingers or toes	73% (8/11)	100% (12/12)	100% (3/3)	86% (6/7)	88% (29/33)
Hypoplastic 5th fingernails or toenails	100% (11/11)	100% (12/12)	100% (3/3)	88% (7/8)	97% (33/34)
Hypoplastic other fingernails and toenails	70% (7/10)	50% (5/10)	67% (2/3)	75% (6/8)	65% (20/31)
Prominent interphalangeal joints	44% (4/9)	27% (3/11)	50% (1/2)	20% (1/5)	33% (9/27)
Prominent distal phalanges	75% (6/8)	50% (5/10)	33% (1/3)	20% (1/5)	50% (13/26)
Scoliosis	78% (7/9)	10% (1/10)	50% (1/2)	29% (2/7)	39% (11/28)

SD, standard deviation.

[a]Submucous cleft palate was observed in another patient.

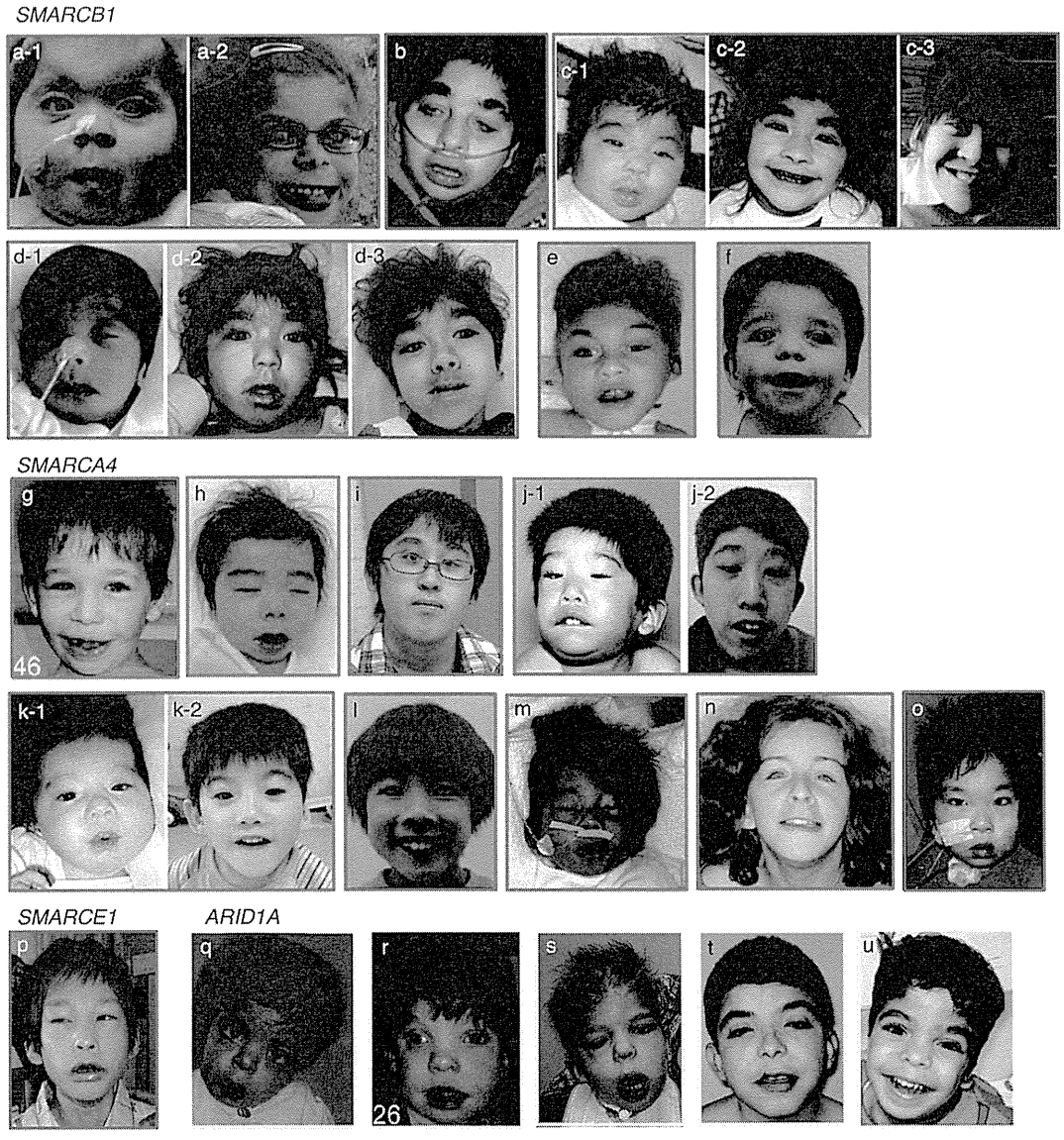

Figure 2. Craniofacial features of patients with mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, and *ARID1A*. *SMARCB1*: L5 (a-1, 2); L37 (b); Y4 at age 2 months (c-1), 6 years (c-2), and 18 years (c-3); Y21 in the neonatal period (d-1), at age 2 years (d-2), and 7 years (d-3); Y29 (e); and K2426 (f). *SMARCA4*: L46 (g); Y32 (h); Y9 at age 18 years (i); Y7 at age 2 years (j-1) and 20 years (j-2); Y5 at age 4 months (k-1) and 5 years and 1 month (k-2); Y14 (l); Y16 in the neonatal period (m); L42 (n); Y17 at age 3 years and 7 months (o). *SMARCE1*: Y24 at age 14 years (p). *ARID1A*: L48 (q); L26 (r); Y8 at age 10 years (s); K2435 (t); and L33 (u). [Figure d-2, m, and s, originally published in Tsurusaki et al. [2012], *in Nature Genetics*; Figure c-1, 2, and 3, d-1 and 3, i, j-1 and 2, k-1 and 2, o, and p, originally published in Kosho et al. [2013], *in American Journal of Medical Genetics Part A*; Figure a, b-1 and 2, g, n, q, r, and u, originally published in Santen et al. [2013], *in Human Mutation*; Figure f and t, originally published in Wieczorek et al. [2013], *in Human Molecular Genetics* by permission of Oxford University Press; Figure e, h, and l, originally published in Tsurusaki et al. [2014], *in Clinical Genetics*]

Skeletal-limb Features

Skeletal-limb features are listed in Table I, illustrated in 3–5, and summarized in Table III. Most of the patients had both hypoplastic 5th fingers/toes and hypoplastic 5th fingernails/toenails. Interestingly, 5th toes and toenails were affected but 5th fingers and fingernails were not affected in Y5 (Fig. 4h-1, 2) and Y14 (3g and 4i) with *SMARCA4* mutations. Other fingernails and/or toenails were affected but 5th fingers/fingernails and toes/toenails were not affected in K2435 (3p and 4r). Frequency of scoliosis is significantly high in patients with *SMARCB1* mutations (severe in Y4 and L33) (Fig. 5), though severe scoliosis was also observed in Y24 with a *SMARCE1* mutation and L33 with an *ARID1A* mutation.

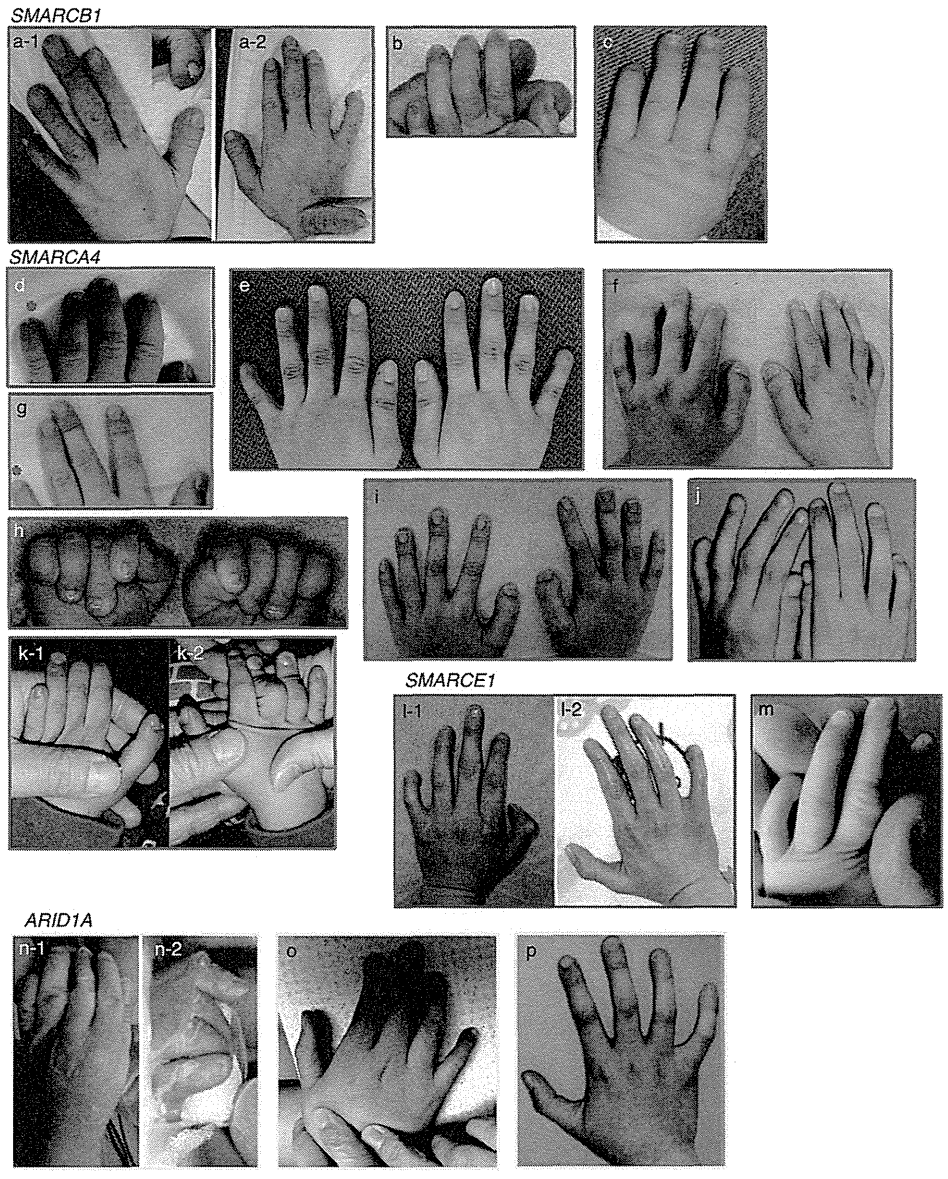

Figure 3. Digital features (hands) of patients with mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, and *ARID1A*. *SMARCB1*: Y4 at age 21 years (a-1, 2), Y29 (b), and K2426 (c). *SMARCA4*: Y32 (d), Y9 at age 18 years (e-1, 2), Y7 at age 20 years (f), Y14 (g), Y16 in the neonatal period (h), Y25 at age 8 years (i), L42 (j), and Y17 at age 3 years and 7 months (k-1, 2). *SMARCE1*: Y24 at age 14 years (l-1, 2), and K2442 (m). *ARID1A*: Y6 in the neonatal period (n-1, 2), Y8 at age 10 years (o), and K2435 (p). [Figure h, originally published in Tsurusaki et al. [2012], *in Nature Genetics*; Figure a-1, 2, e, f, i, k-1, 2, l-1, 2, n-1, 2, and o, originally published in Kosho et al. [2013], *in American Journal of Medical Genetics Part A*; Figure j, originally published in Santen et al. [2013], *in Human Mutation*; Figure c, m, and p, originally published in Wieczorek et al. [2013], *in Human Molecular Genetics* by permission of Oxford University Press; Figure b, d, and g, originally published in Tsurusaki et al. [2014], *in Clinical Genetics*]

Internal Complications

Internal complications are listed in Table II and summarized in Table IV. Respiratory complications included laryngomalacia in three patients with *SMARCA4* mutations (L46, Y16, L42, and Y17) and two patients with *ARID1A* mutations (Y8 and L25), bronchomalacia in two patients with *SMARCA4* mutations (Y14 and Y17), and chronic lung disease with bronchiectasis in a patient with a *SMARCB1* mutation (L37). Cardiovascular complications included a single defect or multiple defects. The most frequent complication was ventricular septal defects (VSD) in seven patients, followed

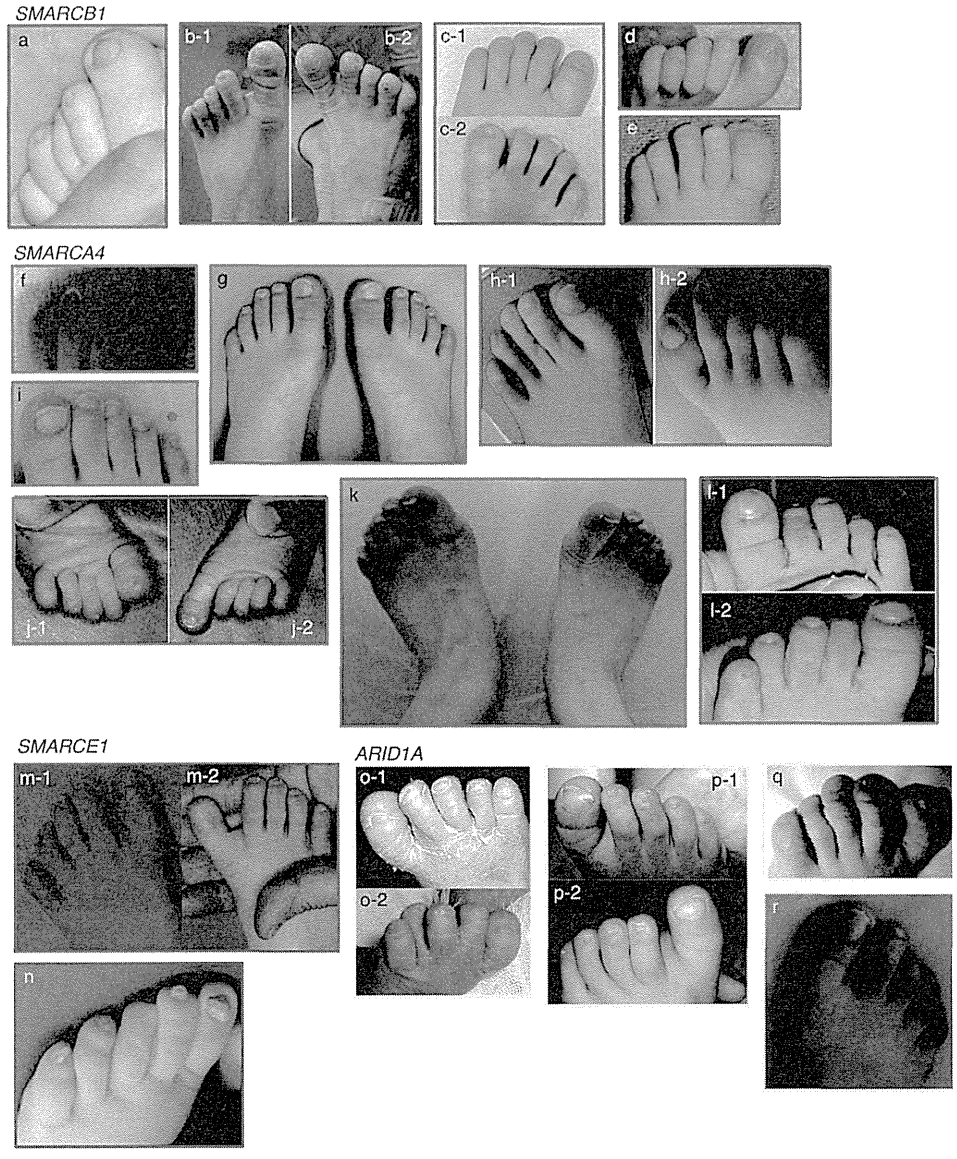

Figure 4. Digital features (toes) of patients with mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, and *ARID1A*. *SMARCB1*: L37 (a), Y4 at age 21 years (b-1, 2), Y21 at age 5 years (c-1, 2), Y29 (d), and K2426 (e). *SMARCA4*: Y32 (f), Y7 at age 20 years (g), Y5 at age 9 years and 10 months (h-1, 2), Y14 (i), Y16 in the neonatal period (j-1, 2), Y25 at age 8 years (k), and Y17 at age 3 years and 7 months (l-1, 2). *SMARCE1*: Y24 at age 14 years (m-1, 2), and K2442 (n). *ARID1A*: Y6 in the neonatal period (o-1, 2), Y8 at age 10 years (p-1, 2), L33 (q), and K2435 (r). [Figure h-2, m-2, originally published in Tsurusaki et al. [2012], *in Nature Genetics*; Figure b-1, 2, c-1, 2, g, h-1, j-1, 2, k, l-1, 2, m-1, o-1, 2, p-1, 2, originally published in Kosho et al. [2013], *in American Journal of Medical Genetics Part A*; Figure a and q, originally published in Santen et al. [2013], *in Human Mutation*; Figure, e, n, and r, originally published in Wieczorek et al. [2013], *in Human Molecular Genetics* by permission of Oxford University Press; Figure d, f, and i, originally published in Tsurusaki et al. [2014], in *Clinical Genetics*]

Cardiovascular complications included a single defect or multiple defects. The most frequent complication was ventricular septal defects (VSD) in seven patients, followed by atrial septal defects (ASD) in six patients, pulmonary stenosis in three, dextrocardia in three, coarctation of aorta (CoA) in two, and aortic stenosis (AS) in two.

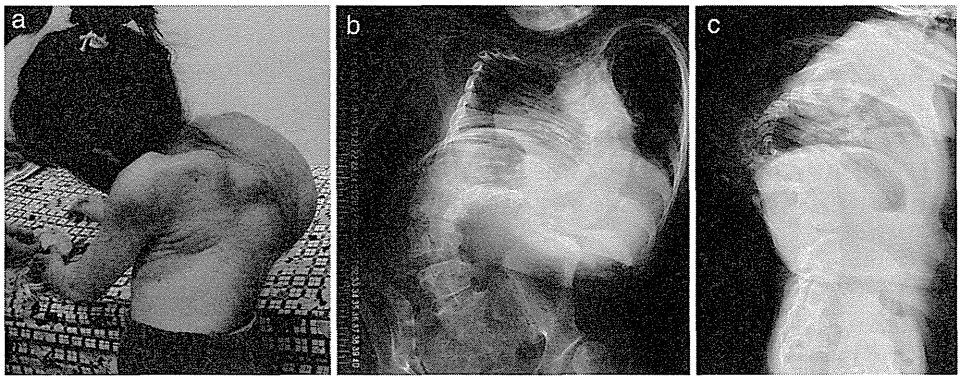

Figure 5. Severe scoliosis in Y4 at age 14 years (a) and 21 years (b, c).

by atrial septal defects (ASD) in six patients, pulmonary stenosis in three, dextrocardia in three, coarctation of aorta (CoA) in two, and aortic stenosis (AS) in two. VSD and patent ductus arteriosus in Y16 and ASD in Y8 were spontaneously closed. Y6, having VSD, CoA, and AS, suffered from atrioventricular block and cardiac decompensation leading to death at age 1 year and 1 month, although CoA was repaired surgically at age 20 days. The most

TABLE IV. Comparison of Clinical Features of Patients Caused by Mutations in Each Gene (Complications, Neurology, Development, and Behavior)

Genes	*SMARCB1*	*SMARCA4*	*SMARCE1*	*ARID1A*	Total
Internal complications					
Cardiovascular	45% (5/11)	42% (5/12)	67% (2/3)	38% (3/8)	44% (15/34)
Gastrointestinal	70% (7/10)	67% (8/12)	50% (1/2)	57% (4/7)	65% (20/31)
Genitourinary	45% (5/11)	25% (3/12)	0% (0/1)	29% (2/7)	32% (10/31)
Hernia	88% (7/8)	55% (6/11)	0% (0/2)	25% (1/4)	56% (14/25)
Hearing and vision					
Hearing impairment	75% (6/8)	33% (4/12)	50% (1/2)	33% (2/6)	46% (13/28)
Visual impairment	56% (5/9)	45% (5/11)	100% (1/1)	75% (3/4)	56% (14/25)
Immunology					
Frequent infection	89% (8/9)	67% (8/12)	67% (2/3)	60% (3/5)	72% (21/29)
Neurology					
Hypotonia	73% (8/11)	73% (8/11)	33% (1/3)	88% (7/8)	73% (24/33)
Seizures	80% (8/10)	17% (2/12)	67% (2/3)	29% (2/7)	44% (14/32)
Structural CNS abnormalities	100% (9/9)	86% (6/7)	100% (2/2)	88% (7/8)	92% (24/26)
Development and intelligence					
Developmental delay and ID					
Severe	73% (8/11)	55% (6/11)	33% (1/3)	57% (4/7)	59% (19/32)
Moderate to severe	9% (1/11)	0% (0/11)	0% (0/3)	14% (1/7)	6% (2/32)
Moderate	9% (1/11)	36% (4/11)	67% (2/3)	0% (0/7)	22% (7/32)
Mild	9% (1/11)	9% (1/11)	0% (0/3)	29% (2/7)	13% (4/32)
Speech impairment					
No words	80% (8/10)	36% (4/11)	67% (2/3)	83% (5/6)	63% (19/30)
Several words	10% (1/10)	18% (2/11)	0% (0/3)	0% (0/6)	10% (3/30)
Sentences	10% (1/10)	45% (5/11)	33% (1/3)	17% (1/6)	27% (8/30)
Bahavior					
Bahavioral abnormalities	50% (4/8)	88% (7/8)	50% (1/2)	60% (3/5)	65% (15/23)

CNS, central nervous system; ID, intellectual disability.

frequent gastrointestinal complications were pyloric stenosis and gastroesophageal reflux both in seven patients, followed by constipation in five. The most frequent genitourinary complication was cryptorchidism in seven patients. The most frequent type of hernia was inguinal in nine patients, followed by umbilical in four.

Malignancy

Only a patient with an *ARID1A* mutation (Y3) had malignancy. He was found to have hepatoblastoma because of abdominal distension at age 1 year and 10 months. The tumor had arisen from the right lobe, progressed with increased levels of liver transaminases, and led him to death at 2 years and 3 months because of paralytic ileus.

There has been increasing evidence to suggest the BAF complex genes to play a significant role in tumor suppression. Overall mutation spectrum in *SMARCB1*, *SMARCA4*, *SMARCE1*, and *ARID1A* has similarities and differences between malignancies/tumor predisposing syndromes and CSS. Germline and somatic truncating/missense mutations in *SMARCB1* (the "p.Arg377His" was found in Y11 and also found as a somatic mutation in four meningiomas [Schmitz et al., 2001]), germline truncating mutations and somatic missense mutations in *SMARCA4*, somatic truncating mutations in *SMARCE1*, and somatic truncating/missense mutations in *ARID1A* were found in malignancies/tumor predisposing syndromes, whereas germline missense mutations in *SMARCB1*, *SMARCA4*, and *SMARCE1* and germline truncating mutations in *ARID1A* were found in CSS [Santen et al., 2012b]. Santen et al. [2012b] published an extensive review focusing on the link between occurrence of ID and tumorigenesis associated with the BAF complex gene alterations. The link between ID and malignancies might be explained by the involvement of the BAF complex in tissue differentiation. Impaired neuronal differentiation would cause ID and erroneous tissue differentiation could lead to aberrant growth and then tumor formation. The link might also be explained by the involvement of epigenetic factors. Germline mutations in some epigenetic modifier genes, such as *NSD1* and *ASXL1*, were identified in ID syndromes, whereas somatic mutations in the same genes were found in malignancies. Presence or absence of tumor predisposition in patients with CSS caused by mutations in the BAF complex genes and necessity of tumor surveillance in these patients remain to be clarified.

There has been increasing evidence to suggest the BAF complex genes to play a significant role in tumor suppression. Overall mutation spectrum in SMARCB1, SMARCA4, SMARCE1, and ARID1A has similarities and differences between malignancies/tumor predisposing syndromes and CSS.

Hearing and Vision

Hearing or visual impairment is listed in Table II and summarized in Table IV. Hearing impairment was severe in three patients, moderate in three, and mild in two. The most frequent ophthalomological abnormality was myopia in six patients, followed by strabismus in three and optic disc coloboma in two.

Immunology

Frequent infection included respiratory tract infection and urinary tract infection, listed in Table II and summarized in Table IV. L37 was diagnosed with immunodeficiency requiring intravenous antibiotics every two weeks.

Neurology

Neurological abnormalities included hypotonia, seizures, and structural abnormalities in the central nervous system (CNS), listed in Table II and summarized in Table IV. Efficacy of antiepileptic drugs was described in three patients (Y4, Y21, and Y24): carbamazepine for Y4, carbamazepine and valproic acid for Y24. The most frequent abnormality was abnormal corpus callosum (hypoplasia or agenesis of corpus callosum) in 22 patients, followed by cerebellar hypoplasia in six and Dandy-Walker malformation in five.

Development and Intelligence

Developmental delay and ID were observed in all the patients, as listed in Table II and summarized in Table IV. Independent sitting was not possible in a total of 7/23 (30%) patients older than 6 months old: in 4/9 (44%) with *SMARCB1* mutations, in 1/9 (11%) with a *SMARCA4* mutation, in 0/1 (0%) with a *SMARCE1* mutation, and in 2/4 (50%) with *ARID1A* mutations. Assuming that these patients would accomplish independent sitting after the last observation of this study, the overall median age of independent sitting was 18 months (n = 23): 36 months in patients with *SMARCB1* mutations (n = 9), 12 months in those with *SMARCA4* mutations (n = 9), and 12.5 months in those with *ARID1A* mutations (n = 4). Independent walking was not possible in a total of 9/25 (36%) patients older than 1 year old: in 5/9 (56%) with *SMARCB1* mutations, in 1/10 (10%) a *SMARCA4* mutation, in 0/2 (0%) with a *SMARCE1* mutation, and in 3/4 (75%) with *ARID1A* mutations. Assuming that these patients would accomplish independent walking after the last observation of this study, the overall median age of independent walking was 36 months (n = 27): 78 months in patients with *SMARCB1* mutations (n = 10), 42 months in those with *SMARCA4* mutations (n = 10), 45 months in those with *SMARCE1* mutations (n = 2), and 19 months in those with *ARID1A* mutations (n = 5).

Speech impairment was observed in all patients. Despite speaking no words, Y4 understood simple commands in daily life and express herself with gestures. Y11 distinguished her family members from others and smiled when called by her name. Y16 understood language and communicated to others with gestures. Among those who spoke several words, Y7 understood simple commands. Among those who spoke sentences, Y9 understood almost everything necessary for daily life, Y25 made simple conversation and read "hiragana" (Japanese cursive characters), and L2 could read and write words.

Behavior

Behavioral abnormalities are listed in Table II and summarized in Table IV. The most frequent abnormality was hyperactivity in 10 patients, followed by self-injurious behavior in three, short attention span in two, and obsession in two. L43 was described to have autistic traits and Y5 was diagnosed with autism spectrum disorder.

Summary of Clinical and Molecular Characteristics of Patients With Mutations of Each Gene

In this review, all previously reported patients with a clinical diagnosis of CSS and mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, or *ARID1A* have been evaluated; and clinical and molecular characteristics of patients mutated in each gene could be revised from description in previous series by Tsurusaki et al. [2012], Kosho et al. [2013], Santen et al. [2013], Wieczorek et al. [2013], and Tsurusaki et al. [2014] as follows.

SMARCB1 Mutations

Thirteen patients have been reported. Growth impairment was mild prenatally and moderate to severe postnatally, and sucking/feeding difficulty was always (100%) observed. They always had thick eyebrows and long eyelashes, usually (70–90%) had sparse scalp hair, hypertrichosis, wide or flat nasal bridge, thin upper lip vermilion, and thick lower lip vermilion; sometimes (40–50%) had ptosis and long philtrum, and occasionally (20–30%) had cleft palate. They always hypoplastic 5th fingernails or toenails, usually had hypoplastic 5th fingers or toes, hypoplastic other fingernails or toenails, prominent distal phalanges, and scoliosis; and sometimes had prominent interphalangeal joints. They usually had gastrointestinal complications and hernia and sometimes had cardiovascular and genitourinary complications. They usually had hearing impairment and frequently (around 60%) had visual impairment. They were usually prone to infection. They always had structural CNS abnormalities, and usually had hypotonia and seizures. They usually had severe developmental delay/ID, only sometimes walked independently, and usually spoke no words. They sometimes had behavioral abnormalities. The mutations, localized around SNF5 domain, are expected to exert dominant-negative or gain-of-function effects. "p.Lys364-del", the only recurrent mutation known in this series, represented strikingly similar phenotypes including characteristic facial coarseness (in early childhood, round face with thick and arched eyebrows, short nose with bulbous tip and anteverted nostrils, long philtrum, small mouth, and micro-retrognathia; later, broad nasal bridge without anteverted nostrils, broad philtrum, large tongue, and protruding jaw), severe developmental delay/ID, but relatively mild internal organ complications.

SMARCA4 Mutations

Twelve patients have been reported. Growth impairment was mild prenatally and mild to moderate postnatally, and sucking/feeding difficulty was almost always observed. They always had hypertrichosis, usually had thick eyebrows, long eyelashes, ptosis, and thick lower lip vermilion; sometimes had sparse scalp hair, flat nasal bridge, and short philtrum; and occasionally had everted upper lip vermilion and cleft palate. Facial coarseness was not evident and pointed chin in older ages was noted. They always had hypoplastic 5th fingers or toes and hypoplastic 5th fingernails or toenails, sometimes had hypoplastic other fingernails or toenails, and occasionally had prominent interphalangeal joints and prominent distal phalanges. They often had gastrointestinal complications and hernia, sometimes had cardiovascular complications, and occasionally had genitourinary complications. They occasionally had hearing impairment and sometimes had visual impairment. They were often prone to infection. They usually had hypotonia and structural CNS abnormalities, and occasionally had seizures. They sometimes had severe developmental delay/ID, usually walked independently, and occasionally spoke no words. They usually had behavioral abnormalities. The mutations, localized widely in the middle of the gene including HAS, DEXDc, and HELICc domains, are expected to exert dominant–negative or gain-of-function effects.

SMARCE1 Mutations

Only three patients have been reported. Growth impairment was mild to moderate prenatally and moderate to severe postnatally, and sucking/feeding difficulty was always observed. They always had hypertrichosis and thick lower lip vermilion, frequently had sparse scalp hair, thick eyebrows, and thin upper lip vermilion; sometimes had long eyelashes, long philtrum, and cleft palate; and occasionally had ptosis. They always had hypoplastic 5th fingers or toes and hypoplastic 5th fingernails or toenails, often had hypoplastic other fingernails or toenails, sometimes had prominent interphalangeal joints and scoliosis, and occasionally had prominent distal phalanges. They often had cardiovascular complications and sometimes had gastrointestinal complications. They sometimes had hearing impairment and always had visual impairment. They were often prone to infection. They always had structural CNS abnormalities, frequently had seizures, and occasionally had hypotonia. They

occasionally had severe developmental delay/ID, always walked independently, and frequently spoke no words. They sometimes had behavioral abnormalities. The mutations, localized within HMG domain, are expected to exert dominant–negative or gain-of-function effects.

ARID1A Mutations

Eight patients have been reported. Growth impairment was mild prenatally and mild to severe postnatally, and sucking/feeding difficulty was always observed. They always had hypertrichosis and long eyelashes, usually had thick eyebrows, wide nasal bridge, and thick lower lip vermilion; frequently had sparse scalp hair; sometimes had ptosis, broad/long philtrum, and thin upper lip vermilion; and occasionally had cleft palate. Some facial coarseness with short nose was also noted. They usually had hypoplastic 5th fingers or toes, hypoplastic 5th fingernails or toenails, and hypoplastic other fingernails or toenails, sometimes had prominent interphalangeal joints and prominent distal phalanges, and scoliosis. They often had gastrointestinal complications, occasionally had cardiovascular and genitourinary complications and hernia, and malignancy in one, resulting in two early deaths (cardiac decompensation, hepatoblastoma). They occasionally had hearing impairment and usually had visual impairment. They were often prone to infection. They usually had hypotonia and structural CNS abnormalities, and occasionally had seizures. They frequently had severe developmental delay/ID, and only occasionally walked independently, and frequently spoke no words, whereas mild ID patients were also present occasionally. They frequently had behavioral abnormalities. The mutations, all truncating and probably mosaic, are expected to exert loss-of-function effects.

Limitation

Although this is the largest series addressing clinical and molecular characteristics of patients with mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, or *ARID1A*, inevitable biases in data collection could be included because of (1) still small number of patients especially those with *SMARCE1* mutations, (2) possible incomplete clinical assessment especially examinations for internal organs, (3) changing phenotypes according to age especially craniofacial features, and (4) recruitment of patients with a clinical diagnosis of CSS.

CONCLUSION

Clinical and molecular features of patients with CSS caused by mutations in *SMARCB1*, *SMARCA4*, *SMARCE1*, or *ARID1A* have been reviewed through reassessment of all reported cases. Cardinal features of CSS included variable degrees of ID predominantly affecting speech, sucking/feeding difficulty, and craniofacial (thick eyebrows, long eyelashes), digital (hypoplastic 5th fingers or toes, hypoplastic 5th fingernails or toenails), and other characteristics (hypertrichosis). In addition, patients with *SMARCB1* mutations had severe neurodevelopmental deficits including severe ID, seizures, CNS structural abnormalities, and no expressive words as well as scoliosis. Especially, those with a recurrent mutation "p.Lys364del" represented strikingly similar phenotypes including characteristic facial coarseness. Patients with *SMARCA4* mutations had less coarse craniofacial appearances and behavioral abnormalities. Patients with *SMARCE1* mutations had a wide spectrum of manifestations from severe to moderate ID. Patients with *ARID1A* also had a wide spectrum of manifestations from severe ID and serious internal complications that could result in early death to mild ID. Mutations in *SMARCB1*, *SMARCA4*, and *SMARCE1* are expected to exert dominant–negative or gain-of-function effects, whereas those in *ARID1A* are expected to exert loss-of-function effects. To obtain comprehensive understanding of the clinical spectrum caused by mutations in the BAF complex genes, next generation sequencing-based genetic screening for all related genes on a larger cohort, such as ID with/without physical features not specific to CSS, would be needed.

Patients with SMARCE1 mutations had a wide spectrum of manifestations from severe to moderate ID. Patients with ARID1A also had a wide spectrum of manifestations from severe ID and serious internal complications that could result in early death to mild ID.

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spectrum converging on altered chromatin remodeling" in *Hum Mol Genet* 22 (25):5121–5135, 2013, courtesy of Oxford University Press. This work was mainly supported by Research Grants from the Ministry of Health, Labour and Welfare, Japan.

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INTRODUCTION

Coffin–Siris Syndrome and Related Disorders Involving Components of the BAF (mSWI/SNF) Complex: Historical Review and Recent Advances Using Next Generation Sequencing

TOMOKI KOSHO*, NORIKO MIYAKE, AND JOHN C. CAREY**

This issue of Seminars in Medical Genetics, *American Journal of Medical Genetics* Part C investigates the human diseases caused by mutations in the BAF complex (also known as the mammalian SWI/SNF complex) genes, particularly focusing on Coffin–Siris syndrome (CSS). CSS is a rare congenital malformation syndrome characterized by developmental delay or intellectual disability (ID), coarse facial appearance, feeding difficulties, frequent infections, and hypoplasia/aplasia of the fifth fingernails and fifth distal phalanges. In 2012, 42 years after the first description of CSS in 1970, five causative genes (*SMARCB1*, *SMARCE1*, *SMARCA4*, *ARID1A*, *ARID1B*), all encoding components of the BAF complex, were identified as being responsible for CSS through whole exome sequencing and pathway-based genetic screening. The identification of two additional causative genes (*PHF6*, *SOX11*) followed. Mutations in another BAF complex gene (*SMARCA2*) and (*TBC1D24*) were found to cause clinically similar conditions with ID, Nicolaides–Baraitser syndrome and DOORS syndrome, respectively. Also, *ADNP* was found to be mutated in an autism/ID syndrome. Furthermore, there is growing evidences for germline or somatic mutations in the BAF complex genes to be causal for cancer/cancer predisposition syndromes. These discoveries have highlighted the role of the BAF complex in the human development and cancer formation. The biology of BAF is very complicated and much remains unknown. Ongoing research is required to reveal the whole picture of the BAF complex in human development, and will lead to the development of new targeted therapies for related disorders in the future. © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Coffin–Siris syndrome (CSS, OMIM# 135900) is a rare congenital malformation syndrome characterized by developmental delay or intellectual disability (ID), coarse facial appearance, feeding difficulties, frequent infections, and hypoplastic-to-absent fifth fingernails and fifth distal phalanges [Levy and Baraitser, 1991; Fleck et al., 2001; Schrier et al., 2012]. In 2012, 42 years after the first description by Coffin and

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Siris [1970], the syndrome was identified to be caused by mutations in several genes encoding components of the BRG1- and BRM-associated factor (BAF) complex, originally called the mammalian SWItch/sucrose nonfermentable (mSWI/SNF)-like complex [Santen et al., 2012a; Tsurusaki et al., 2012]. The importance of the BAF complex in the human neuronal development and cancer occurrence has emerged through the recent discoveries that mutations in their subunit genes and related genes implicated in several ID syndromes including Nicolaides–Baraitser syndrome [NCBRS] as well as CSS, non-syndromic ID, sporadic autism, schizophrenia, and amyotrophic lateral sclerosis [Santen et al., 2012b; Son and Crabtree, 2014] as well as in sporadic cancers/cancer predisposing syndromes [Santen et al., 2012b; Biegel et al., 2014].

Here, we present a special issue of Seminars in Medical Genetics, *American Journal of Medical Genetics* Part C, dedicated to Coffin–Siris syndrome and related disorders involving components of the BAF complex. Included are the newest reviews written by cutting-edge clinical and basic researchers all over the world, on the history of CSS, recent breakthroughs in finding the causative genes of CSS and related disorders using next generation sequencing, the clinical consequences of each gene defect, and the biological roles of the BAF complex.

HISTORICAL REVIEW OF COFFIN-SIRIS SYNDROME

In 1970, the original paper describing CSS was published by Drs. Grange S. Coffin and Evelyn Siris from Sonoma State Hospital in San Francisco [Coffin and Siris, 1970]. They described three girls with growth impairment, severe developmental delay, and lack of the nail and terminal phalanx of the fifth fingers (Figs. 1 and 2). Another patient was reported in the same year by Bartsocas and Tsiantos [1970]. In 1973, two other patients were reported by Weiswasser et al. [1973] who proposed that these patients represented a specific clinical entity designated as "Coffin–Siris syndrome". Carey and Hall [1978] established the clinical entity, describing five new patients (Figs. 1 and 2), as well as the five previously reported by Bartsocas and Tsiantos [1970], Coffin and Siris [1970] and Weiswasser et al. [1973]. Constant features (100% frequency) included variable degrees of ID, nail hypoplasia or absence with predominantly fifth digit involvement, hypotonia, feeding problems in infancy, and retarded bone age. Frequent features (75–90%) included postnatal growth deficiency, microcephaly, wide nasal tip and mouth, prominent lips, eyebrow/eyelash hypertrichosis, and scalp hair hypotrichosis. Significant but less frequent findings included short philtrum (50%), scoliosis (40%), decreased fetal activity (40%), small gestational age (30%), and congenital heart defects (30%). They found the craniofacial phenotype to be mild in the young infant, but progressively more pronounced with increasing age.

In 1991, Levy and Baraitser published a review of 31 previously reported patients, in addition to two new patients [Levy and Baraitser, 1991]. The main features included growth and developmental delay, sparse scalp hair, bushy eyebrows, wide mouth with prominent or thick lips (especially the lower lip), hypertrichosis, and absent or hypoplastic nails of the fifth fingers and toes with absent or hypoplastic phalanges. The mode of inheritance was suggested to be autosomal recessive. Fleck et al. [2001] presented a review of the literature (62 patients from 30 reports) and described 18 new patients based on a survey administered to the international parent support group of the syndrome. These authors proposed that the minimal criteria for the diagnosis of CSS included some degree of developmental delay, coarse facial appearance, hypertrichosis, hypoplastic or absent fifth fingernails or toenails, and hypoplastic or absent fifth distal phalanges. Additional findings that would support the diagnosis included feeding difficulties, frequent infections, delayed dentition, and heart defects. Fleck et al. [2001] also detailed the average ages of developmental milestones (e.g., walked alone at age 22.8 months [n = 13], first word at 23.7 months [n = 10], toilet trained at 6.1 years [n = 6]). However, diagnosis was still difficult because of variability of the phenotype and the existence of the disorder as a specific diagnosis had been debated [Schrier et al., 2012]. Schrier et al. [2012] reviewed all 80 reported patients for common and discriminating features. All patients displayed both hypo/aplasia of the fifth digit phalanges/nails as well as some degree of ID and/or developmental delay. Additionally, a variety of features that were broadly categorized into ectodermal, constitutional, and organ-based anomaly categories were described. They also categorized facial features into two types; "classic" CSS, with coarse appearance, bushy eyebrows, and thick lips and "variant" CSS, with less coarse appearance, thinner eyebrows, and thin vermilion border of the lips. A diagnostic algorithm for CSS including differential diagnoses (e.g., NCBRS, DOORS syndrome) was proposed. In this current issue, Schrier and Deardorff [2014] present a clinical review of the syndrome including historical aspects and healthcare recommendations.

GENE IDENTIFICATION OF COFFIN–SIRIS SYNDROME

As the majority of CSS cases have a sporadic etiology and as this trait is not usually transmitted to the next generation due to the severe phenotype, it was difficult to identify the causative gene(s) by the traditional positional cloning approaches. As is now known, CSS is genetically heterogeneous, which made gene identification more difficult. Following the development of next generation sequencing, comprehensive analyses using whole exome sequencing allowed the identification of de novo heterozygous mutations in various genetic diseases [Ng et al., 2010]. In April, 2012, the same issue of *Nature Genetics* published two papers, demonstrating germline heterozygous mutations in six BAF complex genes (*SMARCB1* at 22q11.23, *SMARCA2* at 9p24.3, *SMARCA4* at 19p13.2, *SMARCE1* at 17q21.2, *ARID1A* at 1p36.11, and *ARID1B* at 6q25.3) in patients affected

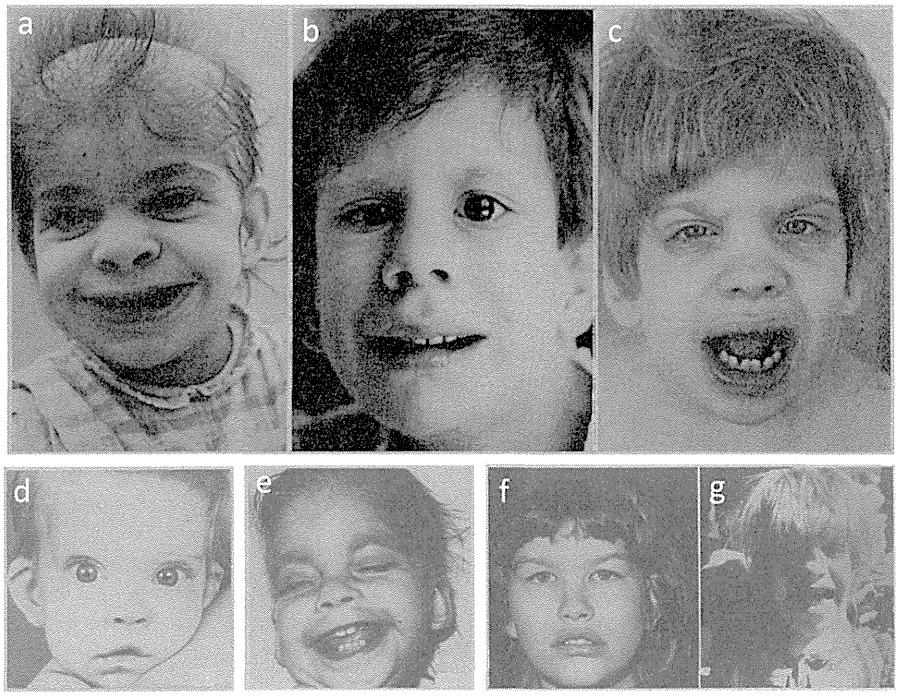

Figure 1. Facial features of patients with Coffin–Siris syndrome. A 6-year-old girl (**a**), a 7-year-old girl (**b**), and an 8-year-old girl (**c**), described in the original paper by Coffin and Siris [1970]. A 10-month-old girl (**d**), a 2-year-old boy (**e**), an 18-year-old girl (**f**), and a 17-year-old girl (**g**), described in the paper that established the disorder [Carey and Hall, 1978]. The 8-year-old girl (**c**) and the 17-year-old girl (**g**) were the same patient.

by CSS [Santen et al., 2012a; Tsurusaki et al., 2012]. In the same year, haploinsufficiency of *ARID1B* was identified in individuals with ID, using copy number analyses and mutation searches for the genes involved [Hoyer et al., 2012]. The same issue of *Nature Genetics* also published a paper, demonstrating *SMARCA2* as the causative gene for NCBRS (OMIM#601358) [Van Houdt et al., 2012]. NCBRS has clinical resemblance to CSS, but is a distinct entity characterized by sparse hair, short stature, microcephaly, brachydactyly, interphalangeal joint swellings, epilepsy, and ID [Nicolaides and Baraitser, 1993; Sousa et al., 2009]. A patient with a *SMARCA2* mutation was diagnosed as CSS in the original paper [Tsurusaki et al., 2012], but was diagnosed again as NCBRS through reassessment of clinical features [Kosho et al., 2013; Tsurusaki et al., 2014b]. Later on, mutations in *PHF6* at Xq26.2, which were originally identified in X-linked mental retardation syndrome Borjeson–Forssman–Lehmann syndrome (BFLS, OMIM#301900) [Lower et al., 2002], were identified in patients with CSS [Wieczorek et al., 2013]. Interestingly, the PHF6 protein is associated with chromatin remodeling process [Todd and Picketts, 2012] and is known to play an important role in neurogenesis downstream of Pax6-BAF complex in mice [Ninkovic et al., 2013]. This year, DOORS syndrome (deafness, onychodystrophy, osteodystrophy, mental retardation, and seizure syndrome, OMIM#220500), an autosomal recessive condition, has been found to be caused by biallelic mutations in *TBC1D24* at 16p13.3 [Campeau et al., 2014a]. Although TBC1D24, regulating Rab proteins, has no apparent relationship to the BAF complex, the syndrome has substantial clinical overlaps to CSS and constitutes one of the most important differential diagnoses of CSS [Schrier et al., 2012]. Actually, a heterozygous mutation in *SMARCB1* has been identified in two patients with the syndrome [Campeau et al., 2014b]. Furthermore, heterozygous mutations in *ADNP* at 20q13.13, encoding a transcription factor involved in the BAF complex, have been identified in patients presenting with dysmorphic facial appearance, autism, ID, hypotonia, and congenital heart defects [Helsmoortel et al., 2014]. Very recently, heterozygous mutations in *SOX11* at 2p25.2 have been reported to cause a mild CSS phenotype [Tsurusaki et al., 2014a]. *SOX11* is the downstream transcription factor of the Pax6-BAF complex, and this discovery shows the importance of the BAF complex and SOX11 transcription network in brain development. This series of gene discoveries sheds new light on the role of the BAF complex in human development and the associated diseases, as reviewed elsewhere in this issue [Miyake et al., 2014].

GENOTYPE-PHENOTYPE CORRELATION

In this issue, the genotype-phenotype correlation in *SMARCB1*, *SMARCA4*,

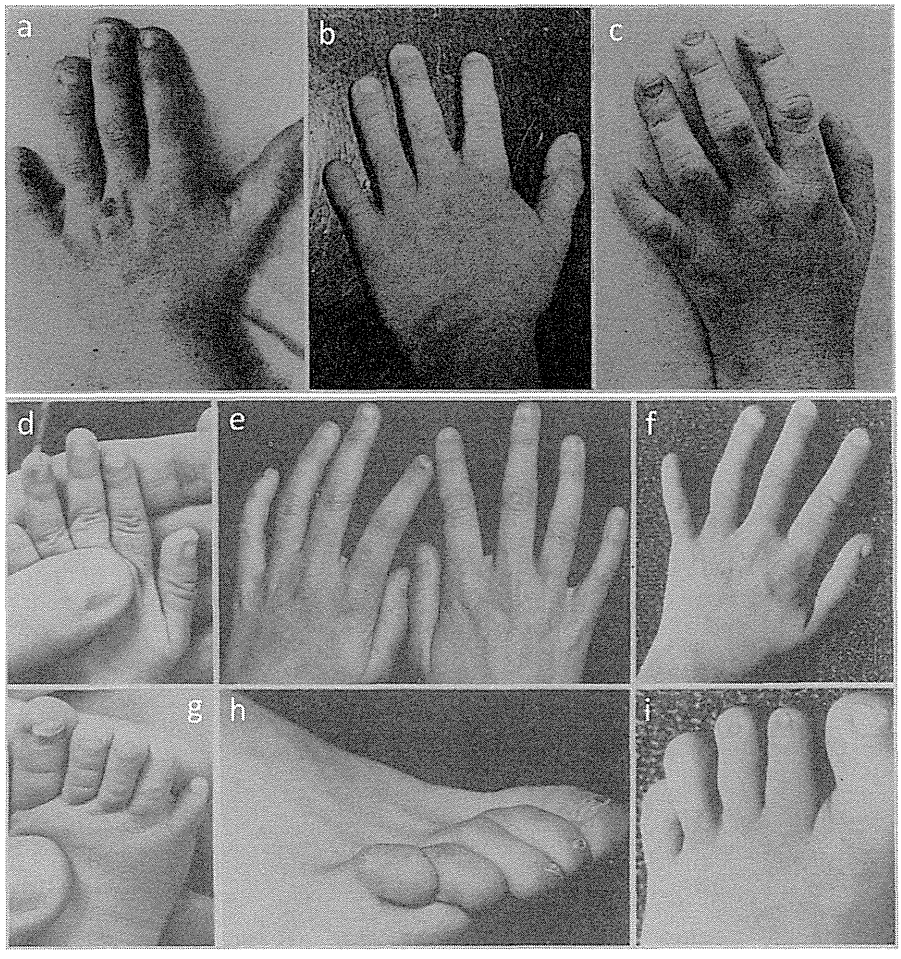

Figure 2. Digital features of patients with Coffin–Siris syndrome. A 6-year-old girl (**a**), a 7-year-old girl (**b**), and an 8-year-old girl (**c**), described in the original paper by Coffin and Siris [1970]. A 10-month-old girl (**d**, **g**), an 18-year-old girl (**e**, **h**), and a 17-year-old girl (**f**, **i**), described in the paper that established the disorder [Carey and Hall, 1978]. The 8-year-old girl (**c**) and the 17-year-old girl (**f**, **i**) were the same patient.

SMARCE1, and *ARID1A*-related CSS is reviewed by Kosho et al. [2014], in *ARID1B*-related CSS and ID syndrome by Santen and Clayton-Smith, [2014], in *SMARCB2*-related NCBRS by Sousa et al. [2014], in *PHF6*-related CSS and Borjeson–Forssman–Lehmann syndrome by Zweier et al. [2014], in *ADNP*-related autism syndrome by Vandeweyer et al. [2014], and in mainly *TBC1D24*-related DOORS syndrome by Campeau et al. [2014b]. Clinical features of patients caused by mutations in each gene are summarized as follows (also in Table I), although generalization would be difficult because the sample sizes were too small and patients were collected from selected cohorts (such as clinical diagnosis as CSS or NCBRS).

SMARCB1

Heterozygous *SMARCB1* mutations have been reported in 13 patients with CSS [Tsurusaki et al., 2012, 2014b; Kosho et al., 2013; Santen et al., 2013; Wieczorek et al., 2013], in two patients called DOORS syndrome [Campeau et al., 2014a], and in a patient diagnosed as Kleefstra syndrome [Kleefstra et al., 2012]. The mutations, all non-truncating (missense or in-frame deletions), are predicted to exert dominant-negative or gain-of-function effects. Usually (70–90%), patients have severe developmental delay or ID and speak no words. Growth impairment is mild prenatally and moderate-to-severe postnatally, and difficulty in sucking/feeding is always observed. Typical facial features include sparse scalp hair, thick eyebrows, long eyelashes, wide or flat nasal bridge, thin upper lip vermilion, and thick lower lip vermilion. Hypertrichosis is always observed. Patients always have hypoplastic fifth fingernails or toenails, and usually had hypoplastic fifth fingers or toes, hypoplastic other fingernails or toenails, prominent distal phalanges, and scoliosis. Usually, patients have complications of the internal organs, hearing impairment,