Received: 7 March 2018 | Revised: 25 May 2018 | Accepted: 21 June 2018

DOI: 10.1002/ajmg.a.40471

WILEY AMERICAN JOURNAL OF medical genetics PART A

ORIGINAL ARTICLE

First data from a parent-reported registry of 81 individuals with Coffin–Siris syndrome: Natural history and management recommendations

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Coffin–Siris syndrome (CSS; MIM 135900) is a multisystem congenital anomaly syndrome caused by mutations in the genes in the Brg-1 associated factors (BAF) complex. Classically, individuals with CSS have been described with hypo- or aplasia of the fifth digit nails or phalanges (hence the term "fifth digit syndrome"). Other physical features seen include growth restriction, coarse facial features, hypertrichosis or hirsutism, sparse scalp hair, dental anomalies, and other organ-system abnormalities. Varying degrees of developmental and intellectual delay are universal. To date, approximately 200 individuals have been described in the literature. With the advent of large-scale genetic testing such as whole-exome sequencing is becoming more available, more individuals are being found to have mutations in this pathway, and the phenotypic spectrum appears to be broadening. We report here a large cohort of 81 individuals with the diagnosis of CSS from the first parent-reported CSS/BAF complex registry in an effort to describe this variation among individuals, the natural history of the syndrome, and draw some gene–phenotype correlations. We propose that changes in the BAF complex may represent a spectrum of disorders, including both *ARID1B*-related nonsyndromic intellectual disability (*ARID1B*-ID) and CSS with classic physical features. In addition, we offer surveillance and management recommendations based on the medical issues encountered in this cohort to help guide physicians and patients' families.

KEYWORDS

Coffin–Siris syndrome, Fifth digit, BAF complex, Natural history, parent-reported registry

1 | INTRODUCTION

Coffin–Siris Syndrome (CSS; MIM 135900) is a rare, multisystem diagnosis that is caused by mutations in genes encoding components of the BRG-1 associated factors (BAF) complex. Initially termed "fifth-digit syndrome," a phenotypic feature that has been used for clinical diagnosis is hypo- or aplasia of the fifth digit nail or phalanges (Carey & Hall, 1978; Coffin & Siris, 1970; Fleck, Pandya, Vanner, Kerkering, & Bodurtha, 2001; Lucaya, Garcia-Conesa, Bosch-Banyeras, & Pons-Peradejordi, 1981; Schrier et al., 2012). Other features that have been associated with CSS include ectodermal abnormalities (such as sparse scalp hair, hirsutism, and abnormal dentition), coarse facial features, and other nonspecific features such as intellectual or developmental delay, hypotonia, gastrointestinal anomalies, cardiac defects, vision anomalies, and hearing loss (Santen et al., 2013; Schrier et al., 2012; Tsurusaki et al., 2014).

The molecular etiology of CSS was first described in 2012 and includes genes encoding components of the BAF complex, including *ARID1A*, *ARID1B*, *ARID2*, *SMARCB1*, *SMARCA4*, and *SMARCE1* (Bramswig et al., 2017; Santen et al., 2012; Tsurusaki et al., 2012). An additional gene that has been identified is *SOX11*;it is involved in transcriptional regulation of the BAF complex and plays a role in neurodevelopment (Hempel et al., 2016; Tsurusaki et al., 2014). Most recently, mutations in the BAF-complex subunit *DPF2* have also been associated with CSS (Vasileiou et al., 2018). The most frequently altered gene in CSS patients is *ARID1B*; however, the clinical phenotype associated with mutations in *ARID1B* are highly variable and may not be as severe as other genotypes (Kosho, Miyake, & Carey, 2014; Santen

et al., 2014; Tsurusaki et al., 2014). Haploinsufficiency of *ARID1B* has also been identified as a common cause of nonsyndromic intellectual disability (Hoyer et al., 2012).

Several genotype–phenotype analyses have been conducted so far for CSS. These studies have explored the relationship between the BAF complex genes and many clinical features known to be involved with CSS (Kosho et al., 2013; Kosho et al., 2014; Santen et al., 2013; Tsurusaki et al., 2014; Wieczorek et al., 2013). To contribute to the current literature and further investigate the breadth of clinical characteristics of CSS, the CSS/BAF pathway international registry was created in 2015. This is a parent-reported registry designed to examine the growth, development, and medical issues associated with individuals with a diagnosis of CSS. We report here the natural history and gene-phenotype analysis of the CSS registry patients to determine the prevalence of the "classic" clinical features typically associated with CSS (fifth digit anomalies, hypertrichosis/hirsutism, and sparse scalp hair). In addition, we hoped to investigate the prevalence of other defining features of CSS that may not have been previously reported in detail in the large genotype–phenotype cohort studies, such as spinal abnormalities, certain central nervous system (CNS) defects, cardiac, and gastrointestinal abnormalities. Based on the prevalence of a variety of features, we propose a preliminary guide regarding surveillance and management of this condition for clinicians caring for these individuals.

2 | METHODS

Registry participants were either referred by colleagues at other medical institutions or self-referred through the CSS support group on Facebook and other social media platforms. Individuals were eligible for enrollment if they had undergone molecular testing that indicated a mutation in the BAF pathway consistent with CSS. The registry protocol and consent was approved by the Eastern Virginia Medical School Institutional Review Board (EVMS IRB). Individuals in this report were enrolled between 2015 and 2017. Patients were enrolled by signing a registry consent form or through the Institutional Review Board's waiver of consent. There are currently 143 patients enrolled in the registry at the time of this manuscript. As of the data analysis in December of 2017, there were 117 registrants. However, only 81 out of the 117 patients had both gene and phenotype data that was available for analysis. Data were collected from parent-completed online surveys through REDCap© software and were verified by available medical records obtained through record releases. A variety of clinical features related to CSS were analyzed during this study, including ectodermal, gastrointestinal, hearing, vision, CNS, cardiac, pulmonary, musculoskeletal, and developmental features. Photographs of individuals' faces, hands, and feet were also requested and obtained with parental consent; several are shown in Figure 1.

Gene–phenotype correlations were conducted based on clinical feature and the specific gene that was mutated. Chi-square tests were used when comparing genotypes and phenotypes to determine the statistical significance between these modalities. Phenotypic frequencies were also calculated. All statistical analysis was conducted using the Statistical Analysis System (SAS) program.

3 | RESULTS

Gene and phenotype data were available for all 81 patients; parents were required to report the gene altered (not the genotype) in the RedCap survey. Fifty two of the 81 individuals had specific genotype information from medical records and parents, and complete medical records were available from the individuals' physicians for 51 of the registrants. Three of the patients reported with *SMARCE1* mutations were previously reported in Zarate et al. (2016). One individual with a *SMARCA4* mutation was previously reported in Santen et al. (2013). There may be some individuals in this registry who have been previously reported in the literature but is unknown for those individuals for whom we do not have complete medical records or could not contact the clinician caring for the child. This was most common for international patients. There were 46 males and 35 females, ranging in age from 1 month to 18 years of age at the time of diagnosis. Three individuals are from Australia, seven from the United Kingdom, three from France, two from the Netherlands, and one each from Denmark, India, and Brazil. The remainders are from the United States.

ARID1B changes were reported in 60% (49/81) of individuals. *SMARCA4* changes were reported in 15% (12/81) of individuals. *SMARCB1* and *SMARCE1* changes were reported in 10% (8/81) and 5% (4/81) of individuals, respectively. *ARID1A* made up 7% (6/81) of the cohort, and there were two individuals (2.5%) reported to have mutations in *ARID2* (Figure 2).

The prevalence of specific features within the entire cohort is illustrated in Figures 3i, and median ages for various developmental milestones are notated in Table 1. The frequency of features according to each gene is delineated in Table 2. Notable gene/phenotype correlations are described below.

3.1 | ARID1A

There are six individuals in the registry with mutations in the *ARID1A* gene. Regarding "classic" phenotypic features, 5/6 individuals were described as having sparse scalp hair and 3/6 had hypertrichosis or hirsutism. About 2/6 individuals reported having any abnormality to the fifth digit, including short phalanges or hypoplastic/aplastic nails.

Corpus callosal abnormalities were the most frequently reported in this group (5/6) compared with the other genes, but this group did not report a significant frequency of other brain abnormalities, including white matter changes, ventricular abnormalities, posterior fossa anomalies, or hydrocephalus. Seizures were reported in 1 of 6 individuals. About 3 of 6 individuals reported scoliosis, but there were no reports of lordosis or kyphosis in this group.

Half of the individuals were reported to have constipation, GE reflux, and use of a feeding tube at some point in time.

Dental anomalies were reported most frequently in this group (5/6), with 4 of 6 reporting abnormal dental shape and 2 of 6 reporting crowding/widely spaced teeth. There were no individuals with delayed dentition. Vision abnormalities were reported in 5 of 6 individuals and included myopia, hyperopia, and strabismus.

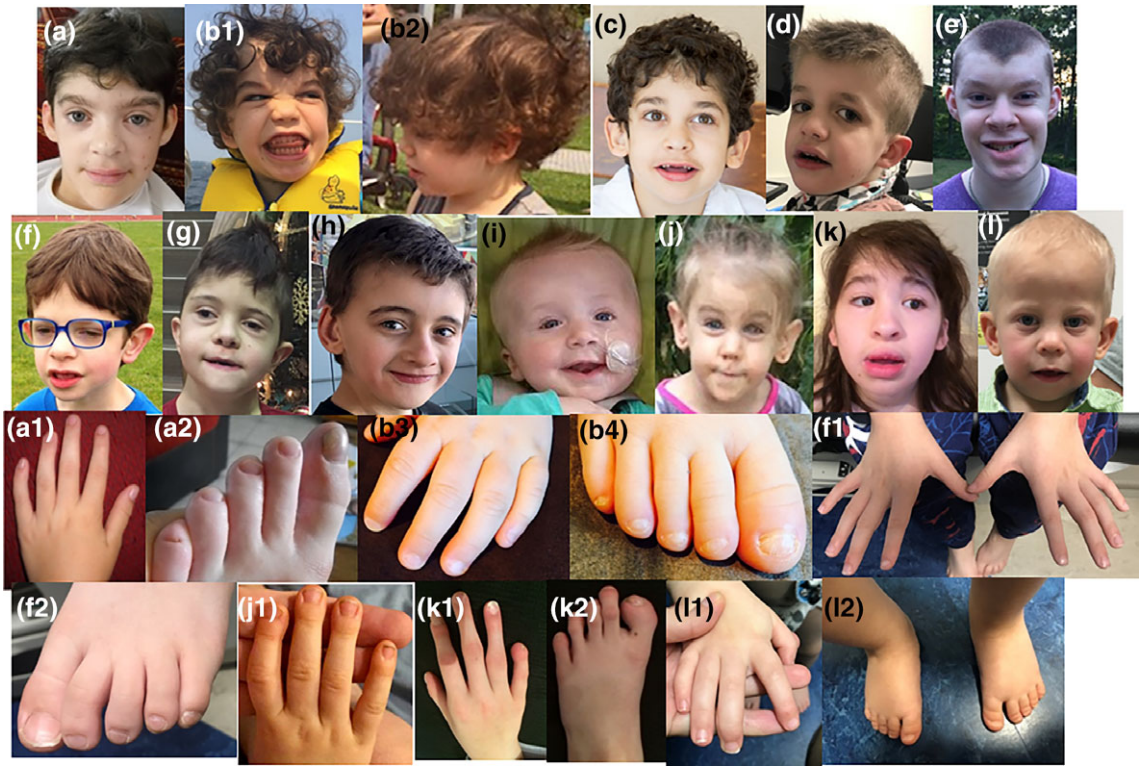

FIGURE 1 (a–e) Face, hand, and foot photos of individuals with CSS. Individuals with mutations in ARID1B. (g, h) ARID1A), (i–k) SMARCA4, (l) SMARCE1, and (m) ARID2. Individual (a) has normal fifth digit fingers but a hypoplastic fifth toenail (a1, a2). Note the small, widely spaced teeth and sparse scalp hair in individual (b). He has normally formed fifth digit fingers and toes. (f) Also has normally formed fifth digit fingers and toes (f1, f2). (j) Prominent distal phalanges to her fingers (j1). (k) Some phalangeal prominence to both her hands and feet (k1, k2). (l) A normally formed fifth digit finger and toes (l1, l2) [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | ARID1B

The *ARID1B* group represented the largest genotype of the cohort, with 49 individuals, and, appears to have the broadest phenotype. Approximately, half of the individuals were reported to have any fifth digit anomaly; 72% reported hypertrichosis or hirsutism, and 35% (17/49) reported sparse scalp hair.

Fourteen percentage (7/49) reported failure to thrive and approximated similar numbers with feeding tube use (7/49), feeding difficulties (6/49) and dysphagia (5/49). However, a total of 28 individuals reported having general "gastrointestinal abnormalities," which may include issues not specifically elicited in the survey.

Dental anomalies were also frequent in this group, with 14 of 49 reporting delayed dentition, 28 of 49 reporting abnormal dental shape, and 6 of 49 reporting with crowding/widely spaced teeth.

Callosal abnormalities were the most frequently reported brain anomaly in *ARID1B*, with 12 of 49 reporting agenesis or dysgenesis of the corpus callosum. Microcephaly was reported in 13 of 49 individuals. Seizures were relatively low in this group, with 8 of 41 reporting a seizure disorder or history of seizures.

Atrial septal defects (ASDs) were the most common cardiac defect (7/49), but others were reported to have ventricular septal defects (VSDs) (3/49), valvar stenosis (2/49), and coarctation of the aorta (1/49).

3.3 | ARID2

As there are only two additional individuals with *ARID2* mutations in this report, it is difficult to draw definitive conclusions about the phenotype in these patients. Nonetheless, we have included them in this cohort to further add this group to the literature. Although it is unclear whether or not *ARID2* mutation are considered a true "Coffin–Siris gene" or represent more of a "Coffin–Siris-like" phenotype requires analysis of more individuals with mutations. However, we noted that both individuals with *ARID2* mutations were reported having feeding difficulties and had G-tubes. Only one individual appeared to have fifth-digit/nail hypo/aplasia. One individual was reported to have white matter abnormalities and an abnormal corpus callosum and the other individual had a history of a normal brain MRI. One individual reported developmental delay, achieving sitting at 8 months, speaking first words at 15 months and not yet walking at 33 months. The other

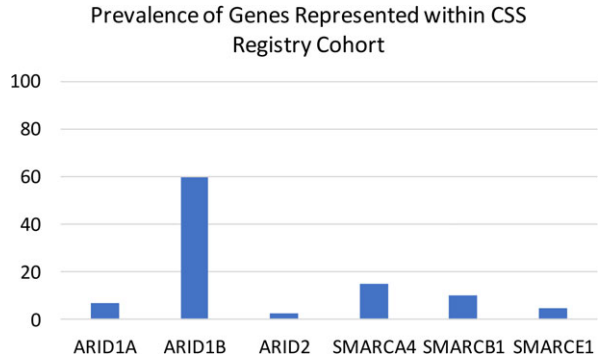

FIGURE 2 Prevalence of genes represented in CSS registry cohort [Color figure can be viewed at wileyonlinelibrary.com]

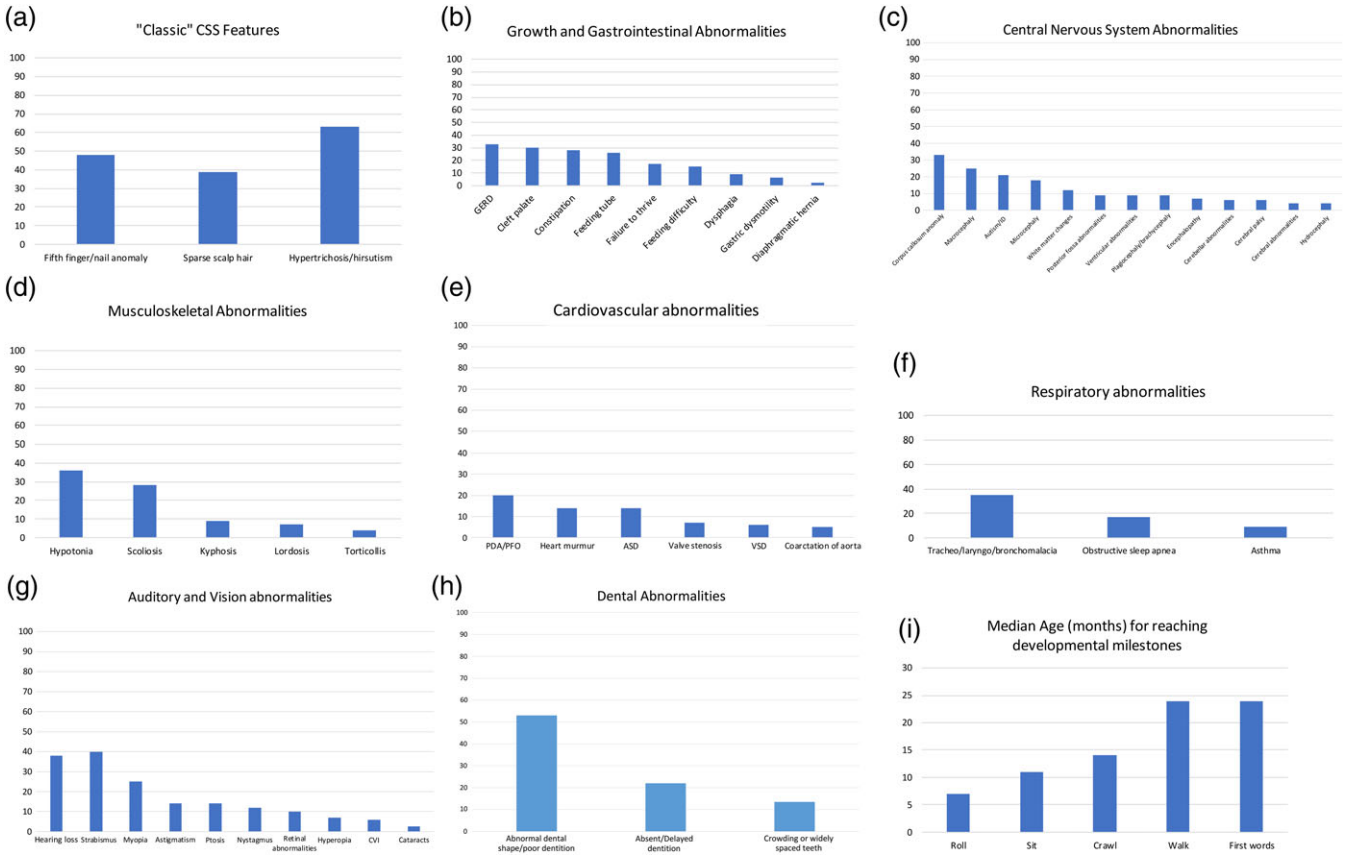

FIGURE 3 (a–i) specific features analyzed within the registry cohort. (a) "Classic" CSS features; (b) growth and gastrointestinal abnormalities; (c) Central nervous system abnormalities; (d) musculoskeletal abnormalities; (e) cardiovascular abnormalities; (f) Respiratory abnormalities; (g) auditory and vision abnormalities; (h) dental abnormalities; (i) median age (in months) of reaching developmental milestones [Color figure can be viewed at wileyonlinelibrary.com]

individual's development has been closer to the range of normal but still delayed (sitting at 8 months, walking at 18 months, speaking his first word at 12 months).

3.4 | SMARCA4

There were 12 individuals total with mutations in the *SMARCA4* gene; 7 of 12 reported fifth digit anomalies, 4 of 12 had sparse scalp hair, and half reported hypertrichosis or hirsutism. Half of the individuals were reported to have a high or cleft palate (6/12). About 5 of 12 reported microcephaly and only 1 of 12 reported a history of seizures; 5 of 12 (42%) reported a diagnosis of scoliosis. One-third of individuals reported a diagnosis of intellectual disability or autism.

3.5 | SMARCB1

There were eight total individuals with mutations in the *SMARCB1* gene. Approximately, a third of this cohort each reported the presence of fifth digit/nail anomalies, hypertrichosis/hirsutism, and sparse scalp hair. On the whole, individuals with these mutations appeared to have a higher frequency of a variety of brain abnormalities than individuals with mutations in other genes. About 3 of 8 reported microcephaly, 3 of 8 reported macrocephaly, 2 of 8 reported posterior fossa abnormalities and cerebellar abnormalities, 5 of 8 reported ventricular abnormalities, and half reported abnormalities with the corpus callosum. Two individuals were reported to have no known brain anomalies. Other abnormalities seen with a higher incidence in this gene also included obstructive sleep apnea (OSA, 38%), strabismus (63%), hearing loss (50%), and use of a feeding tube (63%).

TABLE 1 Median age in months for specific developmental milestones according to age

Milestone (median age in months)	Gene					
	ARID1A	ARID1B	ARID2	SMARCA4	SMARCB1	SMARCE1
Roll	6	6	8	8	7	10
Sit	10	10	11	12	15	11
Crawl	11	14	11.5	15	13	19
Walk	25	24	18	26	30	30
First words	30.5	30	13.5	15.5	12	24

TABLE 2 Number of patients with clinical feature according to gene

	Gene (%)						
	ARID1A	ARID1B	ARID2	SMARCA4	SMARCB1	SMARCE1	Total (%)
Individuals per gene	6	49	2	12	8	4	81
Ectodermal							
Fifth digit and/or nail hypoplasia or aplasia	2 (33)	22 (45)	1 (50)	7 (58)	3 (38)	3 (75)	39 (48)
Sparse scalp hair	5 (83)	17 (35)	0	4 (33)	3 (38)	3 (75)	31 (38)
Hypertrichosis/hirsutism	3 (50)	37 (76)	0	6 (50)	3 (38)	2 (50)	51 (63)
Absent or delayed dentition	0	14 (29)	0	2 (17)	1 (13)	1 (25)	18 (22)
Abnormal dental shape/poor dentition	4 (67)	28 (57)	1 (50)	7 (58)	0	3 (75)	43(53)
Crowding or widely spaced teeth	2 (33)	6 (12)	0	3 (25)	0	0	11(14)
Gastrointestinal							
Constipation	3 (50)	15 (31)	0	5 (42)	0	0	23 (28)
Feeding tube	3 (50)	7 (14)	2 (100)	2 (17)	5 (63)	2 (50)	21 (26)
Cleft/high palate	2 (33)	10 (20)	0	6 (50)	2 (25)	4 (100)	24 (30)
Feeding difficulty	1 (17)	6 (12)	1 (50)	1 (8)	1 (13)	2 (50)	12 (15)
Dysphagia	1 (17)	5 (10)	0	0	0	1 (25)	7 (8)
Delayed gastric emptying/dysmotility	1 (17)	2 (4)	1 (50)	0	1 (13)	0	5 (6)
Pyloric stenosis	0	2 (4)	0	0	1 (13)	1 (25)	4 (5)
Diaphragmatic hernia	0	0	0	1 (8)	0	1 (25)	2 (2)
Central nervous system							
Plagiocephaly/brachycephaly	2 (33)	4 (8)	0	1 (8)	0	0	3 (4)
Microcephaly (less than 3rd centile)	1 (17)	5 (10)	0	5 (42)	3 (38)	1 (25)	15 (19)
Macrocephaly (greater than 97th centile)	2 (33)	13 (27)	1 (50)	1 (8)	3 (38)	0	20 (25)
Posterior fossa abnormalities	1 (17)	3 (6)	0	1 (8)	2 (25)	0	5 (6)
Cerebellar abnormalities	0	3 (6)	0	0	2 (25)	0	5 (6)
Changes in white matter	0	7 (14)	1 (50)	1 (8)	0	1 (25)	10 (12)
Cerebral abnormalities[a]	1 (17)	2 (4)	0	0	0	0	3 (4)
Ventricular abnormalities	0	3 (6)	0	0	5 (63)	0	8 (10)
Corpus callosum abnormalities	5 (83)	12 (24)	1 (50)	2 (17)	4 (50)	1 (25)	25 (30)
Encephalopathy	1 (17)	5 (10)	0	0	0	0	6 (7)
Hydrocephalus	0	0	0	0	3 (38)	0	3 (4)
Cerebral palsy	0	2 (4)	0	0	3 (38)	0	5 (6)
Seizures	1 (17)	8 (16)	0	1 (8)	3 (38)	1 (25)	14 (17)
Autism/intellectual delay[b]	1 (17)	11 (22)	0	4 (33)	1 (13)	0	17 (21)
Musculoskeletal							
Scoliosis	3 (50)	10 (20)	1 (50)	5 (42)	3 (38)	1 (25)	23 (28)
Lordosis	0	6 (12)	0	0	0	0	6 (7)
Kyphosis	0	2 (4)	0	4 (33)	1 (13)	1 (25)	8 (10)
Torticollis	1 (17)	2 (4)	0	0	0	0	3 (4)
Hypotonia	3 (50)	18 (37)	1 (50)	2 (17)	4 (50)	1 (25)	29 (36)
Cardiac							
Heart murmur	1 (17)	5 (10)	0	2 (17)	1 (13)	2 (50)	11 (14)
PFO/PDA	3 (50)	8 (16)	0	1 (8)	3 (38)	2 (50)	16 (20)
ASD	1 (17)	7 (14)	0	0	2 (25)	1 (25)	11 (14)
VSD	0	3 (6)	0	1 (8)	1 (13)	0	5 (6)
Valve stenosis[c]	1 (17)	2 (4)	0	1 (8)	1 (13)	1 (25)	6 (7)
Coarctation of the aorta	1 (17)	1 (2)	0	1 (8)	1 (13)	0	4 (5)
Pulmonary							
Tracheo/bracheo/laryngomalacia	2 (33)	18 (37)	1 (50)	4 (33)	2 (25)	1 (25)	28 (35)
OSA	0	8 (16)	0	3 (25)	3 (38)	0	14 (17)
Asthma	1 (17)	5 (10)	0	0	1 (13)	0	7 (9)
Vision/hearing							

(*Continues*)

TABLE 2 (Continued)

	Gene (%)						
	ARID1A	ARID1B	ARID2	SMARCA4	SMARCB1	SMARCE1	Total (%)
Hearing loss	1 (17)	20 (41)	0	4 (33)	4 (50)	2 (50)	32 (40)
Myopia	2 (33)	12 (24)	0	3 (25)	3 (38)	0	20 (25)
Hyperopia	2 (33)	4 (8)	0	0	0	0	6 (7)
Retinal abnormalities[d]	0	4 (8)	0	1 (8)	3 (38)	0	8 (10)
Strabismus	3 (50)	21 (43)	0	3 (25)	5 (63)	0	32 (40)
Nystagmus	1	4 (8)	0	1 (8)	2 (25)	2 (50)	8 (10)
Astigmatism	3 (50)	5 (10)	0	2 (17)	0	1 (25)	11 (14)
Ptosis	4 (67)	4 (8)	0	1 (8)	2 (25)	0	11 (14)
Cortical visual impairment	0	3 (6)	0	1 (8)	1 (13)	0	5 (6)
Cataracts	0	1 (2)	0	0	1 (13)	0	2 (2)

PFO = patent foramen ovale; PDA = patent ductus arteriosus; ASD = atrial septal defects; VSD = ventricular septal defects; OSA = obstructive sleep apnea.
[a]Including but not limited to: diffuse cerebral volume loss, prominent sulci, underdevelopment of the frontal lobe, and immature cerebral cortex.
[b]Some individuals were not yet old enough to be evaluated for this feature.
[c]Including, but not limited to, mitral valve, aortic valve.
[d]Including, but not limited to, retinal detachment, lattice retinas, retinopathy of prematurity.

3.6 | SMARCE1

There were four total individuals with mutations in the *SMARCE1* gene. The clinical features among patients in this group varied and there did not seem to be any core abnormalities specific to a certain system represented among these patients. Fifth digit/nail abnormalities were reported in 3 of 4 individuals, sparse scalp hair also in 3 of 4, and hypertrichosis/hirsutism in half (2/4).

Many of the gastrointestinal abnormalities that were surveyed were present within this group of patients: feeding tube use in (2/4), feeding difficulty (2/4), and failure to thrive, gastroesophageal reflux disease, dysphagia, pyloric stenosis, and diaphragmatic hernia each reported in 1 of 4 individuals. Other notable features that were reported include abnormal dental shape (3/4), cleft/high arched palate (4/4), heart murmur (2/4), patent foramen ovale (PFO) or patent ductus arteriosus (PDA) (2/4), hearing loss (2/4), and nystagmus (2/4). Seizures were reported in 1 of 4 individuals.

A gene–phenotype analysis was conducted for the clinical features involved in this study (Table 2). On the whole, "classic" features including fifth digit anomalies, hypertrichosis/hirsutism, and sparse scalp hair were reported with lower frequency than prior studies. Other clinical features that have not been discussed in previously reported genotype–phenotype analyses include ventricular brain malformations, white matter changes, cerebral abnormalities, kyphosis, and lordosis. It still appears that individuals with *SMARC*-gene mutations, on the whole, tend to have more significant systemic manifestations, including cardiac, gastrointestinal, and CNS, whereas the *ARID*-genes tended to have more neurodevelopmental abnormalities. This may be explained by the *SMARC*-genes having a more significant contribution to the BAF complex overall. This conclusion may certainly be skewed, however, given greater number of *ARID1B* individuals. In addition, individuals may attain specific diagnoses as they age or as they have additional diagnostic studies performed as needed.

4 | DISCUSSION

Here, we report clinical characteristics and gene/phenotype correlations through the first cohort of parent-reported data for individuals diagnosed with CSS, predominately from the United States, and to recommend surveillance and management strategies for clinicians and parents. Patient and parent-reported registries are a valuable way to collect informative patient data with conditions that are now common enough that small case series are not being pursued. In addition, parent-reported registries are beneficial as it is generally easier to obtain follow-up data through parents on their children. Parents are able to provide specific information about their child's medical issues, patient-reported outcomes and disease progression, as well as quality of life; registries may also provide the opportunity to include diverse and under-represented populations.

With any parent-reported registry, verifiable information through medical records may be difficult to obtain on every individual and is a clear limitation of this study. In that vein, it is also difficult to ascertain whether individuals do not have a particular medical complication because it may have not yet evolved, or if they may not have had a particular evaluation or diagnostic study for an abnormality. This is particular true for some of the developmental assessments (including that for autism and intellectual disability) for which patients may not be old enough to undergo at the time of initial diagnosis.

Reports prior to the advent of available molecular testing for CSS have provided information about "classic" clinical features to propose a diagnostic strategy of CSS. Through this registry cohort, we have found that the classic clinical features were not necessarily present with the frequency previously reported. The feature for which the syndrome has been named may not always be evident in individuals with CSS, as only 48% of the total patients in our cohort reported a fifth digit phalanx or nail anomaly.

Previous genotype–phenotype correlation studies have demonstrated differences among the phenotypes of various patients with

TABLE 3 Gene–phenotype comparison of classic CSS clinic features in the literature

References		Classic CSS clinical feature		
		Fifth digit and/or nail (hand or foot)	Sparse scalp hair	Hypertrichosis and/or hirsutism
Present study	ARID1A	2/6 (33%)	5/6 (83%)	3/6 (50%)
	ARID1B	22/49 (45%)	17/49 (35%)	37/49 (76%)
	ARID2	1/2 (50%)	0/2 (0%)	0/2 (0%)
	SMARCA4	7/12 (58%)	4/12 (33%)	6/12 (50%)
	SMARCB1	3/8 (38%)	3/8 (38%)	3/8 (38%)
	SMARCE1	3/4 (75%)	3/4 (75%)	2/4 (50%)
Santen et al. (2013)	ARID1A	Nails: 4/4 (100%) Phalanx: 2/4 (50%)	0/4 (0%)	3/4 (75%)
	ARID1B	Nails: 19/28 (68%) Phalanx: 5/22 (23%)	18/28 (64%)	26/28 (93%)
	SMARCA4	Nails: 4/4 (100%) Phalanx: 2/3 (66%)	1/4 (25%)	4/4 (100%)
	SMARCB1	Nails: 3/4 (75%) Phalanx: 2/3 (66%)	3/4 (75%)	4/4 (100%)
	SMARCE1	Nails: 0/1 (0%) Phalanx: 0/1 (0%)	0/1 (0%)	1/1 (100%)
Kosho et al. (2014)	ARID1A	Nails: 6/7 (86%) Phalanx: 2/4 (50%)	3/5 (60%)	7/7 (100%)
	SMARCA4	Nails: 12/12 (100%) Phalanx: 12/12 (100%)	5/12 (42%)	12/12 (100%)
	SMARCB1	Nails: 11/11 (100%) Phalanx: 8/11 (73%)	10/11 (91%)	8/11 (73%)
	SMARCE1	Nails: 3/3 (100%) Phalanx: 3/3 (100%)	2/3 (67%)	2/2 (100%)
Tsurusaki et al. (2014)	ARID1B	Nails: 11/15 (73%) Phalanx (hand): 5/14 (37%) Phalanx (foot): 7/12 (58%)	7/15 (47%)	14/15 (93%)
	SMARCA4	Nails: 2/2 (100%) Phalanx (hand): — Phalanx (foot): —	1/2 (50%)	2/2 (100%)
	SMARCB1	Nails: 1/1 (100%) Phalanx (hand): 2/2 (100%) Phalanx (foot): 2/2 (100%)	1/1 (100%)	1/1 (100%)

CSS = Coffin–Siris syndrome.

different genetic variants. A summary of the "classic" findings of CSS in the literature are summarized in Table 3. Santen et al. (2013) demonstrated several manifestations of CSS in a cohort study of 63 patients with a clinical diagnosis of CSS. Many of these patients had molecular testing confirming a variant in *ARID1A*, *ARID1B*, *SMARCA4*, *SMARCB1*, or *SMARCE1*. This cohort demonstrated several manifestations of CSS including intellectual disability (98%), hypertrichosis (93%), hypotonia (83%), feeding problems (76%), underdeveloped nails (76%), short fifth finger (65%), and sparse scalp hair (61%). Tsurusaki et al. (2013) conducted a similar genotype–phenotype correlation study in 49 patients with suspected CSS, 29 of whom had mutations in *SMARCB1*, *SMARCA4* or *ARID1B*. The results of this study were similar to the study of Santen et al. In the present study, many of these classic clinical features were present at much lower prevalence than presented in the studies by Santen et al. (2013) and Tsurusaki et al. (2014). The present study combined underdeveloped fifth digit nails and short fifth finger/toe into one clinical category and still had a lower percentage than those presented in the previous studies.

The results of the gene–phenotype correlations represented in the present study may represent the heterogeneity of the population who are being found with mutations in genes in the BAF pathway. However, statistical significance is difficult to demonstrate with an overall small patient population. In addition, previously reported patients may have had mutation studies conducted based on the presence of these classic features, leading to selection bias. As larger-scale tests such as whole-exome sequencing (WES) are becoming more widely available, we anticipate that individuals who may not have fit a clinical diagnosis of CSS previously but rather presented with more nonspecific features are now being diagnosed with the condition.

Of note, two patients with changes in *ARID2* were reported in this study. The *ARID2* gene was first reported as a cause of intellectual disabilities by Shang et al., 2015 and was tied to the CSS phenotype by Bramswig et al., 2017. One of the two patients with *ARID2* mutations had hypoplasia of the fifth toenail, and both individuals had varying degrees of developmental delay and other neurologic and organ-system related issues. This supports the current hypothesis that the *ARID2* gene may cause a CSS-like phenotype but again cannot conclude a definitive correlation due to lack of statistical significance.

Prior to the elucidation of the molecular etiology of CSS, the diagnosis was based on the presence of the classic clinical features of CSS

TABLE 4 Recommended surveillance for individuals with CSS

At diagnosis
Vision and hearing screening
Echocardiogram/cardiology evaluation if <1 year of age
Bone age studies if evidence of delayed growth
Gastroenterology evaluation if feeding difficulties or failure to thrive
Immunology evaluation if history of significant infections
Dental exam after teeth eruption
Scoliosis evaluation
Developmental assessment/neuropsychiatric consultation
Ongoing
Vision exams (yearly)
Scoliosis evaluations (yearly)
Developmental assessments (at least yearly)
Dental exams (twice yearly)

CSS = Coffin–Siris syndrome.

including fifth digit and/or nail hypoplasia or aplasia, sparse scalp hair, hypertrichosis/hirsutism, and developmental abnormalities. The presence of the previously reported "classic" clinical features may no longer be useful in the diagnosis of CSS based on the results of this study. The present study supports the necessity of using molecular reports to confirm the diagnosis of CSS. As genetic technology continues to advance, large-scale testing such as WES will continue to be used as a possible first- or second-tier test for individuals with nonspecific dysmorphic facial features, organ-system anomalies, and developmental delay/intellectual disabilities. We suspect that more individuals with CSS will be identified through these means; although the presence of classic features of CSS should alert the clinician to potentially suspect the condition, we emphasize the broad variability of the phenotype to suggest that the absence of these features does not exclude CSS as a possibility.

While individuals with *ARID1B* mutations who have been diagnosed with *ARID1B*-related intellectual disability (*ARID1B*-ID) syndrome seem to lack the other physical features seen in patients with CSS, and thus are felt to be nonsyndromic, it may be that mutations in the BAF pathway cause a spectrum of disease, with *ARID1B*-related ID at one end, and what is now termed CSS, with classic features, at the other. The term "BAFopathy" may not catch on in the genetic community as well as, for example, "RASopathies," but may be a more appropriate term among clinicians to represent the phenotypic variability seen in individuals with mutations in this pathway. The term "SWI/SNF-related ID syndromes" has been proposed previously (Kosho et al., 2013).

Due to this broad range of phenotypes, the management of patients with CSS may vary based on their specific needs. Based on the findings from this study, we have recommended a number of baseline evaluations that may be of benefit for individuals with CSS (Table 4). Many of these evaluations may have already been performed in the initial workup of these patients as they present with symptoms.

Based on the frequency of vision abnormalities and hearing loss, initial vision and audiology testing may be of benefit. Although a baseline electroencephalogram (EEG) may not necessary, parents and clinicians should be aware of the possibility of seizures in this population and should be vigilant for signs and symptoms of such. Cardiac manifestations in patients with CSS suggest that a baseline echocardiogram would be useful, particularly in infancy. If children are diagnosed at an older age, the likelihood of a significant cardiac anomaly is less likely, and imaging may not be of as much use.

Clearly, failure to thrive and feeding difficulties will warrant a gastroenterology evaluation and may include swallow studies, upper GI imaging, or endoscopies. Early dental assessments may be of benefit to identify any crowding or issues related to delayed dentition. Individuals should continue to be monitored for any changes in spinal curvature, particularly as they age.

In this particular study, endocrinologic abnormalities were not specifically analyzed, but it remains unclear if individuals with CSS have growth hormone deficiency, thyroid abnormalities, or other hormonal aberrations. It may be of benefit to have individuals with CSS assessed by an endocrinologic specialist particularly if there is evidence of growth delay. Growth impairment that is responsive to growth hormone has been demonstrated previously in *Arid1b* haploinsufficient mice (Celen et al., 2017).

In addition, specific immunodeficiencies have not been assessed in this population, but it is the authors' experience that many families report frequent infections in these individuals. We would recommend a baseline immunologic evaluation for any children who have recurrent significant infections such as recurrent pneumonias, skin infections, or abscesses.

Evaluation for autism spectrum and ADHD would be of benefit, perhaps as soon as the diagnosis is made, as well as an assessment by early intervention services for various therapies.

We also would recommend a baseline neuropsychiatric or developmental evaluation for all individuals with CSS given the prevalence of developmental delay and cognitive issues, particularly as they enter the school setting.

As more individuals with mutations in the BAF pathway are diagnosed, we anticipate the management recommendations may change, but it remains clear that these patients continue to have multiple medical needs that need close monitoring and surveillance. Additional cohort studies will help to aid both clinicians and families navigate this complex condition.

ACKNOWLEDGMENTS

The authors would like to sincerely thank all the families and patients who participated in this registry and the clinicians caring for them. Dr. Schrier Vergano is on the medical advisory board for Ambry Genetics but has received no compensation in relationship to this work.

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How to cite this article: Mannino EA, Miyawaki H, Santen G, Schrier Vergano SA. First data from a parent-reported registry of 81 individuals with Coffin–Siris syndrome: Natural history and management recommendations. *Am J Med Genet Part A*. 2018;176A:2250–2258. https://doi.org/10.1002/ajmg.a.40471