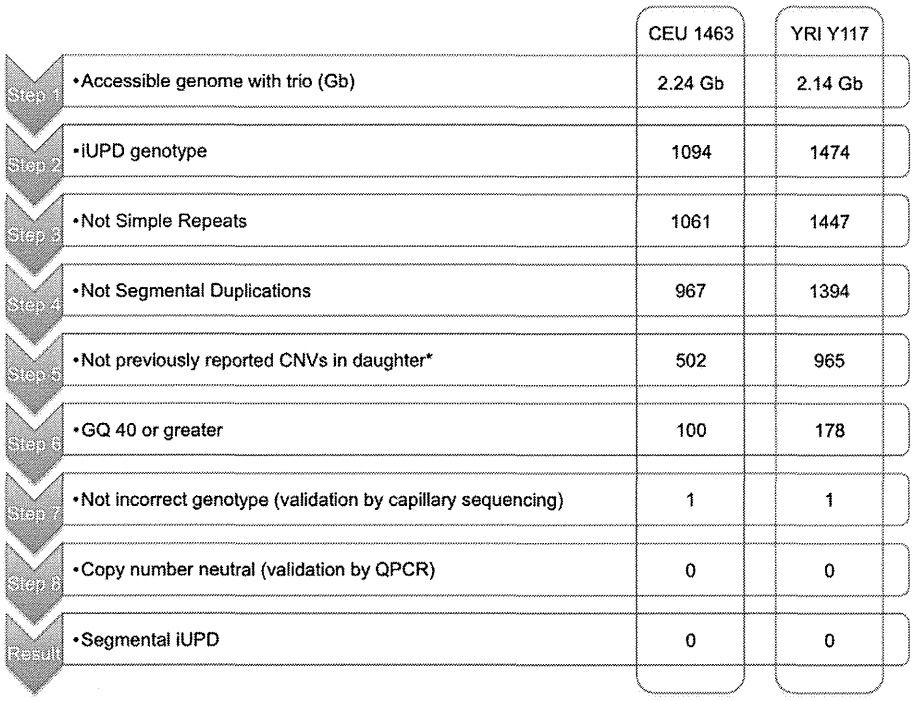

Fig. 2. Study design and summary of iUPD segment analysis using whole-genome sequencing (WGS) data of HapMap FID CEU 1463 and YRI Y117 trios, respectively. GQ, genotype quality; qPCR, quantitative polymerase chain reaction. *Previously reported CNV regions (Conrad et al., 2010; Kidd et al., 2008; McCarroll et al., 2008; Mills et al., 2011).

within the organism. Therefore, undifferentiated cells would require error-less repair mechanisms. HR would be a suitable repair mechanism for such cells, because intact homologous chromosomes are used as repair templates. Indeed, embryonic stem cells (ESCs) repair DSBs more frequently using the error-free HR pathway rather than the error-prone NHEJ (Tichy, 2011; Tichy and Stambrook, 2008). HR (also called gene conversion) can occur between sister chromatids, homologous chromosomes or homologous sequences on either the same chromatid or different chromosomes (Chen et al., 2007). Although the extent of genetic loss is minimal if HR results in a non-crossover gene conversion, crossover gene conversion leads to iUPD of the large region of the chromosome in daughter cells (Moynahan and Jasin, 1997, 2010; Stark and Jasin, 2003). The occurrence of inter-allelic HR causing human inherited disease is rare (Chen et al., 2007). To our knowledge, homozygous nonsense mutations due to inter-allelic HR have been reported in a patient with campomelic dysplasia (Y440X) in SRY-box 9 (SOX9) (Pop et al., 2005). This case indicates that inter-allelic HR in early stage embryogenesis can occur.

To assess the possibility that inter-allelic HR occurs in the human genome during the period between postzygotic cells and the early embryonic stage to maintain the higher fidelity of genomic integrity, we investigated the traits of iUPD genotypes using NGS data during the pilot phase 2 of the 1000 Genomes Project. However, we could not find direct evidence of segmental iUPD after the accurate reconfirmation process including capillary sequencing and qPCR. Some parts of the reference sequence are inaccessible because of high-copy repeats or segmental duplications. This is a limitation of the current NGS technology producing short sequence reads. Indeed, 20% of the reference genome was inaccessible in the trio project (Altshuler et al., 2010). From our data, the accessible genome per CEU and YRI trio set were 2.24 Gb and 2.14 Gb, respectively (Table 1). Because the total length of the human reference genome, including the gap was composed of about 3.08 Gb, 27.2% and 30.5% of data in CEU and YRI trio, respectively, were not analyzed in this study. Furthermore, the use of only two trios might be too small a scale and low-level mosaicism is often difficult to detect accurately. However, the data presented here provides evidence that segmental UPD during normal development could not be a constitutive event in order to maintain genomic integrity.

Constitutive UPD is very rare. Robinson (2000) determined that UPD for an average chromosome occurs in 1/80,000 births (0.00125%) and UPD for any chromosome can be expected in roughly 1/3,500 births (0.02857%), based on the frequency of UPD15. Liehr (2010) suggested that the rate of UPD in human population might be even lower than 1 in 5,000 or less. We studied 173 trios using genome-wide SNP array and WGS data using NGS, and identified one case with segmental iUPD. Segmental UPD for any chromosome can be expected in 1/173 births which equals a rate of 0.57803%. Based on the investigated autosomal chromosome pairs, we estimate the rate of segmental UPD to be one per 3806 chromosome pairs that equals a rate of 0.02627%. We found a higher frequency of UPD events than the previously reported frequency by Robinson and Liehr. These data imply the possibility of hidden segmental UPD in normal individuals. However, we found just only one UPD in 3806 chromosome pairs, we need analyze more trio samples and that would give the accurate rate of whole chromosomal and/or segmental UPD.

iUPD resulting from a somatic recombination can cause LOH. Somatic recombination leading to mosaic segmental UPD could occur in any individual and it is likely to be mosaic or in a heterogeneous cell population with increased cell division. In fact, the studies by Laurie et al. (2012) and Jacobs et al. (2012) found that detectable mosaic genomic variations including segmental UPD were rare (1%) in adults younger than 50 but that its prevalence increased to 2–3% in individuals older than 70. We detected 21 LTAs over 200 kb in the process of UPD screening using SNP microarray (Table 1 and supplementary Figs. 2 and 3). These genomic alterations may reflect that CNVs or segmental UPD result from somatic recombination in restricted soma (for example, in hematopoietic cells) or during cell culture, as with aging. Although most sample data analyzed here was derived from DNA of LCLs (170 trios from HapMap), we suggest that segmental UPD occurring in early developmental stages in individuals in the general population can be detected. However, we cannot totally negate the possibility that one

segmental UPD identified in this study arose during passage in the artificial culture.

Studies of UPD have only been performed in cases with relevant phenotypic features and included only a few markers. These facts suggest that researchers may overlook UPD in normal development and miss shorter segmental UPD, because UPD of many chromosomal regions results in no obvious abnormalities (Kotzot and Utermann, 2005; Robinson, 2000). In addition, lethal genotypes due to UPD during early embryonic development would be undetectable. We suggest that trio genome analysis with enhanced sequence accuracy could provide new findings for the risk of recessive disorders, because one mutant allele from one parent can be transmitted to a child and result in a homozygous state due to iUPD. To the best of our knowledge, this is the first systematic study over whole chromosomal and segmental UPD in the human genome without abnormal phenotype using familial trios.

5. Conclusions

The current study assessed the presence of whole chromosome and segmental UPD in general populations using genome-wide SNP microarray and WGS data. We provided evidence that segmental UPD in normal development is not a constitutive event in order to maintain genomic integrity. Although we identified one obvious segmental paternal iUPD in one HapMap sample, we could not find direct evidence of shorter segmental iUPD. This suggested three possibilities, 1) human cells repress the usage of inter-allelic homologous sequences as a template for HR, even at the early embryonic stage, 2) shorter iUPD segments are unidentifiable because of absent informative markers within the limited short segment, 3) UPD could be present in inaccessible genome regions when using current NGS with short reads. Investigation of segmental UPD in general populations will help to expand our general understanding of normal development in humans.

Conflict of interest

None of the authors of this paper declares a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.gene.2012.10.035.

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RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Clinical Correlations of Mutations Affecting Six Components of the SWI/SNF Complex: Detailed Description of 21 Patients and a Review of the Literature

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Mutations in the components of the SWItch/sucrose nonfermentable (SWI/SNF)-like chromatin remodeling complex have recently been reported to cause Coffin–Siris syndrome (CSS), Nicolaides–Baraitser syndrome (NCBRS), and *ARID1B*-related intellectual disability (ID) syndrome. We detail here the genotype-phenotype correlations for 85 previously published and one additional patient with mutations in the SWI/SNF complex: four with *SMARCB1* mutations, seven with *SMARCA4* mutations, 37 with *SMARCA2* mutations, one with an *SMARCE1* mutation, three with *ARID1A* mutations, and 33 with *ARID1B* mutations. The mutations were associated with syndromic ID and speech impairment (severe/profound in *SMARCB1*, *SMARCE1*, and *ARID1A* mutations; variable in *SMARCA4*, *SMARCA2*, and *ARID1B* mutations), which was frequently accompanied by agenesis or hypoplasia of the corpus callosum. *SMARCB1* mutations caused "classical" CSS with typical facial "coarseness" and significant digital/nail hypoplasia. *SMARCA4* mutations caused CSS without typical facial coarseness and with significant digital/nail hypoplasia. *SMARCA2* mutations caused NCBRS, typically with short stature, sparse hair, a thin vermillion of the upper lip, an everted lower lip and prominent finger joints. A *SMARCE1* mutation caused CSS without typical facial coarseness and with significant digital/nail hypoplasia. *ARID1A* mutations caused the most severe CSS with severe physical complications. *ARID1B* mutations caused CSS without typical facial coarseness and with mild digital/nail hypoplasia, or caused syndromic ID. Because of the common underlying mechanism and overlapping clinical features, we propose that these conditions be referred to collectively as "SWI/SNF-related ID syndromes". © 2013 Wiley Periodicals, Inc.

Key words: Coffin–Siris syndrome; SWI/SNF complex; *SMARCB1*; *SMARCA4*; *SMARCA2*; *SMARCE1*; *ARID1A*; *ARID1B*; Nicolaides–Baraitser syndrome; intellectual disability (ID)

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INTRODUCTION

Coffin–Siris syndrome (CSS; OMIM 135900) was first described by Coffin and Siris [1970]. It is a rare congenital anomaly 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 [Devy and Baraitser, 1991; Fleck et al., 2001; Schrier et al., 2012]. We recently reported on mutations in six genes encoding components of the SWItch/sucrose nonfermentable (SWI/SNF)-like chromatin remodeling complex in 20 of 23 patients clinically diagnosed with CSS: *SMARCB1* in four patients, *SMARCA4* in six, *SMARCA2* in one, *SMARCE1* in one, *ARID1A* in three, and *ARID1B* in five [Tsurusaki et al., 2012]. In the same journal issue, truncating mutations in *ARID1B* were reported in three patients with CSS and microdeletions encompassing *ARID1B* were reported in three patients with ID and remnants of CSS [Santen et al., 2012]. Furthermore, missense mutations of *SMARCA2* were reported in 36 patients with Nicolaides–Baraitser syndrome (NCBRS; OMIM#601358) [van Houdt et al., 2012]. NCBRS was first described by Nicolaides and Baraitser [1993] and it is a recently delineated condition characterized by severe ID with absent/limited speech, seizures, short stature, sparse hair, typical facial characteristics, brachydactyly, prominent finger joints, and broad distal phalanges; the main differential diagnosis is CSS [Sousa et al., 2009]. *ARID1B* has also been reported to be a cause of ID. Nagamani et al. [2009] reported four patients with interstitial deletion of 6q25.2–q25.3 including *ARID1B*, all of whom manifested microcephaly, developmental delay, facial characteristics, and hearing impairment, and two of whom had agenesis of the corpus callosum. Halgren et al. [2012] reported eight patients with haploinsufficiency of *ARID1B* (de novo chromosomal translocation involving *ARID1B* in one, intragenic deletions in three, and microdeletion including *ARID1B* in four), who manifested agenesis or hypoplasia of the corpus callosum, ID with speech impairment, and autism. Hoyer et al. [2012] very recently concluded that haploinsufficiency of *ARID1B* is a relatively frequent cause of moderate-to-severe ID from their findings that 0.9% (8/887) of patients with unexplained ID had truncating mutations in the gene. Michelson et al. [2012] also very recently reported a patient with an interstitial 1.19 Mb deletion of 6q25.2 including *ARID1B* and *ZDHHC14*, who manifested global developmental delay, facial characteristics, dysgenesis of the corpus callosum, limb anomalies, and genital hypoplasia.

To delineate the clinical consequences of mutations affecting components of the SWI/SNF complex (CSS, NBS, and *ARID1B*-related ID syndrome), we report the individual clinical information for 20 previously reported patients [Tsurusaki et al., 2012] as well as an additional patient with an *SMARCA4* mutation. Furthermore, we create a comprehensive list of all reported patients (including our series) with mutations affecting components of the SWI/SNF complex (Tables Ia–Ic), which will be helpful when discussing similarities and differences among these conditions.

CLINICAL REPORTS

SMARCB1 Mutations

SMARCB1-1 (Subject 4 [Tsurusaki et al., 2012]; Fig. 1a–i): She was born at 42 weeks of gestation after an uncomplicated prenatal period. Her birth weight was 3,008 g (−0.5 SD). She had: cleft palate with exudative otitis media; congenital dislocation of the right hip; pectus excavatum; sucking/feeding difficulty. She underwent surgical correction of cleft palate and insertion of ventilation tubes at age 2 6/12 years. Hearing aids were required for bilateral, severe, mixed hearing impairment with a threshold of 80–90 dB. At age 4 years, she developed tonic seizures, which were treated with carbamazepine. Scoliosis, found at age 2 years, progressed with a Cobb angle of ≈150°. She showed hypotonia and motor development was severely delayed: she raised her head at age 1 8/12 years, sat alone at 2 3/12 years, and walked independently at 7 years. From ages 12 to 18 years, she vomited frequently and had recurrent infections. She had multiple dental caries, treated under general anesthesia at age 16 years. At age 21 years, she weighs 30 kg (−3.4 SD), her height is 112.5 cm (−8.4 SD), and her occipitofrontal circumference (OFC) is 51.2 cm (−2.9 SD). She understands simple commands in daily life, expresses herself with gestures, and likes to play portable personal computer games, but speaks no words. She has serious behavioral problems such as impulsiveness, hyperactivity, and self-injurious behaviors (including skin picking). She becomes exhausted easily.

SMARCB1-2 (Subject 11 [Tsurusaki et al., 2012]): Her prenatal period was complicated by intrauterine growth retardation. She was born at 38 weeks of gestation. Her birth weight was 2,088 g (−1.8 SD), length was 42 cm (−2.9 SD), and OFC was 33 cm (0 SD). She had a small ventricular septal defect (VSD). Diaphragmatic hernia was corrected surgically at age 5 months. She had sucking/feeding difficulties. She showed hypotonia and motor development was severely retarded: she rolled over at age 3 years. Generalized seizures developed and were controlled with valproic acid. Magnetic resonance imaging (MRI) of the brain showed cerebellar hypoplasia and Dandy–Walker malformation. She had visual impairment that was corrected with spectacles; hearing impairment with a threshold of 60 dB in the right ear and 50 dB in the left ear was noted. At age 7 years, her weight is 12 kg (−3.1 SD) and height is 105 cm (−2.7 SD). She sits for several seconds with her hands, distinguishes her family members from others, and smiles when called by her name. She has visual and hearing impairment.

SMARCB1-3 (Subject 21 [Tsurusaki et al., 2012]; Fig. 1j–p): Her prenatal period was complicated by intrauterine growth retardation and oligohydramnios. She was born at 38 weeks of gestation, followed by resuscitation through endotracheal intubation. Her birth weight was 1,746 g (−2.6 SD). Surfactant treatment was undertaken for pulmonary hemorrhage. She had micrognathia, exotropia, and a dark complexion. She suffered from complex partial seizures. She sucked poorly and then had feeding difficulty associated with gastroesophageal reflux (GER), which required gastrostomy. She showed hypotonia with severe delay in motor development. A hypoplastic corpus callosum was observed. At age 7 years, she weighs 12 kg (−3.0 SD), has a height of 97 cm (−4.5 SD), and an OFC of 44 cm (−5.1 SD). She is unable to sit alone, and moves by rolling over. She cannot communicate with others or speak any words, but smiles when she appears to be happy.

SMARCB1-4 (Subject 22 [Tsurusaki et al., 2012]): He was born at 37 weeks of gestation. His birth weight was 2,784 g (+0.2 SD). He was admitted to hospital as a newborn for treatment of transient tachypnea. He had pyloric stenosis that was corrected surgically. He sucked poorly and then had feeding difficulties associated with GER, requiring gavage-feeding and resulting in failure to thrive. He showed hypotonia and motor development was severely delayed. MRI of the brain showed hypoplasia of the corpus callosum. He suffered from recurrent respiratory tract infections. At age 2 years, he weighed 9.7 kg (−2.3 SD), his height was 83.4 cm (−2.2 SD), and had an OFC of 43 cm (−3.3 SD). At age 3 years, he rolls over, but cannot sit alone or speak words.

SMARCA4 Mutations

SMARCA4-1 (Subject 9 [Tsurusaki et al., 2012]; Fig. 2a–c): He was born at 39 weeks of gestation. His birth weight was 2,880 g. Sucking or feeding difficulties were not reported, but abdominal distension occurred in infancy and constipation was frequent in childhood. Possible seizures developed once at age 1 2/12 years with unconsciousness but without electrocardiographic abnormalities. The submucosal cleft palate was corrected surgically at age 1 6/12 years. Congenital torticollis with vestigial (right) and shortened (left) cleidomastoid muscles was corrected surgically. His right chest was funnel-shaped with a hypoplastic right pectoral major muscle. Exudative otitis media in the left ear was recurrent. He showed hypotonia in his infancy and motor development was mildly delayed: he raised his head at age 4 months, sat alone at 10 months, crawled at 11 months, and stood alone at 1 3/12 years. His hair has been bristly and gray-streaked since childhood. His upper teeth were misaligned. At age 18 years, his height is 159 cm (−1.8 SD) and OFC is 53 cm (−2.3 SD). He can walk independently, talk (albeit with a stutter), and understand almost everything necessary for daily life. He has myopia and mild astigmatism which are corrected with spectacles. He has nocturnal enuresis which he finds hard to control.

SMARCA4-2 (Subject 7 [Tsurusaki et al., 2012]; Fig. 2d–g): His prenatal period was complicated by intrauterine growth retardation. He was born at 40 weeks of gestation. His birth weight was 2,250 g (−2.2 SD). He showed respiratory insufficiency and had sucking/feeding difficulties associated with laryngomalacia. He had bilateral ptosis, myopia, lacrimal duct stenosis, bilateral sensorineural hearing loss, and ankyloglossia. He showed hypotonia and motor development was severely delayed: he raised his head in late infancy, sat alone at age 2 years, and walked independently at 6 years. At age 20 years, he weighs 60 kg (−0.2 SD), has a height of

TABLE IA. Clinical Features of Patients With Mutations in the Components of SWI/SNF Complex

Gene	*SMARCB1*				*SMARCA4*						
Patient (subject no. in the previous report§)	1 (4)	2 (11)	3 (21)	4 (22)	1 (9)	2 (7)	3 (5)	4 (16)	5 (25)	6 (17)	7
Age at publication (years of age)	21	7	7	2	18	20	9	11	16	4	8
Sex	F	F	F	M	M	M	M	M	F	M	F
Mutation	p.Lys364del	p.Arg377His	p.Lys364del	p.Lys364del	p.Lys546del	p.Thr859Met	p.Arg885Cys	p.Leu921Phe	p.Met1011Thr	p.Arg1157Gly	p.Arg885His
Growth											
Prenatal growth (birth weight/length)#	−0.5/?	−1.8/−2.9	−2.6/?	+0.2/?	–	−2.2/?	−1.2/−0.9	−1.7/−1.6	−1.0/−1.9	−1.1/−2.3	−2.6/−2.7
Postnatal growth (weight/height)†	−3.4/−8.4	−3.1/−2.7	−3.0/−4.5	−2.3/−2.2	?/−1.8	−0.2/−2.6	−1.5/−3.2	−1.8/−3.1	−1.9/−1.9	−3.0/−3.4	−1.9/−1.8
Psychomotor											
Developmental delay/intellectual disability‡	Severe	Severe	Severe	Severe	Mild	Severe	Severe	Severe	Severe	Severe	Moderate
Speech delay	NW	NW	NW	NW	Mild	SW	NW	NW	SC	NW	Mild
Seizures	+	+	–	–	+	–	–	+	–	–	–
Hypotonia	+	+	+	+	+	+	+	–	+	–	+
Autistic features/behavioral abnormalities	HA,Im,SH		–			HA, Im	ASD (HA, HS, Ob, SH)	–	RB		HA
Microcephaly (≤2 SD) (SD score)	+(−2.9)	–	+(−5.1)	+(−3.3)	+(−2.3)	+(−3.8)	+(−3.6)	+(−2.9)	+(−2.3)	+(−2.7)	+(−3.0)
Brain anomaly		CH,DW	HCC	HCC			HCC,HCV			HCC	–
Craniofacial											
Sparse hair	+	+	+	+	–	+	–	+	–	+	–
Thick eyebrows	+	+	+	+	+	+	+	+	+	+	+
Thick eyelashes	+	+	+	+	+	+	+	+	+	+	+
Ptosis	–	+	+	+	+	+	+	+	–	+	+
Abnormal ears	+	+	+	+	–	+	+	+	+	+	–
Nasal bridge	Broad	Broad	Broad	Broad	Narrow	Narrow	Normal	Flat	Flat	Flat	Flat
Thick, anteverted alae nasi	–	–	–	+	–	–	–	–	–	–	–
Wide mouth	+	+	+	+	–	–	+	–	+	–	+
Philtrum	Broad		Long	Long	Short	Short	Short		Short		Short
Upper lip vermilion feature	Thin		Thin	Thick	Everted	Everted	Everted	Thin	Everted	–	
Thick lower lip vermilion	+	+	+	+	–	+	+	+	+	+	+
Palatal abnormality	C	C	H	H	SMCP	H	C	H	H	C	H
Skeletal–limb											
Hypoplastic/absent fifth finger/toe	Fi/T	Fi/T	Fi/T	Fi/T	Fi	Fi/T	T	Fi/T	Fi/T	Fi/T	T
Hypoplastic/absent nail (fifth finger/toe)	Fi/T	+	Fi/T	Fi/T	Fi	Fi/T	T	Fi/T	Fi/T	Fi/T	T
Hypoplastic/absent nail (other fingers/toes)	Fi/T		Fi/T	Fi/T		Fi/T	T	Fi/T	Fi/T	Fi/T	–
Prominent interphalangeal joints	+		–	–	–	+	–	–	+	–	–
Prominent distal phalanges	+	+	–	–	+	+	+	+	+	–	
Scoliosis/spinal abnormalities	+		+	+	–	+	–	–	–	–	–
Joint laxity		–	+	+	–	+	+	–	+	–	+
Others											
Hirsutism	+	–	+	+	+	+	+	+	+	+	+
Congenital heart defects	–	VSD	–	+	–	–	–	VSD, PDA	–	MA, PA, SRV, AtSD, PDA	+
Genitourinary defects	–			+	–		Cr	–	–	Cr	–
Gastrointestinal abnormalities	–	–	GER	PS		GOO	Co	DU	Co	GER	GER
Inguinal (I)/umbilical (U) hernia	–	–	I	I	–	I	–	I	–	Om	I/U
Sucking difficulty	+	+	+	+	–	+	+	+	+	+	+
Feeding difficulty	+	+	+	+	–	+	+	+	+	+	+
Frequent vomiting	+										+
Hearing impairment	+	+	+		–	+	+	–	+	–	–
Visual impairment		+	+		+	+	+	+	+	–	–
Recurrent infections	+	–	+	+	–	+	–	+	+	+	+

+, present; −, absent; blank, data not available; §, Tsurusaki et al. [2013]; #, SD score; †, SD acore; ‡, at latest assessment; ASD, autism spectrum disorder; AtSD, atrial septal defect; C, cleft palate; CH, cerebellar hypoplasia; Co, constipation; Cr, cryptorchidism; DU, duodenal ulcer; DW, Dandy-Walker malformation; F, female; Fi, finger; GER, gastroesophageal reflux; GOO, gastric outlet obstruction; H, high palate; HA, hyperactivity; HCC, hypoplastic corpus callosum; HCV, hypoplastic cerebellar vermis; HS, hypersensitivity; I, inguinal; Im, impulsiveness; M, male; MA, mitral atresia; NW, no words; Ob, obsession; Om, omphalocele; PA, pulmonary atresia; PDA, patent ductus arteriosus; PS, pyloric stenosis; RB, repetitive behavior; SC, simple conversation; SH, self-harming behavior; SMCP, submucosal cleft palate; SRV, single right ventricle; SW, several words; T, toe; VSD, ventricular septal defect

TABLE IB. Clinical Features of Patients With Mutations in the Components of SWI/SNF Complex

Gene	*SMARCA2*		*SMARCE1*	*ARID1A*			*ARID1B*			
Patient (subject no. in the previous report§)	1 (19)	NCBRS(n = 36)	1 (24)	1 (3)	2 (6)	3 (8)	1 (1)	2 (15)	3 (23)	4 (10)
Age at publication (years of age)	8	2 3/12–32	14	2	1	10	13	7	10	11
Sex	M	21M,15F	F	M	M	M	M	M	F	M
Mutation	Partial deletion [van Houdt et al., 2012]	Missense	p.Tyr73Cys	p.Ser11Alafs*91	p.Gln920*	p.Arg1335*	p.Ile560Glyfs*89	p.Gln635*	p.Arg1102*	p.Asp1878Metfs*96
Growth										
Prenatal growth (birth weight/length)#	−2.6/−3.1	10/34	−2.3/?	−1.0/−1.4	−0.6/−1.1	−	−0.9/+0.4	−1.2/−1.2	+0.5/−1.7	−1.0/−1.1
Postnatal growth (weight/height)†	−2.1/−3.8	19/36	−4.4/−6.8	−6.2/−8.9	−5.5/−8.2	50th/3rd	−0.5/−1.4	−1.1/−1.1	+1.5/−1.3	−0.5/−2.4
Psychomotor										
Developmental delay/intellectual disability‡	Moderate	3Mild,9Moderate, 24Severe	Severe	Severe	Severe	Severe	Moderate	Severe	Mild	Mild
Speech delay	NW	13/33NW	NW	NW	NW	NW	NW	NW	Mild	Mild
Seizures	+	22/35	+	−	−		−	+	+	−
Hypotonia	+		+	+	+	−	+	+	+	+
Autistic features/behavioral abnormalities	−					HA	ASD (HA, Im, O)	ASD (Im)	−	−
Microcephaly (≦2 SD) (SD score)	+(−3.3)	19/34	+(−6.7)	+(−3.7)	+(−3.1)	−(50th)	−(+0.7)	−(−1.4)	−(+1.8)	−(−1.1)
Brain anomaly				ACC, CH,DW	ACC	HCC	−		ACC, Colp	−
Craniofacial										
Sparse hair	−	35/36	+	+	+	+	+	−	−	+
Thick eyebrows	+		+	+	+	+	+	+	+	+
Thick eyelashes	+	23/35	+	+	+	+	+	+	+	+
Ptosis	+		+	−	−	−	−	−	−	−
Abnormal ears	+		+	+	+	+	+	+	−	+
Nasal bridge	Broad	22/36Narrow	Narrow	Broad	Broad		Broad	Broad	Broad	Broad
Thick, anteverted alae nasi	+	32/36	−			−	−	+	−	−
Wide mouth	+	34/36	+	+	+	+	+	+	−	+
Philtrum	Broad	31/36Broad, 29/36Long	Long	Short	Broad	Long	Broad	Broad	Long	Long
Upper lip vermilion feature		27/36Thin			Everted		Thin	Thick	Thin	Thin
Thick lower lip vermilion	+	32/36	+	+	+	+	−	+	+	+
Palatal abnormality	−		C	C	C	H	H	H	H	H
Skeletal—limb										
Hypoplastic/absent fifth finger/toe	−		Fi/T		Fi/T	Fi/T	Fi/T	Fi/T	Fi	Fi/T
Hypoplastic/absent nail (fifth finger/toe)	−		Fi/T	+	Fi/T	Fi/T	Fi/T	T	Fi	Fi/T
Hypoplastic/absent nail (other fingers/toes)	−		Fi/T	Fi/T		Fi/T	Fi/T	T	−	Fi/T
Prominent interphalangeal joints	+	28/35	−		−	−	−	−	−	+
Prominent distal phalanges	+	21/35	−		−	+	+	+	−	+
Scoliosis/spinal abnormalities	+	10/34		+		−	+	−	−	+
Joint laxity	−			+	+	−	+	+	−	+
Others										
Hirsutism	+		+	+	+	+	+	+	+	+
Congenital heart defects	−	6/34	TR,MR,AS	CoA, AtSD, VSD	CoA, AS, VSD	AtSD	−	−	−	+
Genitourinary defects	Cr, HS	13/20Cr,2/32VUR	−		HS, Cr	−	−	−	−	Cr
Gastrointestinal abnormalities	−				AA, RUF	IO, GER	−	−	−	−
Inguinal (I)/umbilical (U) hernia	I/U	14/35	−	−	−	I	−	−	−	−
Sucking difficulty	+		+	+	+	+	+	+	+	+
Feeding difficulty	+		+	+	+	+	+	+	+	+
Frequent vomiting	+									
Hearing impairment	+			+	−	+	−	+	−	−
Visual impairment	+			−			+	−	+	−
Recurrent infections	−	+	+	+	+	+	+	+	+	+

+, present; −, absent; blank, data not available; §, Tsurusaki et al. [2013]; #, SD score;†, SD acore; ‡, at latest assessment; AA, anal atresia; ACC, agenesis of corpus callosum; AS, aortic stenosis; ASD, autism spectrum disorder; AtSD, atrial septal defect; C, cleft palate; CH, cerebellar hypoplasia; CoA, coarctation of aorta; Colp, colpocephaly; Cr, cryptorchidism; DW, Dandy-Walker malformation; F, female; Fi, finger; GER, gastroesophageal reflux; H, high palate; HA, hyperactivity; HCC, hypoplastic corpus callosum; HS, hypospadias; Im, impulsiveness; IO, intestinal obstruction; M, male; MR, mitral regurgitation; NBS, Nicolaides-Baraitser syndrome; NW, no words; O, obsession; RUF, retrourethral fistula; T, toe; TR, tricuspid regurgitation; VSD, ventricular septal defect; VUR, vesicoureteral reflux; fractions in the previous publications show patient numbers "feature-positive/data available"

TABLE IC. Clinical Features of Patients With Mutations in the Components of SWI/SNF Complex

Gene				***ARID1B***		
Patient (subject no. in the previous report§)	5 (12)	n = 4	n = 8	n = 9	n = 6	n = 1
Age at publication (years of age)	19	11/12–4	3–46	3 3/12–20	2–40	2
Sex	M	2M,2F	2M,6F	4M,5F	1M,5F	M
Mutation	Del (9.2Mb)	Del (3.77–13.81Mb) [Nagamani et al., 2009]	7Del (0.2–14.5Mb),1Tra [Halgren et al., 2012]	1Del(2.5Mb),1Dup(exon 5/6),3Ns,4Fs [Hoyer et al., 2012]	3Del(0.73–2.72),2Ns,1Fs [Santen et al., 2012]	Del(1.19Mb) [Michelson et al., 2012]
Growth						
Prenatal growth (birth weight/length)#	−2.3/−3.?	3/4		0/9	0/6	−
Postnatal growth (weight/height)†	−2.3/−6.1	1/3	5/7	3/9	3/6	−
Psychomotor						
Developmental delay/mental retardation‡	Severe	4/4(2Moderate, 2Severe)	8/8	5Moderate,4Severe	2Moderate, 4Severe	Moderate
Speech delay	NW	4/4(3NW, 1SW)	8/8(3NW,5SW)	9/9(2NW, 2SW, 3Se)	6/6(2NW, 3Severe, 1Moderate)	NW
Seizures	+	1FC	3/6	3/9		
Hypotonia	−	2	7/8	7/9		+
Autistic features/behavioral abnormalities	HA		5/7	1	1	
Microcephaly (≤2 SD) (SD score)	+	4/4	1/6	2/9	0/6	−
Brain anomaly	−?	2/3(ACC + Colp)	4/5(1ACC, 3HCC, 1HCV)	0/6	4/4(3ACC, 1HCC, 2Colp)	HCC
Craniofacial						
Sparse hair	+		1	1	1	
Thick eyebrows	+		1		6/6	
Thick/long/prominet eyelashes	−					
Ptosis	−	1				
Abnormal ears	+	2	1	7/9		
Nasal bridge	Narrow	3Broad	3Broad			
Thick, anteverted alae nasi						Broad
Wide mouth	−		2	1		+
Philtrum	Long	2Long	2Long	1Long		
Upper lip vermilion feature		2*Thin*	3*Thin*,1*Thick*	6/9(6*Thin*)		*Thin*
Thick lower lip vermilion	−	2Thick	3			
Palatal abnormality	H	2H		2/9(2H)		
Skeletal-limb						
Hypoplastic/absent fifth finger/toe	Fi/T				2/6(2Fi)	
Hypoplastic/absent nail (fifth finger/toe)	+		1T	1T	2/6(2Fi)	
Hypoplastic/absent nail (other fingers/toes)				1?	1/6	
Prominent interphalangeal joints	+					
Prominent distal phalanges	−	1				
Scoliosis/spinal abnormalities	+		1	1		
Joint laxity	−		3/4		3/5	
Others						
Hirsutism	+		3/4	2		3/6
Congenital heart defects	MR	1AtSD	1AtSD	2/9(1AtSD)	1AtSD	
Genitourinary defects	−	1PSW	1Cr, 1DoUr, 2RL	2Cr, 1MU	1RL, 1DoUr	
Gastrointestinal abnormalities	GU, GER		1Co, 1AA	1AA		
Inguinal (I)/umbilical (U) hernia	−					
Sucking difficulty	−	3	4			+
Feeding difficulty	−		5	+		
Frequent vomiting						
Hearing impairment	−	4	1/2	1/9	+	
Visual impairment	−	1St, 1Am	2Hy, 2My, 2St,1 Cat, 1Ny		3St/9,4My	2St
Recurrent infections	+	1	1			

+, present; −, absent; blank, data not available; §, Tsurusaki et al. [2013]; #, SD score; †, SD acore; ‡, at latest assessment; AA, anal atresia; ACC, agenesis of corpus callosum; Am, amblyopia; AtSD, atrial septal defect; Cat, cataract; Co, constipation; Colp, colpocephaly; Cr, cryptorchidism; Del, deletion; Dup, duplication; DoUr, double ureter; F, female; Fi, finger; Fs, frameshift mutation; GER, gastrointestinal reflux; GU, gastric ulcer; H, high palate; HA, hyperactivity; HCC, hypoplastic corpus callosum; HCV, hypoplastic cerebellar vermis; Hy, hypermetropia; M, male; MR, mitral regurgitation; MU, megaureter; My, myopia; Ns, nonsense mutation; NW, no words; Ny, nystagmus; PSW, penoscrotal webbing; RL, renal lithiasis; Se, sentences; St, strabismus; SW, several words; T, toe; Tra, translocation; fractions in the previous publications show patient numbers "feature-positive/data available"

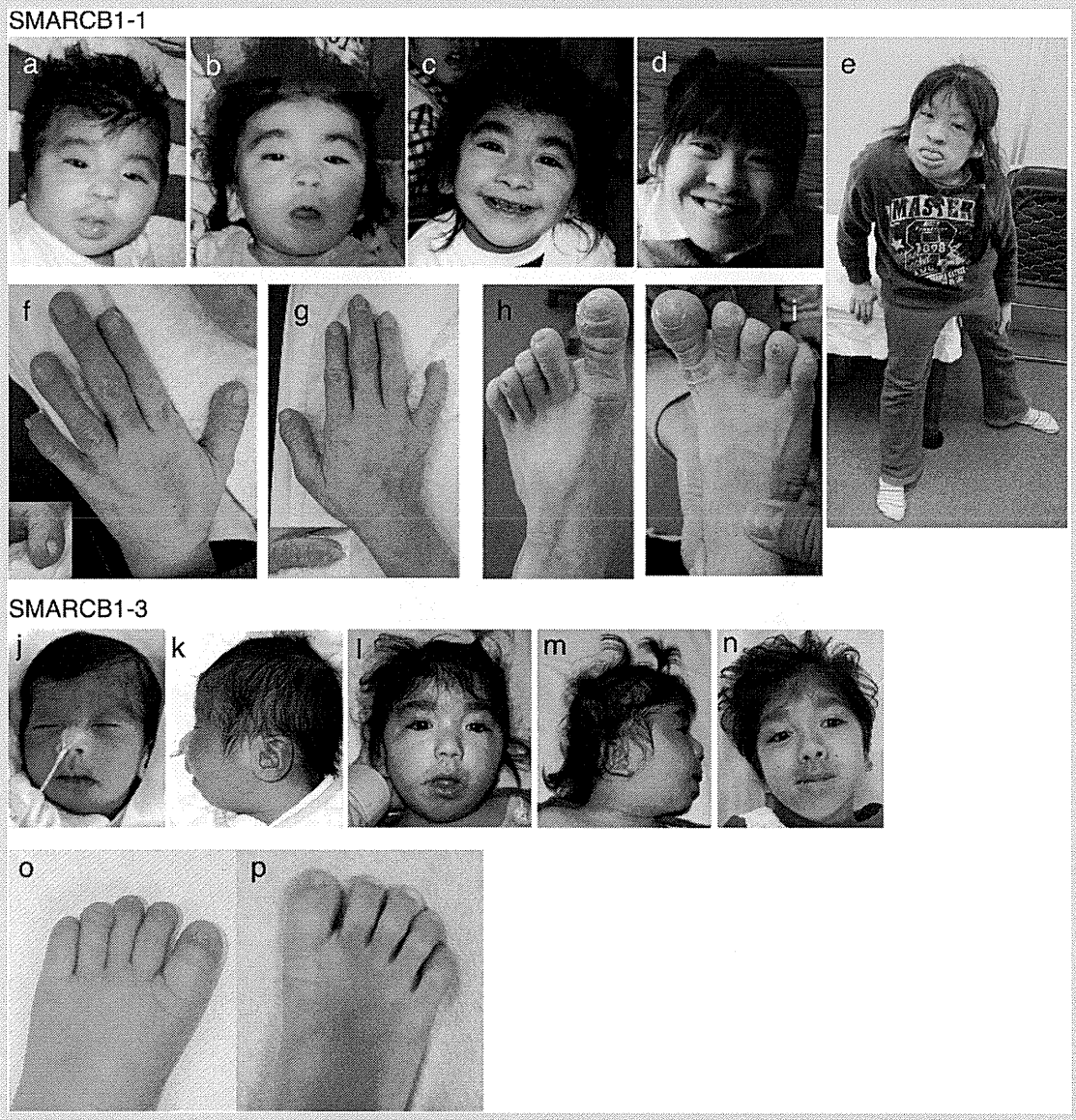

FIG. 1. Clinical photographs of patients with an *SMARCB1* mutation. SMARCB1-1: Craniofacial features at age 2 months (a), 1 year (b), 6 years (c), and 18 years (d). Note a round face with thick and arched eyebrows, a short nose with a bulbous tip and anteverted nostrils, a long philtrum, a small mouth, and micro-retrognathia in the early childhood. Later, note a broad nasal bridge without anteverted nostrils, a broad philtrum, a large tongue, and a protruding jaw. Poor posture due to severe scoliosis (e) as well as hypoplastic fingers (f, g) and toes (h, i) with nail hypoplasia, prominent interphalangeal joints, and prominent distal phalanges are noted at age 21 years. SMARCB1-3: Craniofacial features in the neonatal period (j, k), at age 2 years (l, m), and 7 years (n). Note a round face with thick and arched eyebrows, a short nose with anteverted nostrils, a long philtrum, a small mouth, and micro-retrognathia in early childhood. Later, note a broad nasal bridge and a protruding jaw. Feet at age 5 years (o, p). Note hypoplasia of the bilateral fifth toes and hypoplasia of all toenails. (Figure 1 originally published in Tsurusaki et al. [2012], in *Nature Genetics*.)

156 cm (−2.6 SD), and an OFC of 51.2 cm (−3.8 SD). He suffers from constipation, nocturnal enuresis, and unstable body temperature. He understands simple commands and speaks several words. He is friendly but also hyperactive and impulsive.

SMARCA4-3 (Subject 5 [Tsurusaki et al., 2012]; Fig. 2h–o): Increased nuchal translucency thickness was shown by fetal ultrasonography. He was born at 41 weeks of gestation. His birth weight was 2,756 g (−1.2 SD), length was 48 cm (−0.9 SD), and OFC was 32.0 cm (−0.9 SD). He was gavage-fed due to sucking/feeding difficulties until 7 months of age. He had right cryptorchidism which was corrected surgically at age 1 year. He showed hypotonia and motor development was delayed: he raised his head at age