ARID1B Syndrome

https://www.ncbi.nlm.nih.gov/books/NBK131811/

SummaryClinical characteristics.Coffin-Siris syndrome (CSS) is classically characterized by aplasia or hypoplasia of the distal phalanx or nail of the fifth and additional digits, developmental or cognitive delay of varying degree, distinctive facial features, hypotonia, hirsutism/hypertrichosis, and sparse scalp hair. Congenital anomalies can include malformations of the cardiac, gastrointestinal, genitourinary, and/or central nervous systems. Other findings commonly include feeding difficulties, slow growth, ophthalmologic abnormalities, and hearing impairment.Diagnosis/testing.Before the molecular basis was known, the diagnosis of CSS was based solely on clinical findings (although consensus clinical diagnostic criteria have not yet been published). The diagnosis of CSS is established in a proband with suggestive findings by identification of a heterozygous pathogenic variant in one of the genes listed in Table 1.Management.Treatment of manifestations: Occupational, physical, and/or speech therapies to optimize developmental outcomes. Feeding therapy, nutritional supplementation and/or gastrostomy tube placement as needed to meet nutritional needs. Routine management of ophthalmologic abnormalities and hearing loss.Surveillance: Yearly evaluation by a developmental pediatrician to assess developmental progress and therapeutic and educational interventions; follow up with a gastroenterologist and feeding specialists as needed to monitor feeding and weight gain. Routine follow up of ophthalmologic and/or audiologic abnormalities.Genetic counseling.CSS is inherited in an autosomal dominant manner; however, most affected individuals have the disorder as the result of de novo CSS-causing pathogenic variant. If the CSS-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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Management.Treatment of manifestations: Occupational, physical, and/or speech therapies to optimize developmental outcomes. Feeding therapy, nutritional supplementation and/or gastrostomy tube placement as needed to meet nutritional needs. Routine management of ophthalmologic abnormalities and hearing loss.Surveillance: Yearly evaluation by a developmental pediatrician to assess developmental progress and therapeutic and educational interventions; follow up with a gastroenterologist and feeding specialists as needed to monitor feeding and weight gain. Routine follow up of ophthalmologic and/or audiologic abnormalities.

Genetic counseling.CSS is inherited in an autosomal dominant manner; however, most affected individuals have the disorder as the result of de novo CSS-causing pathogenic variant. If the CSS-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

DiagnosisFormal clinical diagnostic criteria for Coffin-Siris syndrome (CSS) have not been established; however, several key features are useful in making a clinical diagnosis.Suggestive FindingsCoffin-Siris syndrome (CSS) should be suspected in individuals with the following findings [Fleck et al 2001, Schrier et al 2012, Kosho et al 2014b, Santen et al 2014]:Fifth-digit nail / distal

phalanx hypoplasia/aplasia. Typically, individuals with a clinical diagnosis of CSS have either aplasia or hypoplasia of the distal phalanx or absence of the nail, typically involving the fifth finger, but other digits may also be affected (Figure 1C, D, E, F). Toes can also be affected, where the finding tends to involve multiple digits.Developmental or cognitive delay of variable degreeFacial features [Schrier et al 2012]. Individuals with typical features demonstrate a wide mouth with thick, everted upper and lower lips, broad nasal bridge with broad nasal tip, thick eyebrows, and long eyelashes. Together, these features can give a suggestion of coarseness in individuals with CSS (Figure 1A, B).Hypotonia that is central in originHirsutism/hypertrichosis. Hair growth in atypical areas (e.g., the back) or excessive hair growth on the arms or faceSparse scalp hair, especially in infancy, particularly in the temporal regionsFigure 1. Coffin-Siris syndrome classic features Facial features (i.e., bushy eyebrows, coarse facies, and thick, everted lips) in (A) a clinically diagnosed boy age five years and (B) a clinically diagnosed man age 29 yearsEstablishing the DiagnosisThe diagnosis of CSS is established in a proband with suggestive findings and a heterozygous pathogenic variant in one of the genes listed in Table 1 identified by molecular genetic testing.Note: Identification of a heterozygous variant of uncertain significance in one of the genes listed in Table 1 does not establish or rule out the diagnosis of this disorder.Molecular testing approaches typically include use of a multigene panel or more comprehensive

genomic testing.Note: Serial single-gene testing in the order in which pathogenic variants most commonly occur is another option, but given the number of genes associated with this phenotype, such testing is not commonly done. However, because mutation of ARID1B is found in a relatively large number of affected individuals compared to mutation in the other genes listed in Table 1, sequence analysis of ARID1B, followed by gene targeted deletion/duplication analysis, can be considered as a first step. If this is not diagnostic, use of a multigene panel or more comprehensive genomic testing is often performed next.A multigene panel that includes the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not

associated with the condition discussed in this GeneReview; thus, clinicians need to determine which multigene panel provides the best opportunity to identify the genetic cause of the condition. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. Exome sequencing is most commonly used; genome sequencing is also possible.For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.Table 1. Molecular Genetic Testing Used in Coffin-Siris SyndromeView in own windowGene 1Proportion of CSS Attributed to Pathogenic Variants in Gene 2Proportion of Pathogenic Variants 3 Detected by MethodSequence analysis 4Gene-targeted deletion/duplication analysis 5

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genes surrounding the ARID1B locus.9. Only seven individuals with pathogenic variants in this gene have been reported [Gazdagh et al 2019].10. Fewer than ten affected individuals have been identified with mutation in this gene [Milone et al 2020].11. Individuals initially ascertained with CSS when younger have been found to have pathogenic variants in PHF6. Most of these have acquired facial features more consistent with Borjeson-Forssman-Lehmann syndrome as they age [Wieczorek et al 2013]. See Differential Diagnosis.12. Only two affected individuals with a CCS phenotype have been reported to have mutation in this gene [Wieczorek et al 2013].13. Reevaluation of an individual initially thought to have CSS concluded that findings were more consistent with Nicolaides-Baraitser syndrome [Tsurusaki et al 2012, Van Houdt et al 2012]; however, since a number of individuals with SMARCA2 pathogenic variants were initially ascertained with CSS, the authors have included them. See Differential Diagnosis.14. Evidence indicates that pathogenic variants in SMARCA4, SMARCB1, and SMARCE1 act through a gain-of-function mechanism, suggesting that large pathogenic deletions or duplications are unlikely to occur; however, in-frame deletions or duplications of relevant domains may be pathogenic; one such deletion in SMARCA4 has been reported (see Molecular Genetics).15. Approximately 15 individuals have been found to have mutation of this gene and features that could be consistent with CSS; however, only four had classic features [Machol et al 2019].16. Only four individuals with a CCS phenotype have been reported to have mutation in this gene [Zawerton et al 2019].17. Tsurusaki et al [2014a]

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20. Approximately 40% of individuals with CSS did not have a pathogenic variant in one of the known genes [Tsurusaki et al 2012, Santen et al 2013, Wieczorek et al 2013, Tsurusaki et al 2014b].Karyotype and chromosomal microarray (CMA). Many individuals who present with congenital anomalies and developmental delay have their chromosomes evaluated through karyotype and/or CMA as part of the initial evaluation. If an individual presenting with features of CSS does not have a pathogenic variant identified by the testing described, a karyotype and/or CMA

should be considered based on the occurrence of rare rearrangements that have been reported to cause CSS [Backx et al 2011, Halgren et al 2012, Malli et al 2014].

Suggestive FindingsCoffin-Siris syndrome (CSS) should be suspected in individuals with the following findings [Fleck et al 2001, Schrier et al 2012, Kosho et al 2014b, Santen et al 2014]:Fifth-digit nail / distal phalanx hypoplasia/aplasia. Typically, individuals with a clinical diagnosis of CSS have either aplasia or hypoplasia of the distal phalanx or absence of the nail, typically involving the fifth finger, but other digits may also be affected (Figure 1C, D, E, F). Toes can also be affected, where the finding tends to involve multiple digits.Developmental or cognitive delay of variable degreeFacial features [Schrier et al 2012]. Individuals with typical features demonstrate a wide mouth with thick, everted upper and lower lips, broad nasal bridge with broad nasal tip, thick eyebrows, and long eyelashes. Together, these features can give a suggestion of coarseness in individuals with CSS (Figure 1A, B).Hypotonia that is central in originHirsutism/hypertrichosis. Hair growth in atypical areas (e.g., the back) or excessive hair growth on the arms or faceSparse scalp hair, especially in infancy, particularly in the temporal regionsFigure 1. Coffin-Siris syndrome classic features Facial features (i.e., bushy eyebrows, coarse facies, and thick, everted lips) in (A) a clinically diagnosed boy age five years and (B) a clinically diagnosed man age 29 years

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(c) individuals with mildly or variably syndromic intellectual disability [Nagamani et al 2009, Halgren et al 2012, Hoyer et al 2012, Michelson et al 2012] for whom available clinical information is insufficient to determine the similarity to CSS. Of note, these individuals may have complex clinical findings due to the involvement of additional genes surrounding the ARID1B locus.9. Only seven individuals with pathogenic variants in this gene have been reported [Gazdagh et al 2019].10. Fewer than ten affected individuals have been identified with mutation in this gene [Milone et al 2020].11. Individuals initially ascertained with CSS when younger have been found to have pathogenic variants in PHF6. Most of these have acquired facial features more consistent with Borjeson-Forssman-Lehmann syndrome as they age [Wieczorek et al 2013]. See Differential Diagnosis.12. Only two affected individuals with a CCS phenotype have been reported to have mutation in this gene [Wieczorek et al 2013].13. Reevaluation of an individual initially thought to have CSS concluded that findings were more consistent with Nicolaides-Baraitser syndrome [Tsurusaki et al 2012, Van Houdt et al 2012]; however, since a number of individuals with SMARCA2 pathogenic variants were initially ascertained with CSS, the authors have included them. See Differential Diagnosis.14. Evidence indicates that pathogenic variants in SMARCA4, SMARCB1, and SMARCE1 act through a gain-of-function mechanism, suggesting that large pathogenic deletions or duplications are unlikely to occur; however, in-frame deletions or duplications of relevant domains may be pathogenic; one such deletion in SMARCA4 has been reported (see Molecular Genetics).15. Approximately 15 individuals have been found to have mutation of this gene and features that could be consistent with CSS; however, only four had classic features [Machol et al 2019].16. Only four individuals with a CCS phenotype have been reported to have mutation in this gene [Zawerton et al 2019].17.

Tsurusaki et al [2014a]

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Only seven individuals with pathogenic variants in this gene have been reported [Gazdagh et al 2019].

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Clinical CharacteristicsClinical DescriptionThe following information has been compiled from data included in two reports by the Coffin-Siris Syndrome International Collaborators [Kosho et al 2014b, Santen et al 2014]. This section focuses on features common to the molecular subtypes; the findings that vary in frequency or severity between genetic etiologies are noted in Genotype-Phenotype Correlations.Early CharacteristicsPrenatal findings are typically unremarkable, with growth within normal limits. Rarely, CNS or cardiac anomalies, IUGR, and microcephaly have been noted.Infancy. Although many individuals with Coffin-Siris syndrome (CSS) may not be clinically distinguishable at birth, several of the congenital anomalies may be noted:Hypoplasia of the fifth digits/nails. Most individuals have at a minimum brachydactyly of the fifth digit (seen in 65%

of affected infants) and hypoplasia of one or more nails (80%). It should be noted that some individuals with a molecularly confirmed diagnosis of CSS have little or no fifth digit involvement.Dysmorphic facial features (~30% at birth). Because facial features typically coarsen over time, the characteristic facies may not be apparent until later in childhood.Hirsutism often notedMalformations affecting the CNS and cardiac and genitourinary systems (See Findings in Childhood.)Other findings appearing in infancy that may be the first indication of CSS:Feeding problems (90%) and slow growthHypotonia (75%)Seizures (50%)Hearing impairment (45%)Visual impairment (~40%)Findings in ChildhoodDevelopmental delays. The developmental/cognitive delay is typically apparent when delayed developmental milestones are noted and/or formal cognitive testing is performed.On average, children with CSS learn to sit at 12 months, walk at 30 months, and speak their first words at 24 months.Expressive language is more severely affected than receptive language, with no speech in a significant subset of individuals.Intellectual disability is present in most and typically moderate to severe (IQ range: 40 to 69); however, IQ as high as 97 has been reported [Santen et al 2012].Behavioral abnormalities include hyperactivity (~10%), aggressiveness (~10%), and occasionally autistic features.

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CNS malformations include Dandy-Walker variant, gyral simplification, and agenesis of the corpus callosum.Seizures and tics. A variety of types of seizures are reported. There is no typical age of onset for seizures or tics.Hypotonia (75%), noted in infancy, is typically persistent.Facial features (See Figure 1.)Coarse facies (95%)Thick eyebrows (90%)Prominent eyelashes (85%)Flat nasal bridge (50%)Short nose (50%)Anteverted nares (50%)Broad nasal tip (75%)Wide nasal base (50%)Thick alae nasi (70%)Broad philtrum (70%)Wide mouth (80%)Thin vermilion of the upper lip (50%)Thick vermilion of the lower lip (80%)

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Cardiac anomalies (35%) including ventricular septal defects, atrial septal defects, tetralogy of Fallot, and patent ductus arteriosusRenal and genitourinary malformations (~35%) including cryptorchidism most commonly, but also horseshoe kidney, hypospadias, and other abnormalitiesTumor risk. Although pathogenic variants in a subset of the genes causing CSS have been implicated in tumorigenesis (see Cancer and Benign Tumors), data on tumor risk in CSS are lacking. Tumors have been reported in three individuals with CSS:Hepatoblastoma was reported in one of eight individuals with an ARID1A pathogenic variant [Tsurusaki et al 2012, Kosho et al 2014b].An individual with a 4.2-Mb deletion that included (among 14 genes) ARID1B developed papillary thyroid cancer [Vengoechea et al 2014].Multiple studies have reported an individual who has CSS, schwannomatosis, and a pathogenic variant in SMARCB1 [Carter et al 2012, Schrier et al 2012, Gossai et al 2015].PrognosisIn the absence of long-term studies, information on life span in individuals with Coffin-Siris syndrome is not available. Children have been reported to die of aspiration pneumonia and/or seizures, although this is not common [Schrier et al 2012]. Efforts are in progress by the Coffin-Siris Syndrome International Consortium [Kosho et al 2014a] to better understand prognosis in individuals with CSS.Phenotype Correlations by GenePhenotype

correlations by gene have been seen in clinically diagnosed individuals with pathogenic variants in ARID1A, ARID1B, ARID2, DPF2, SMARCA4, SMARCB1, SMARCC2, SMARCE1, SOX4, and SOX11 [Wieczorek et al 2013, Kosho et al 2014b, Santen et al 2014, Tsurusaki et al 2014a, Hempel et al 2016, Vasileiou et al 2018, Gazdagh et al 2019, Machol et al 2019, Zawerton et al 2019].ARID1B. Individuals with pathogenic ARID1B variants are typically at the milder end of the spectrum of CSS and often have normal growth. Moderately severe feeding problems are noted in two thirds, seizures in one third, and hypoplasia of the corpus callosum in one third. Facial gestalt is consistent with CSS, albeit at times milder.ARID2. Affected individuals typically do not have birth defects.SMARCA4. Individuals with a pathogenic variant in SMARCA4 appear to have growth impairment that is mild prenatally and mild to moderate postnatally; sucking/feeding difficulty is almost always observed. While individuals can sometimes have severe developmental delays, significant behavioral challenges tend to be more characteristic. Facial features have demonstrated less coarseness, while hypoplastic fifth fingers or toes and hypoplastic fifth fingernails or toenails are a near-constant finding (and hypoplasia of other fingernails or toenails an occasional finding). Prominence of interphalangeal joints and distal phalanges is also noted in some.SMARCB1. Individuals with a pathogenic variant in SMARCB1 typically have a more severely affected phenotype and all have growth impairment, usually mild prenatally and moderate to severe postnatally, with sucking/feeding difficulty. Structural CNS abnormalities with hypotonia and seizures are typical findings accompanied by severe developmental delay/intellectual disability; individuals are typically nonverbal. Typical skeletal findings include hypoplastic fifth fingers or toes, hypoplastic other fingernails or toenails, prominent distal phalanges, and scoliosis. Some individuals may walk independently. Gastrointestinal complications and hernia as well as cardiovascular and genitourinary complications are common.SMARCE1. Individuals with pathogenic SMARCE1 variants tend to have severe intellectual disability, typical facial gestalt, and hypoplastic or absent fifth finger- and toenails associated with hypoplasia of other nails. The hands are characterized by long and slender fingers. Individuals are typically small for gestational age and have postnatal short stature and severe microcephaly, complex congenital heart defects, feeding difficulties, and

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PrevalenceFewer than 200 individuals with molecularly confirmed Coffin-Siris syndrome have been reported, indicating that the diagnosis is rare. However, this is likely an underestimate, as not all individuals may have come to medical attention.In addition, the identification of a pathogenic variant

in ARID1B in some members of a large cohort with intellectual disability [Hoyer et al 2012] suggests that the prevalence of pathogenic variants in genes associated with CSS (and possibly of subtle phenotypic features of CSS) may be higher than currently appreciated among those with intellectual disability.

Genetically Related (Allelic) DisordersNo phenotypes other than those discussed in this GeneReview have been associated with pathogenic variants in ARID1A, ARID2, DPF2, SMARCC2, SMARCE1, SOX4, or SOX11.Phenotypes in addition to classic Coffin-Siris syndrome have been associated with pathogenic variants of ARID1B, SMARCA4, and SMARCB1.ARID1B. Both pathogenic variants in and microdeletions containing ARID1B have been reported in several individuals with isolated intellectual disability (ID) [Nagamani et al 2009, Hoyer et al 2012, Michelson et al 2012]. Deletions have also been reported in several individuals with features in addition to ID, including agenesis of the corpus callosum (ACC), seizures, hypertrichosis, hearing loss, and myopia [Santen et al 2014]. See ARID1B-Related Disorder.SMARCA4. Heterozygous germline pathogenic variants in SMARCA4 have been reported to cause the rhabdoid tumor predisposition [Schneppenheim et al 2010, Hasselblatt et al 2011, Biegel et al 2014].SMARCB1. One individual with Kleefstra syndrome has been found to have a heterozygous de novo p.Arg37His variant [Kleefstra et al 2012]. This variant is at the N-terminus of the protein, while those in CSS have been localized at the C-terminal end of the SNF5 domain (see Molecular Pathogenesis).Heterozygous germline pathogenic variants in SMARCB1 have been reported to cause the rhabdoid tumor predisposition syndrome via the classic two-hit model of tumorigenesis [Roberts & Biegel 2009, Biegel et al 2014].Heterozygous germline pathogenic variants in SMARCB1 cause schwannomatosis, an autosomal dominant tumor suppressor syndrome with reduced penetrance, characterized by a predisposition to develop multiple schwannomas and (less frequently) meningiomas [Merker et al 2012].Of note, several individuals initially ascertained as having CSS were subsequently found to have pathogenic variants in SMARCA2 [Santen et al 2012, Tsurusaki et al 2012] or PHF6 [Wieczorek et al 2013]. Further review of these individuals has suggested that they

more consistently fit the diagnoses of Nicolaides-Baraitser and Borjeson-Forssman-Lehmann syndromes, respectively [Kosho et al 2014b, Tsurusaki et al 2014b, Zweier et al 2014]. See Table 1, footnotes 8 and 13, and Differential Diagnosis.

ARID1B. Both pathogenic variants in and microdeletions containing ARID1B have been reported in several individuals with isolated intellectual disability (ID) [Nagamani et al 2009, Hoyer et al 2012, Michelson et al 2012]. Deletions have also been reported in several individuals with features in addition to ID, including agenesis of the corpus callosum (ACC), seizures, hypertrichosis, hearing loss, and myopia [Santen et al 2014]. See ARID1B-Related Disorder.

SMARCA4. Heterozygous germline pathogenic variants in SMARCA4 have been reported to cause the rhabdoid tumor predisposition [Schneppenheim et al 2010, Hasselblatt et al 2011, Biegel et al 2014].

SMARCB1. One individual with Kleefstra syndrome has been found to have a heterozygous de novo p.Arg37His variant [Kleefstra et al 2012]. This variant is at the N-terminus of the protein, while those in CSS have been localized at the C-terminal end of the SNF5 domain (see Molecular Pathogenesis).

Heterozygous germline pathogenic variants in SMARCB1 have been reported to cause the rhabdoid tumor predisposition syndrome via the classic two-hit model of tumorigenesis [Roberts & Biegel 2009, Biegel et al 2014].

Heterozygous germline pathogenic variants in SMARCB1 cause schwannomatosis, an autosomal dominant tumor suppressor syndrome with reduced penetrance, characterized by a predisposition to develop multiple schwannomas and (less frequently) meningiomas [Merker et al 2012].

Differential DiagnosisNicolaides-Baraitser syndrome

(NCBRS) is characterized by sparse scalp hair, prominence of the interphalangeal joints and distal phalanges due to decreased subcutaneous fat, characteristic coarse facial features, microcephaly, seizures, and developmental delay/intellectual disability. Developmental delay / intellectual disability is severe in nearly half of individuals with NCBRS, moderate in a third, and mild in the remainder. Nearly a third never develop speech. Of note, after heterozygous SMARCA2 pathogenic variants were identified in NCBRS [Van Houdt et al 2012], reevaluation of an individual initially thought to have CSS determined that findings were more consistent with NCBRS [Tsurusaki et al 2012]. Inheritance is autosomal dominant; to date, all affected individuals have had a de novo SMARCA2 pathogenic variant.Borjeson-Forssman-Lehmann syndrome (BFLS) (OMIM 301900) is typically characterized by males with severe intellectual disability, epilepsy, hypogonadism, hypometabolism, marked obesity, swelling of subcutaneous tissue of face, narrow palpebral fissure, and large but not deformed ears. Females with pathogenic variants in PHF6, which causes BFLS, demonstrate some phenotypic overlap with individuals with CSS [Wieczorek et al 2013]. The two syndromes, however, are still considered distinctly separate entities [Zweier et al 2013].Mosaic trisomy 9. An individual with mosaic trisomy 9 had features similar to those of CSS, including facial features (wide, bulbous nose), hirsutism, and hypoplasia of the fifth digits [Kushnick & Adessa 1976].Brachymorphism-onychodysplasia-dysphalangism (BOD) syndrome (OMIM 113477) is characterized by short stature, tiny dysplastic nails, short fifth fingers, a wide mouth with broad nose, and mild intellectual deficits [Verloes et al 1993, Elliott & Teebi 2000]. This latter characteristic is most likely to distinguish individuals with BOD syndrome from those with CSS, as the cognitive disability in CSS is nearly always moderate to severe. Inheritance appears to be autosomal dominant.DOORS (deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures) syndrome. Features in common with CSS include hypoplastic terminal phalanges and/or nail anomalies, deafness, and neurologic abnormalities. DOORS syndrome is inherited in an autosomal recessive manner and is caused by biallelic pathogenic variants in TBC1D24 (see TBC1D24-Related Disorders).Fetal alcohol spectrum (FAS). Small nails, prenatal and postnatal

growth retardation, dysmorphic facial features, and cognitive disabilities may be seen in FAS.Fetal hydantoin/phenytoin embryopathy. Small nails with hypoplasia of distal phalanges, dysmorphic facial features, digitalized thumbs, low hairline, short or webbed neck, growth retardation, and cognitive disabilities have been described in this syndrome, caused by prenatal exposure to phenytoin.Mabry syndrome (hyperphosphatasia with mental retardation syndrome 1; OMIM 239300). Mabry syndrome is characterized by delayed development, seizures, coarse facial features, hypoplastic fifth digits, and elevated serum concentrations of alkaline phosphatase [Gomes & Hunter 1970, Kruse et al 1988, Thompson et al 2010]. It is inherited in an autosomal recessive manner and caused by biallelic pathogenic variants in PIGV [Krawitz et al 2010].Cornelia de Lange syndrome (CdLS). Classic CdLS is characterized by distinctive craniofacial features (arched eyebrows, synophrys, upturned nose, small teeth, microcephaly); growth retardation; and limb anomalies, which can at times include fifth finger hypoplasia similar to CSS. Other findings may include cardiac defects, gastrointestinal anomalies, and genitourinary malformations. Pathogenic variants in NIPBL, SMC1A, SMC3, HDAC8, or RAD21 are causative. CdLS is inherited in an autosomal dominant (NIPBL, SMC3, and RAD21) or X-linked (SMC1A and HDAC8) manner.4q deletion syndrome. This chromosome deletion syndrome results in a characteristic curved, volar, fifth-digit nail, which may resemble a hypoplastic distal phalanx.BICRA-related disorder (OMIM 619325) is classically characterized by coarse facial features including microcephaly, frontal bossing, epicanthal folds, prominent nasal tips, and low-set ears. These features are also commonly expressed in individuals with CSS. Barish et al [2020] identified 14 individuals with pathogenic variants in BICRA, all of whom have coarse facial features and varying magnitudes of intellectual disability. While phenotypic similarities between CSS and BICRA have been identified, an assessment of a larger cohort of individuals with BICRA pathogenic variants will be needed to determine whether it is clinically similar to or distinct from CSS. BICRA-related disorder is inherited in an autosomal dominant manner.SMARCD1-related disorder (OMIM 618779). Nixon et al [2019] identified five individuals with pathogenic variants in SMARCD1. These individuals presented with developmental delay, intellectual disability, hypotonia, and feeding difficulties. While similarities between CSS and

SMARCD1-related disorder have been identified, an assessment of a larger cohort of individuals with SMARCD1 variants will be needed to determine whether it is clinically similar or distinct from CSS. SMARCD1-related disorder is inherited in an autosomal dominant manner.

ManagementEvaluations Following Initial DiagnosisTo establish the extent of disease and needs of an individual diagnosed with Coffin-Siris syndrome (CSS), the following evaluations are recommended:Consultation with a clinical geneticist and/or genetic counselorNeurologic and/or developmental examination to record developmental milestones and identify neurologic symptoms or deficitsEvaluation for occupational, speech, or physical therapy as neededGastrointestinal evaluation for feeding difficulties or poor growthDietary evaluation by a nutritionist as neededOphthalmologic examination, including a dilated fundus examination and visual acuityAudiology evaluation with auditory brain stem response testing and otoacoustic emission testing to assess for hearing lossEchocardiogram to evaluate for structural cardiac defectsRenal ultrasonography to evaluate for structural kidney or genitourinary anomaliesTreatment of ManifestationsThe following are appropriate:Occupational, physical, and/or speech therapies to optimize developmental outcomesFeeding therapy, nutritional supplementation, and/or gastrostomy tube placement as needed to meet nutritional needsSpectacles as needed to correct refractive errors and surgery as needed for strabismus and/or ptosisHearing aids as neededPrevention of Secondary ComplicationsTherapies and interventions which can prevent secondary complications mirror the recommended treatments for an individual’s particular needs. This may include developmental therapies, appropriate cardiac, gastrointestinal, and neurologic evaluations and treatments, and ophthalmologic and audiologic surveillance.SurveillanceSurveillance includes the following:Yearly evaluation by a developmental pediatrician to assess developmental progress and therapeutic and educational interventionsAnnual follow up with a gastroenterologist and feeding specialists as needed to monitor feeding and weight gainRegular follow up of ophthalmologic and/or audiologic abnormalitiesBecause of the rarity of tumors in CSS, the utility of tumor surveillance has not been determined.Evaluation of Relatives at RiskSee Genetic Counseling for issues related to

testing of at-risk relatives for genetic counseling purposes.Pregnancy ManagementAs no females with CSS have been reported to reproduce, potential complications of pregnancy are unknown.Therapies Under InvestigationSearch ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Evaluations Following Initial DiagnosisTo establish the extent of disease and needs of an individual diagnosed with Coffin-Siris syndrome (CSS), the following evaluations are recommended:Consultation with a clinical geneticist and/or genetic counselorNeurologic and/or developmental examination to record developmental milestones and identify neurologic symptoms or deficitsEvaluation for occupational, speech, or physical therapy as neededGastrointestinal evaluation for feeding difficulties or poor growthDietary evaluation by a nutritionist as neededOphthalmologic examination, including a dilated fundus examination and visual acuityAudiology evaluation with auditory brain stem response testing and otoacoustic emission testing to assess for hearing lossEchocardiogram to evaluate for structural cardiac defectsRenal ultrasonography to evaluate for structural kidney or genitourinary anomalies

Consultation with a clinical geneticist and/or genetic counselor

Neurologic and/or developmental examination to record developmental milestones and identify neurologic symptoms or deficits

Evaluation for occupational, speech, or physical therapy as needed

Gastrointestinal evaluation for feeding difficulties or poor growth

Dietary evaluation by a nutritionist as needed

Ophthalmologic examination, including a dilated fundus examination and visual acuity

Audiology evaluation with auditory brain stem response testing and otoacoustic emission testing to assess for hearing loss

Echocardiogram to evaluate for structural cardiac defects

Renal ultrasonography to evaluate for structural kidney or genitourinary anomalies

Treatment of ManifestationsThe following are appropriate:Occupational, physical, and/or speech therapies to optimize developmental outcomesFeeding therapy, nutritional supplementation, and/or gastrostomy tube placement as needed to meet nutritional needsSpectacles as needed to correct refractive errors and surgery as needed for strabismus and/or ptosisHearing aids as needed

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Spectacles as needed to correct refractive errors and surgery as needed for strabismus and/or ptosis

Hearing aids as needed

Prevention of Secondary ComplicationsTherapies and interventions which can prevent secondary complications mirror the recommended treatments for an individual’s particular needs. This

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Evaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.Mode of InheritanceCoffin-Siris syndrome (CSS) is inherited in an autosomal dominant manner. Most affected individuals reported to date have had a de novo pathogenic variant.Risk to Family Members

Parents of a proband

Most probands reported to date have the disorder as the result of a de novo CSS-causing pathogenic variant.The proportion of cases caused by a de novo pathogenic variant is unknown, but likely approaches 100%, given the paucity of reports of affected parents in the literature.Recommendations for the evaluation of parents of a proband with an apparent de novo pathogenic variant include testing of the parents for the pathogenic variant identified in the proband.If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, the proband most likely has a de novo pathogenic variant. In rare cases, a parent may have germline mosaicism [Ben-Salem et al 2016].Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotype. Therefore, an apparently negative family history cannot be fully confirmed until appropriate evaluations have been performed.

Sibs of a proband

The risk to the sibs of the proband depends on the genetic status of the proband’s parents.In the rare circumstance that a parent of the proband is affected and is heterozygous for a CSS-causing pathogenic variant, the risk to the sibs is 50%.When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.If the pathogenic variant found in the

proband cannot be detected in the leukocyte DNA of either parent, the empiric recurrence risk to sibs is approximately 1% because of the theoretic possibility of parental germline mosaicism.One report of CSS in two sisters and partial expression in their father has been published [Haspeslagh et al 1984], suggesting parental somatic (and germline) mosaicism. However, there has been no molecular confirmation of the diagnosis, and the affected family members may have a disorder other than CSS.Offspring of a proband. Each child of an individual with CSS has a 50% chance of inheriting the CSS-related pathogenic variant.Other family members. The risk to other family members depends on the status of the proband's parents: in the rare event of an affected parent, other family members may be at risk.Related Genetic Counseling Issues

Family planning

The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to couples who have had an affected child.DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).Prenatal Testing and Preimplantation Genetic TestingRisk to future pregnancies is presumed to be low as the familial proband most likely has a de novo CSS-causing pathogenic variant. However, prenatal testing or preimplantation genetic testing are options to consider, as the risk may be greater than in the general population because of the possibility of parental germline mosaicism.Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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Related Genetic Counseling Issues

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The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to couples who have had an affected child.

Prenatal Testing and Preimplantation Genetic TestingRisk to future pregnancies is presumed to be low as the familial proband most likely has a de novo CSS-causing pathogenic variant. However, prenatal testing or preimplantation genetic testing are options to consider, as the risk may be greater

than in the general population because of the possibility of parental germline mosaicism.Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

Coffin-Siris Syndrome Foundation

Phone: 720-514-9904Email: Foundation@coffinsiris.org

www.coffinsiris.org

Genetic and Rare Diseases Information Center (GARD)

Phone: 888-205-2311

Coffin-Siris Syndrome

American Association on Intellectual and Developmental Disabilities (AAIDD)

Phone: 202-387-1968Fax: 202-387-2193

www.aaidd.org

CDC - Developmental Disabilities

Phone: 800-CDC-INFOEmail: cdcinfo@cdc.gov

Intellectual Disability

MedlinePlus

Intellectual Disability

Clinical Registry of Individuals with Coffin-Siris Syndrome and Other BAF-Related Phenotypes

Email: Samantha.vergano@chkd.org

CoRDS Registry

Sanford ResearchPhone: 605-312-6300

CoRDS Registry

Coffin-Siris Syndrome Foundation

Phone: 720-514-9904

Email: Foundation@coffinsiris.org

www.coffinsiris.org

Genetic and Rare Diseases Information Center (GARD)

Phone: 888-205-2311

Coffin-Siris Syndrome

American Association on Intellectual and Developmental Disabilities (AAIDD)

Phone: 202-387-1968

Fax: 202-387-2193

www.aaidd.org

CDC - Developmental Disabilities

Phone: 800-CDC-INFO

Email: cdcinfo@cdc.gov

Intellectual Disability

MedlinePlus

Intellectual Disability

Clinical Registry of Individuals with Coffin-Siris Syndrome and Other BAF-Related Phenotypes

Email: Samantha.vergano@chkd.org

CoRDS Registry

Sanford Research

Phone: 605-312-6300

CoRDS Registry

Molecular GeneticsInformation in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.Table A.Coffin-Siris Syndrome: Genes and DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

ARID1A

1p36.11

AT-rich interactive domain-containing protein 1A

ARID1A @ LOVD

ARID1A

ARID1A

ARID1B

6q25.3

AT-rich interactive domain-containing protein 1B

ARID1B @ LOVD

ARID1B

ARID1B

ARID2

12q12

AT-rich interactive domain-containing protein 2

ARID2

ARID2

DPF2

11q13.1

Zinc finger protein ubi-d4

DPF2 @ LOVD

DPF2

DPF2

SMARCA4

19p13.2

Transcription activator BRG1

SMARCA4 database

SMARCA4

SMARCA4

SMARCB1

22q11.23

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1

SMARCB1 database

UKE Hamburg SMARCB1 database

SMARCB1

SMARCB1

SMARCC2

12q13.2

SWI/SNF complex subunit SMARCC2

SMARCC2

SMARCC2

SMARCE1

17q21.2

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1

SMARCE1 @ LOVD

SMARCE1

SMARCE1

SOX4

6p22.3

Transcription factor SOX-4

SOX4

SOX4

SOX11

2p25

Transcription factor SOX-11

SOX11

Data are compiled from the following standard references: gene from

HGNC;

chromosome locus from

OMIM;

protein from UniProt.

For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.Table B.OMIM Entries for Coffin-Siris Syndrome (View All in OMIM) View in own window

135900COFFIN-SIRIS SYNDROME 1; CSS1

184430SRY-BOX 4; SOX4

600898SRY-BOX 11; SOX11

601607SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY B, MEMBER 1; SMARCB1

601671D4, ZINC, AND DOUBLE PHD FINGERS FAMILY, MEMBER 2; DPF2

601734SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY C, MEMBER 2; SMARCC2

603024AT-RICH INTERACTION DOMAIN-CONTAINING PROTEIN 1A; ARID1A

603111SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY E, MEMBER 1; SMARCE1

603254SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY A, MEMBER 4; SMARCA4

609539AT-RICH INTERACTION DOMAIN-CONTAINING PROTEIN 2; ARID2

614556AT-RICH INTERACTION DOMAIN-CONTAINING PROTEIN 1B; ARID1B

617808COFFIN-SIRIS SYNDROME 6; CSS6

618027COFFIN-SIRIS SYNDROME 7; CSS7

618362COFFIN-SIRIS SYNDROME 8; CSS8

618506INTELLECTUAL DEVELOPMENTAL DISORDER WITH SPEECH DELAY AND DYSMORPHIC FACIES; IDDSDFMolecular PathogenesisMany of the proteins identified in CSS to date encode human homologs of proteins first identified in yeast and drosophila in the BRG1- and BRM-associated factor (BAF) complex, originally called the mammalian switch/sucrose non-fermentable (mSWI/SNF)-like nucleosome remodeling complex. This complex contains a DNA-stimulated ATPase activity capable of destabilizing histone-DNA interactions in an

ATP-dependent manner [Ronan et al 2013]. SOX11 is predicted to act downstream of the BAF complex in neurogenesis and conversion of postnatal glia into neurons [Ninkovic et al 2013].Table 2. Coffin-Siris Syndrome: Mechanism of Disease CausationView in own windowGene 1Mechanism

ARID1A

Loss of function

ARID1B

Loss of function

ARID2

Loss of function

DPF2

Loss of function

PHF6

SMARCA4

Dominant-negative or gain of function

SMARCB1

Dominant-negative or gain of function

SMARCC2

Loss of function

SMARCE1

Dominant-negative or gain of function

SOX4

Loss of function

SOX11

Loss of function1. Genes from Table 1 in alphabetic order.Table 3. Coffin-Siris Syndrome: Gene-Specific Laboratory ConsiderationsView in own windowGene 1Special Consideration

ARID1A

Many pathogenic variants appear to be mosaic, a finding that should be taken into account when analyzing sequence data.

ARID1B

Alternatively spliced transcript variants encoding different isoforms have been described.

SMARCA4

Multiple transcript variants encoding different isoforms have been found for this gene.

SOX11

Pathogenic variants in SOX11 include partial- or whole-gene deletions or de novo missense variants in the HMG-box DNA-binding domain. 31. Genes from Table 1 in alphabetic order.2. Gazdagh et al [2019]

3. Tsurusaki et al [2014a], Hempel et al [2016]Table 4. Coffin-Siris Syndrome: Notable Pathogenic Variants by GeneView in own windowGene 1Reference SequencesDNA Nucleotide ChangePredictedProtein ChangeComment [Reference]

SMARCB1

NM_003073.5

NP_003064.2

c.1085AGA[2]p.Lys364delRecurrent de novo pathogenic variant; affected persons had strikingly similar clinical manifestations. 2

SMARCC2

NM_001330288.2

c.1926+1G>TSplicing variantRecurrent de novo splicing variant; affected persons have developmental delays, minimal or absent speech, and hypotonia. 3Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the

classification of variants.GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.1. Genes from Table 1 in alphabetic order2.

Kosho et al [2014b]

3.

Machol et al [2019]

Cancer and Benign TumorsSMARCA4. Heterozygous germline pathogenic variants in SMARCA4 have been reported to cause rhabdoid tumor predisposition; likewise, somatic pathogenic variants in SMARCA4 have been found in atypical teratoid and rhabdoid tumors [Schneppenheim et al 2010, Hasselblatt et al 2011, Biegel et al 2014].SMARCB1. Heterozygous germline pathogenic variants in SMARCB1 have been reported to cause the rhabdoid tumor predisposition syndrome in which most tumors are associated with biallelic loss-of-function variants, and correspondingly, somatic pathogenic variants in the SMARCB1 have been found in atypical teratoid and rhabdoid tumors [Roberts & Biegel 2009, Biegel et al 2014].

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AT-rich interactive domain-containing protein 1A

ARID1A @ LOVD

ARID1A

ARID1A

ARID1B

6q25.3

AT-rich interactive domain-containing protein 1B

ARID1B @ LOVD

ARID1B

ARID1B

ARID2

12q12

AT-rich interactive domain-containing protein 2

ARID2

ARID2

DPF2

11q13.1

Zinc finger protein ubi-d4

DPF2 @ LOVD

DPF2

DPF2

SMARCA4

19p13.2

Transcription activator BRG1

SMARCA4 database

SMARCA4

SMARCA4

SMARCB1

22q11.23

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1

SMARCB1 database

UKE Hamburg SMARCB1 database

SMARCB1

SMARCB1

SMARCC2

12q13.2

SWI/SNF complex subunit SMARCC2

SMARCC2

SMARCC2

SMARCE1

17q21.2

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1

SMARCE1 @ LOVD

SMARCE1

SMARCE1

SOX4

6p22.3

Transcription factor SOX-4

SOX4

SOX4

SOX11

2p25

Transcription factor SOX-11

SOX11

Data are compiled from the following standard references: gene from

HGNC;

chromosome locus from

OMIM;

protein from UniProt.

For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Coffin-Siris Syndrome: Genes and Databases

GeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

ARID1A

1p36.11

AT-rich interactive domain-containing protein 1A

ARID1A @ LOVD

ARID1A

ARID1A

ARID1B

6q25.3

AT-rich interactive domain-containing protein 1B

ARID1B @ LOVD

ARID1B

ARID1B

ARID2

12q12

AT-rich interactive domain-containing protein 2

ARID2

ARID2

DPF2

11q13.1

Zinc finger protein ubi-d4

DPF2 @ LOVD

DPF2

DPF2

SMARCA4

19p13.2

Transcription activator BRG1

SMARCA4 database

SMARCA4

SMARCA4

SMARCB1

22q11.23

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1

SMARCB1 database

UKE Hamburg SMARCB1 database

SMARCB1

SMARCB1

SMARCC2

12q13.2

SWI/SNF complex subunit SMARCC2

SMARCC2

SMARCC2

SMARCE1

17q21.2

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Table B.OMIM Entries for Coffin-Siris Syndrome (View All in OMIM) View in own window

135900COFFIN-SIRIS SYNDROME 1; CSS1

184430SRY-BOX 4; SOX4

600898SRY-BOX 11; SOX11

601607SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY B, MEMBER 1; SMARCB1

601671D4, ZINC, AND DOUBLE PHD FINGERS FAMILY, MEMBER 2; DPF2

601734SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY C, MEMBER 2; SMARCC2

603024AT-RICH INTERACTION DOMAIN-CONTAINING PROTEIN 1A; ARID1A

603111SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY E, MEMBER 1; SMARCE1

603254SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY A, MEMBER 4; SMARCA4

609539AT-RICH INTERACTION DOMAIN-CONTAINING PROTEIN 2; ARID2

614556AT-RICH INTERACTION DOMAIN-CONTAINING PROTEIN 1B; ARID1B

617808COFFIN-SIRIS SYNDROME 6; CSS6

618027COFFIN-SIRIS SYNDROME 7; CSS7

618362COFFIN-SIRIS SYNDROME 8; CSS8

618506INTELLECTUAL DEVELOPMENTAL DISORDER WITH SPEECH DELAY AND DYSMORPHIC FACIES; IDDSDF

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Molecular PathogenesisMany of the proteins identified in CSS to date encode human homologs of proteins first identified in yeast and drosophila in the BRG1- and BRM-associated factor (BAF) complex, originally called the mammalian switch/sucrose non-fermentable (mSWI/SNF)-like

nucleosome remodeling complex. This complex contains a DNA-stimulated ATPase activity capable of destabilizing histone-DNA interactions in an ATP-dependent manner [Ronan et al 2013]. SOX11 is predicted to act downstream of the BAF complex in neurogenesis and conversion of postnatal glia into neurons [Ninkovic et al 2013].Table 2. Coffin-Siris Syndrome: Mechanism of Disease CausationView in own windowGene 1Mechanism

ARID1A

Loss of function

ARID1B

Loss of function

ARID2

Loss of function

DPF2

Loss of function

PHF6

SMARCA4

Dominant-negative or gain of function

SMARCB1

Dominant-negative or gain of function

SMARCC2

Loss of function

SMARCE1

Dominant-negative or gain of function

SOX4

Loss of function

SOX11

Loss of function1. Genes from Table 1 in alphabetic order.Table 3. Coffin-Siris Syndrome:

Gene-Specific Laboratory ConsiderationsView in own windowGene 1Special Consideration

ARID1A

Many pathogenic variants appear to be mosaic, a finding that should be taken into account when analyzing sequence data.

ARID1B

Alternatively spliced transcript variants encoding different isoforms have been described.

SMARCA4

Multiple transcript variants encoding different isoforms have been found for this gene.

SOX11

Pathogenic variants in SOX11 include partial- or whole-gene deletions or de novo missense variants in the HMG-box DNA-binding domain. 31. Genes from Table 1 in alphabetic order.2. Gazdagh et al [2019]

3. Tsurusaki et al [2014a], Hempel et al [2016]Table 4. Coffin-Siris Syndrome: Notable Pathogenic Variants by GeneView in own windowGene 1Reference SequencesDNA Nucleotide ChangePredictedProtein ChangeComment [Reference]

SMARCB1

NM_003073.5

NP_003064.2

c.1085AGA[2]p.Lys364delRecurrent de novo pathogenic variant; affected persons had strikingly similar clinical manifestations. 2

SMARCC2

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c.1926+1G>TSplicing variantRecurrent de novo splicing variant; affected persons have developmental delays, minimal or absent speech, and hypotonia. 3Variants listed in the table

have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.1. Genes from Table 1 in alphabetic order2.

Kosho et al [2014b]

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SOX11

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Table 4. Coffin-Siris Syndrome: Notable Pathogenic Variants by GeneView in own windowGene 1Reference SequencesDNA Nucleotide ChangePredictedProtein ChangeComment [Reference]

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NP_003064.2

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Genes from Table 1 in alphabetic order

Kosho et al [2014b]

Machol et al [2019]

Cancer and Benign TumorsSMARCA4. Heterozygous germline pathogenic variants in SMARCA4 have been reported to cause rhabdoid tumor predisposition; likewise, somatic pathogenic variants in SMARCA4 have been found in atypical teratoid and rhabdoid tumors [Schneppenheim et al 2010, Hasselblatt et al 2011, Biegel et al 2014].SMARCB1. Heterozygous germline pathogenic variants in SMARCB1 have been reported to cause the rhabdoid tumor predisposition syndrome in which most tumors are associated with biallelic loss-of-function variants, and correspondingly, somatic pathogenic variants in the SMARCB1 have been found in atypical teratoid and rhabdoid tumors [Roberts & Biegel 2009, Biegel et al 2014].

Chapter NotesAcknowledgmentsDr Schrier Vergano would like to acknowledge Ashley Vasko, BS, and Catherine Nguyen, MS, who assisted with the 2021 revision of this chapter.Author NotesAll of the authors of this review study the clinical features and molecular basis of the Coffin-Siris syndrome.Revision History12 August 2021 (aa) Revision: added genes: BICRA, DPF2, SMARCC2,

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