

# Clinical Features, Diagnostic Criteria, and Management of Coffin–Siris Syndrome

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Coffin–Siris syndrome (OMIM#135900) is a multiple congenital anomaly syndrome classically characterized by hypo- or aplasia of the fifth digit nails or phalanges, as well as coarse facial features, sparse scalp hair, and moderate to severe cognitive and/or developmental delay. The recent identification of molecular etiologies has served to effectively characterize a large set of patients who have been described with Coffin–Siris between the time of its initial description and the present. However, despite recent advances, a number of patients who traditionally fit the diagnosis have yet to have identified causes. This could be due to patients who lie outside the defined phenotype, or alternatively, to additional as yet unidentified genes which may play roles. Here we outline the range of clinical features described in the broader diagnostic category, review the continuing phenotypic challenges and note those subsets of patients for whom molecular causes have yet to be clarified. Finally, we discuss recommendations for clinical management of these individuals. © 2014 Wiley Periodicals, Inc.

**KEY WORDS:** Coffin–Siris; BAF pathway; diagnostic criteria; fifth-digit; developmental delay

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## INTRODUCTION

Coffin–Siris syndrome (CSS) (OMIM #135900) is a multiple malformation syndrome initially described by Coffin and Siris in 1970. The original three probands showed coarse facial features, sparse scalp hair, and notably, hypoplasia of the fifth digit phalanges/nails [Coffin and Siris, 1970]. This latter feature would become a key cue for considering the disorder, resulting in an alternative name of “fifth-digit syndrome.” Recently, genes in the SWI–SNF/BAF pathway have been shown to be causative [Santen et al., 2012a; Tsurusaki et al., 2012; Santen et al., 2013; Wieczorek et al., 2013; Tsurusaki et al., 2014]. Genes in this pathway have also been implicated in the clinically overlapping Nicolaides–Baraitser

syndrome (NCBRS, OMIM#601358) [Van Houdt et al., 2012; Santen et al., 2013; Wieczorek et al., 2013] and non-syndromic intellectual disability [Hoyer et al., 2012]. Each of these specific diagnoses for which genes have been identified will be discussed in detail in the reviews in this series. However, here we will discuss the evolution of the clinical features of the disorder, the broad clinical characteristics subsequently described, and how the discovery of the molecular basis has added to our refining and defining subsets of this phenotype.

## REPORTS OF COFFIN–SIRIS CASES PRIOR TO A MOLECULAR ETIOLOGY

Since its first description in the literature and the gene identification, approxi-

mately 80 individuals were reported with CSS. While molecular criteria are helpful when positive, there are still no widely accepted clinical criteria and key diagnostic features have been outlined that most closely correlated with a convincing diagnosis.

Several reviews in the literature described cohorts diagnosed with CSS in efforts to define and classify the phenotype. Carey and Hall [1978] reported five new cases of CSS and reviewed the previous four. All probands had developmental delay, hypoplasia to the fifth digit nails or phalanges, feeding difficulties in infancy, and hypertrichosis. Three years later, Lucaya et al. [1981] examined four new patients to bring the literature total to 16; again, the most common findings were developmental

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delay, hypoplastic digits/nails, and body hypertrichosis. The majority also displayed sparse scalp hair and coarse facial

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features, including bushy eyebrows, full lips, and a wide mouth.

In 2001, Fleck et al. [2001] reviewed 18 additional cases and summarized the literature to that point with a goal of defining features necessary for the diagnosis of CSS. Their efforts utilized a survey distributed among an international support group and they concluded that developmental delay or mental retardation of some degree, feeding difficulties, “coarse” facial features, frequent infections, and hypoplastic to a plastic fifth digit nails or phalanges were the most often reported features.

#### **ASSESSMENT OF CLASSIC AND ATYPICAL FEATURES OF COFFIN–SIRIS LITERATURE CASES**

In 2012, Schrier et al. [2012] examined all 80 probands previously published in the literature for common and discriminating features. Perhaps as a result of a selection bias for the diagnosis, all displayed both hypo/aplasia of the fifth digit phalanges/nails as well as some degree of intellectual and/or developmental delay. Because of this, these two features were considered prerequisite,

although not sufficient for the clinical diagnosis of CSS. Additionally, probands displayed a variety of features that were broadly categorized into ectodermal, constitutional, and organ-based anomaly categories. Ectodermal changes included hypertrichosis/hirsutism (93%), paradoxically sparse scalp hair (68%), and dental anomalies (96%). Short stature (66%), intrauterine growth retardation (IUGR)/failure to thrive (FTT) (67%) comprised abnormalities of overall growth. The most common organ-related problems included congenital heart defects (46%), spinal anomalies (66%), and craniofacial anomalies. Although limited by literature-based data, overall, there did not appear to be a strong correlation between cognitive ability and the severity of either digit or systemic anomalies.

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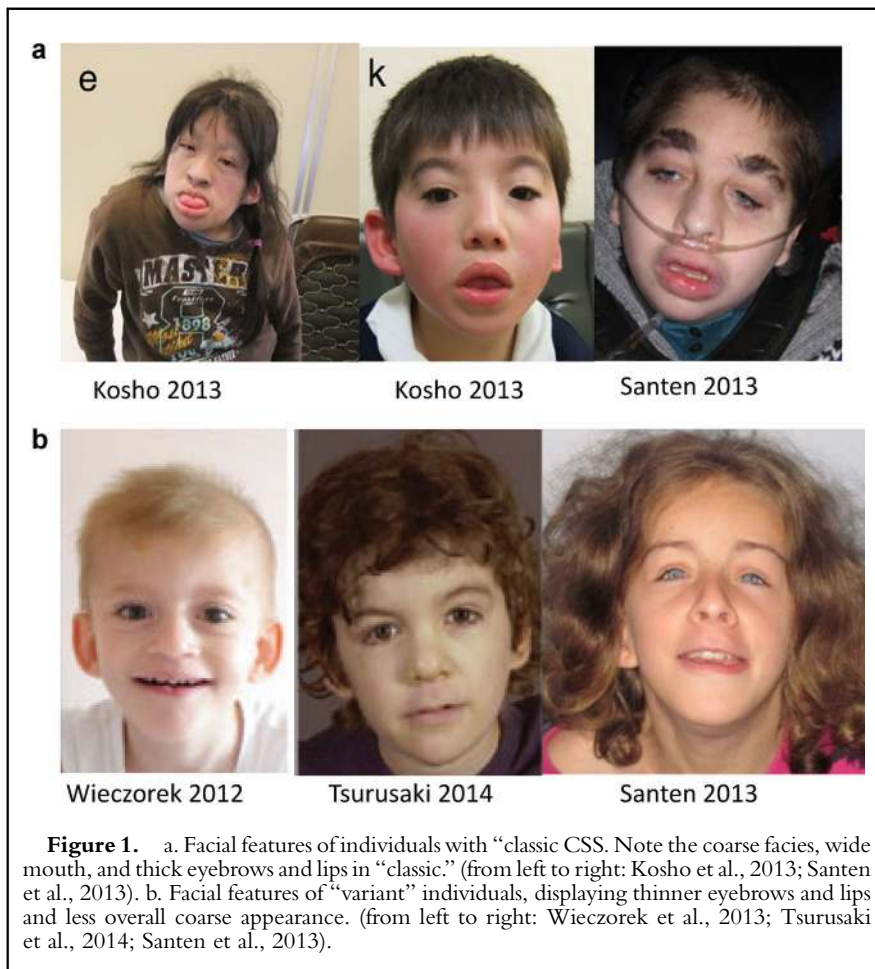
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lips, and was defined to be consistent with “classic” CSS. A second group demonstrated patients with less coarse, more refined features, including thinner eyebrows and thin vermilion border of the lips and were collectively termed “variant” CSS (Fig. 1). While a subset of reported probands had predominately classic features, a significant number displayed both classic and variant characteristics, strongly suggesting a phenotypic spectrum. It was hypothesized that the differences in facial features represent underlying genetic heterogeneity of the disorder, and possibly even distinctly different molecular mechanisms that would converge on elements of a similar phenotype.

There are a large number of case reports in the literature that describe rare clinical features in one or two subject with CSS that have not been seen in the larger cohort studies. Some of these are quite interesting. Two articles have reported individuals with a clinical diagnosis of CSS who also had premature thelarche [Brunetti-Pierrri et al., 2003; Flynn and Milunsky, 2006]. Although short stature and delayed bone age have been reported frequently in the literature, no hormonal abnormalities have been demonstrated consistently and only one proband has been reported with growth hormone deficiency [Baban et al., 2008].

Historically, there are rare instances of varied tumors in individuals with clinical diagnoses of CSS; both medulloblastoma [Rogers et al., 1988] and neuroblastoma [Pollono et al., 2009] have each been seen, as has schwannomatosis [Schrier et al., 2012]. Given the identification of the SWI-SNF/BAF pathway in these disorders and in cancer, this topic is quite relevant [Santen et al., 2012b] but further discussion of tumor growth and the SWI-SNF pathway is discussed elsewhere in this edition.

The range of features noted in the literature prior to the identification of a molecular basis is reflected in those described for mutation-positive individuals [Tsurusaki et al., 2012; Kosho et al., 2013; Santen et al., 2013; Wiczorek et al., 2013; Tsurusaki et al., 2014].



**Figure 1.** a. Facial features of individuals with “classic CSS. Note the coarse facies, wide mouth, and thick eyebrows and lips in “classic.” (from left to right: Kosho et al., 2013; Santen et al., 2013). b. Facial features of “variant” individuals, displaying thinner eyebrows and lips and less overall coarse appearance. (from left to right: Wieczorek et al., 2013; Tsurusaki et al., 2014; Santen et al., 2013).

While refined genotype–phenotype observations are outlined in other articles in this edition, there are clearly more “classic” individuals with mutations in the *SMARC* genes (*SMARCB1*, *SMARCA2*, *SMARCE1*). Individuals with *SMARCA2* mutations suggesting the clinical diagnosis of NCBRS [Van Houdt et al., 2012] can demonstrate coarse facial features, sparse scalp hair, and cognitive/developmental delay overlapping with CSS; however, individuals with NCBRS typically display prominent phalangeal joints to the hands and feet, rather than the underdevelopment seen in CSS [Sousa et al., 2009].

There is a wider degree of variation in facial features in those individuals with mutations in *ARID1A* and *ARID1B*. Although individuals with mutations in these genes range from “classic” coarse facies to the milder thin-browed, thin-lipped facies, probands with *ARID1B*

mutations appear to be most severely affected overall from a health standpoint [Kosho et al., 2013; Santen et al., 2013].

#### CLINICAL RECOMMENDATIONS FOR CARE OF INDIVIDUALS WITH COFFIN–SIRIS SYNDROME

Based on the phenotypes seen in individuals the classical literature with CSS, as well as those with mutations in currently identified genes, we propose management guidelines to prevent and treat potential complications (Table I). Probands should have yearly evaluations by a primary care physician or geneticist to coordinate complex care. Surveillance by subspecialists should be catered to an individual’s specific needs [Schrier Vergano et al., 1993].

Neurologic evaluations should be considered for individuals with seizures

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***Neurologic evaluations should be considered for individuals with seizures or other neurologic deficits; however, given the high frequency of seizures or tics in several reports a baseline EEG may be warranted.***

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Neurologic and neurodevelopmental assessments may also be necessary to evaluate for ADD/ADHD, behavioral problems, or autistic spectrum features. Careful neurodevelopmental evaluations will assist in defining physical therapy and educational plans that are typically needed for subjects.

Small stature or short stature are often due to intrinsic growth issues from the underlying etiology, however, feeding difficulties and overt failure to thrive can result as well. These nutritional issues are often assessed by Gastroenterology, Endocrinology, or Nutrition to determine and dietary or hormonal interventions. Growth should be monitored closely. There is no evidence at the current time to suggest that growth hormone supplementation is beneficial. Probands should have yearly evaluations with gastroenterology or feeding specialists to monitor feeding and weight gain. Nutritional supplementation or G-tube placement may be necessary to facilitate weight gain.

Cardiology evaluations, including an echocardiogram should be considered to assess for structural cardiac anomalies. Given the prevalence of both renal and brain malformations, a renal ultrasound should be performed and a brain MRI or CT is strongly considered. Ophthalmologic examinations are recommended annually to include a dilated fundus examination with visual acuity testing and correction as needed. Audiologic evaluations should involve auditory

**TABLE I. Clinical Management Recommendations for Coffin-Siris Syndrome**

Assessment	At diagnosis	Follow-up frequency	Specific concerns or activities
Genetic	X	Yearly	Oversee testing, counseling regarding etiology, and recurrence
Cardiac	X	As needed	Congenital malformations, EKG, Echocardiogram
Gastrointestinal	X	Yearly	Anal atresia, gastric, and duodenal abnormalities
Dietary/Nutrition	X	As needed	Feeding difficulty
Renal U/S	X	As needed	Renal anomalies, cryptorchidism
Ophthalmologic	X	Every 2–3 years	Lacrimal duct stenosis, myopia, strabismus
Skeletal	X	Yearly	Spinal anomalies, scoliosis
Immune		As needed	Consider immune screening if frequent infections
Audiology	X	Every 2–3 years	Hearing loss
Neurology	X	As needed	Seizures, malformations
Developmental	X	Yearly	Speech, physical and occupational therapy

brainstem response testing with otoacoustic emission.

As we learn more about the spectrum of disorders implicated in the BAF pathway, new phenotypic features and a refining of our understanding of currently known clinical features will continue to emerge. Certainly the ease of diagnosis is currently assisted with molecular testing and genotype-phenotype correlations will continue to be clarified. Nonetheless, the clinician should remain aware of the breadth of variability in these disorders to enable effective and accurate diagnosis. Despite its phenotypic heterogeneity, key features of CSS have become clearer and have further enabled individuals with a clinical or molecular diagnosis to receive effective clinical care. As our understanding of the molecular mechanisms behind CSS and other SWI/SNF disorders expands, the ultimate goal of therapeutic interventions becomes more tangible. Gene therapy and even medications to alter chromatin remodeling and ameliorate both physical and potentially cognitive features is anticipated. Ongoing efforts will need to be aimed at improving understanding of the natural history and organizing international collaborations. This will enable early establishment of the diagnoses, careful characterization of these patients and enable a global approach to improving the care and therapies for these individuals to optimize their health and intellectual potentials.

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