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NLM Citation: Vergano SA, van der Sluijs PJ, Santen G. *ARID1B*-Related Disorder. 2019 May 23. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

ARID1B-Related Disorder

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Created: May 23, 2019.

Summary

Clinical characteristics

ARID1B-related disorder (*ARID1B*-RD) constitutes a clinical continuum, from classic Coffin-Siris syndrome to intellectual disability with or without nonspecific dysmorphic features. Coffin-Siris syndrome 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, hypertrichosis, and sparse scalp hair. Frequencies of other features, such as developmental delay (with speech often more affected than motor development), is consistent across the clinical spectrum, and may include malformations of the cardiac, gastrointestinal, genitourinary, and/or central nervous systems. Other findings seen in individuals with *ARID1B*-RD include feeding difficulties, slow growth, ophthalmologic abnormalities, hearing impairment, seizures, attention-deficit/hyperactivity disorder, and autistic features.

Diagnosis/testing

The diagnosis of *ARID1B*-RD is established by identification of a heterozygous pathogenic variant in *ARID1B* by molecular genetic testing.

Management

Treatment of manifestations: Standard treatment for strabismus, refractive error, hearing loss, congenital heart defects, obstructive sleep apnea, constipation, gastroesophageal reflux, cryptorchidism, scoliosis, and seizure disorders. For significant feeding issues, a nasogastric and/or gastrostomy tube may be required. Developmental therapies, including speech/language and feeding therapy, is recommended for those with developmental delay.

Surveillance: At least annual assessment of developmental progress and educational needs; annual ophthalmology evaluation and assessment for scoliosis (until growth is complete). Audiology evaluation, behavior assessment, and hormonal evaluation/bone age as needed based on symptoms. Those with seizures should be monitored as clinically indicated.

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Genetic counseling

ARID1B-related disorder is inherited in an autosomal dominant fashion. With the exception of two families in which a parent and child had features consistent with *ARID1B*-related disorder, all individuals diagnosed to date have the disorder as the result of a *de novo* pathogenic variant. Once the *ARID1B* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

ARID1B-Related Disorder: Included Phenotypes [1]
• *ARID1B* intellectual disability • *ARID1B* intellectual disability with nonspecific dysmorphic features • *ARID1B* Coffin-Siris syndrome [2]

1. For other genetic causes of these phenotypes see Differential Diagnosis.
2. See also Coffin-Siris Syndrome.

Diagnosis

Heterozygous pathogenic variants in *ARID1B* lead to a phenotypic spectrum, from Coffin-Siris syndrome (CSS) (with dysmorphic features and/or organ system involvement) to intellectual disability with or without nonspecific dysmorphic features. See Coffin-Siris Syndrome for more information.

Note: The information presented in the Coffin-Siris syndrome *GeneReviews* chapter includes information on individuals with CSS from a variety of genetic causes including *ARID1B* but is not specific to individuals with a pathogenic variant in *ARID1B*.

Suggestive Findings

ARID1B Coffin-Siris syndrome (*ARID1B*-CSS) **should be suspected** in individuals with the following findings [Fleck et al 2001, Schrier et al 2012, Kosho et al 2014, Santen et al 2014]:

- Fifth-digit nail and/or distal phalanx hypoplasia (although other digits may be affected) OR aplasia of the hands or feet
- Developmental or cognitive delay of variable degree
- Typical facial features including a wide mouth with thick, everted vermilion of the upper and lower lips, broad nasal bridge with broad nasal tip, thick eyebrows, and long eyelashes
- Central hypotonia
- Hypertrichosis in atypical areas (e.g., the back) or excessive hair growth on the arms or face
- Sparse scalp hair, especially in infancy, particularly in the temporal regions

Though admittedly a large group, *ARID1B* intellectual disability with or without nonspecific dysmorphic features (*ARID1B*-ID) **should be considered** in individuals presenting with the following clinical findings:

- Mild-to-profound developmental delay (DD) and/or intellectual disability (ID)
  AND
- Any of the following features presenting in infancy or childhood:
  - Generalized hypotonia of infancy
  - Infant feeding difficulties
  - Spasticity
  - Epilepsy (predominately tonic-clonic)
  - Behavior problems, such as attention-deficit/hyperactivity disorder (ADHD) and autistic features

- Cryptorchidism
- Laryngomalacia
- Myopia
- Delayed speech development
- Suggestive dysmorphic features (see Clinical Description)

Establishing the Diagnosis

The diagnosis of an *ARID1B*-related disorder **is established** in a proband with suggestive clinical features by identification of a heterozygous pathogenic (or likely pathogenic) variant in *ARID1B* by molecular genetic testing (see Table 1).

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis and exome sequencing) depending on the phenotype.

Classic *ARID1B* Coffin-Siris Syndrome

When the phenotypic findings suggest the diagnosis of *ARID1B*-CSS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ARID1B* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic or whole-gene deletions or duplications.
- **A Coffin-Siris syndrome multigene panel** that includes *ARID1A*, *ARID1B*, *ARID2*, *DPF2*, *PHF6*, *SMARCA2*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SOX11*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) 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.

ARID1B Intellectual Disability with or without Nonspecific Dysmorphic Features

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability (ID) typically begins with chromosomal microarray analysis (CMA). If CMA is not diagnostic, the next step is typically either a multigene panel or exome sequencing:

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP (single-nucleotide polymorphism) arrays to detect genome-wide large deletions/duplications (including *ARID1B*) that may not be detected by sequence analysis.

- **An intellectual disability multigene panel** that includes *ARID1B* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder an intellectual disability multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Exome sequencing,** which does not require the clinician to determine which gene is likely involved, yields results similar to an ID multigene panel but has two advantages: (1) a multigene panel may not include all rare genes recently identified as causing ID; and (2) exome sequencing may be able to detect pathogenic variants in genes which – for technical reasons – do not sequence well.

  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 *ARID1B*-Related Disorder

Gene [1]	Phenotype	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ARID1B	Coffin-Siris syndrome	Sequence analysis [3]	71/80 [4]
		Gene-targeted deletion/ duplication analysis [5]	9/80 [6]
	ARID1B intellectual disability	Sequence analysis [3]	54/63 [7, 8]
		CMA [9]	9/63 [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. van der Sluijs et al [2019]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Microdeletions of chromosome 6q25.3 that include *ARID1B* have been reported in: (a) children with CSS ascertained prior to the understanding of the molecular basis of CSS [Tsurusaki et al 2012]; (b) children ascertained with a microdeletion containing *ARID1B* and secondarily noted to have features similar to CSS [Santen et al 2012]; and (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.
7. Santen et al [2013]
8. Although the Santen et al [2013] study included sequence analysis results of individuals with clinical features of Coffin-Siris syndrome, it is the only study where all affected individuals underwent both MLPA and sequencing analysis, and therefore likely reflects the mutational spectrum best.
9. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *ARID1B*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 6q25.3 region. CMA designs in current clinical use target the 6q25.3 region.

Clinical Characteristics

Clinical Description

Most individuals with a heterozygous pathogenic variant in *ARID1B* have some features consistent with Coffin-Siris syndrome.

Note: (1) The Coffin-Siris syndrome *GeneReviews* chapter includes information on individuals with CSS from a variety of genetic causes including *ARID1B* but is not specific to individuals with a pathogenic variant in *ARID1B*. (2) Approximately 1/2 to 2/3 of individuals with molecularly confirmed CSS have a pathogenic variant in *ARID1B* [van der Sluijs et al 2019]. More data are needed to determine which CSS features are found more or less frequently in individuals with a pathogenic variant in *ARID1B*.

To date, approximately 100 individuals who do not have the classic Coffin-Siris syndrome phenotype have been identified with a heterozygous pathogenic variant in *ARID1B* [Santen et al 2013, Santen et al 2014, Ben-Salem et al 2016, Mannino et al 2018, van der Sluijs et al 2019].

A comparison between individuals with a heterozygous pathogenic variant in *ARID1B* with an a priori clinical diagnosis of CSS and a group without the a priori clinical diagnosis suggests that apart from CSS-specific features (hypo/aplasia of the fifth digits or nails of the hands/feet, sparse scalp hair, coarse facial features,

hypertrichosis) there are no major differences between the two groups [van der Sluijs et al 2019]. Therefore, the Authors treat them as a single entity, *ARID1B*-related disorder (*ARID1B*-RD).

Developmental delay (DD) and intellectual disability (ID). Intellectual disability ranges from profound to very mild, and intelligence quotients (IQs) in the normal range have been identified in some individuals with *ARID1B*-RD. Most affected individuals have developmental delay, with speech often more affected than motor development. An estimated 25% of affected individuals do not develop verbal language skills [van der Sluijs et al 2019].

Neurologic/epilepsy

- **Hypotonia** is a frequent finding (40%-80% of affected individuals).
- **Epilepsy.** Approximately one third of individuals with *ARID1B*-RD have experienced seizures, predominately of the tonic-clonic type. Additional individuals may have abnormal EEGs without apparent clinical seizure activity. Those with overt seizures appear to respond well to standard anti-seizure medications. The age of onset of seizures ranges from birth to mid-teenage years [van der Sluijs et al 2019].

Behavior problems. Individuals with *ARID1B*-RD appear to be at increased risk for a diagnosis of ADHD or autism, but the overall prevalence is not known, as many individuals now receiving the diagnosis at a younger age may not yet be old enough to evaluate for certain neurodevelopmental abnormalities. There does not appear to be an increased prevalence of self-harm, aggression, or sleep disturbances. Some behavior abnormalities may be exacerbated by an individual's degree of speech delay and difficulty with communication.

Growth. There are limited data regarding prenatal growth in individuals with *ARID1B*-RD. Postnatal growth data show the following:

- **Weight** may be normal or below average but appears to be in proportion to other growth parameters.
- The majority of affected individuals appear to have a **length/height** 0 to 2 SD below the mean; data are not sufficient to predict final adult height.

  Bone age appears to be delayed in approximately 50% of individuals who have been evaluated.
- **Head circumference** is normal in a majority of individuals with *ARID1B*-RD.

Gastrointestinal problems. Feeding difficulties are common and appear to approximate those seen in individuals with a diagnosis of CSS from a variety of genetic causes.

- Individuals with feeding difficulties commencing around the time of birth appear to have more severe issues and tend to require a feeding tube of some type (nasogastric or gastrostomy tube).
- In older children, milder feeding difficulties may occur, including oral aversion, particularly in those who required tube feeding as an infant or younger child.
- Constipation and gastroesophageal reflux disease are also common and may approximate that seen in individuals with CSS or other genetic syndromes with varying degrees of neurologic impairment [Mannino et al 2018].

Sensory impairment

- Approximately 25%-30% of affected individuals have some **vision abnormality**, although this frequency may not be significantly different from that of individuals with CSS from a variety of genetic causes [Mannino et al 2018]. The most frequently reported abnormalities include myopia, strabismus, and astigmatism.
- Similarly, 25%-40% of affected individuals have some degree of **hearing loss**, the most common being congenital sensorineural hearing loss, although conductive hearing loss has also been reported [Mannino

et al 2018, van der Sluijs et al 2019]. The range of severity of sensorineural hearing loss is not precisely known.

Neuroimaging. Of those individuals who have undergone brain imaging, approximately 30%-40% demonstrate brain anomalies. The most common abnormality is hypo- or aplasia of the corpus callosum [van der Sluijs et al 2019]. Delayed myelination or other white matter changes, colpocephaly, mega cisterna magna, and enlarged Virchow-Robin spaces are also seen. Additional brain abnormalities may be detected as more individuals undergo imaging.

Other associated features

- **Respiratory abnormalities.** Laryngomalacia has been documented, although it does not appear to occur more frequently than in individuals with CSS due to a variety of genetic causes [Mannino et al 2018, van der Sluijs et al 2019]. Asthma and obstructive sleep apnea have also been reported but may approximate the frequency of the general population.
- **Genitourinary (GU) abnormalities.** The most commonly reported GU abnormality appears to be cryptorchidism in males; structural renal abnormalities have been seen but the frequency of specific malformations is not known.
- **Musculoskeletal.** Scoliosis is seen with greater frequency than in the general population and may be acquired as affected individuals age. Shortened fifth digits or hypoplastic nails in the hands or feet may also be seen, as these are classically associated with CSS.
- **Dysmorphic features.** Affected individuals may have some features also seen in individuals with CSS from a variety of genetic causes, including sparse scalp hair, long eyelashes, hypertrichosis, and coarse facial features; more specifically, individuals may have thick alae nasi, a long philtrum, and a thick vermilion of the lower lip.

Prognosis. It is unknown if life span in individuals with *ARID1B*-RD is abnormal. One reported individual is alive at age 51 years [Santen, personal observation], and a woman age 60 years has also been reported [Määttänen et al 2018], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

To date, only loss-of-function variants (e.g., nonsense, splice site, frameshift, whole-gene deletions) cause *ARID1B*-RD. Missense variants do not appear to be pathogenic in general; however, a single missense variant in a proband (who had agenesis of the corpus callosum [ACC]) and the proband's mother (who did not have ACC but had mild ID) was described as *de novo* in the mother [Mignot et al 2016].

There do not appear to be specific genotype-phenotype correlations among individuals with *ARID1B*-related disorder to distinguish individuals with *ARID1B* intellectual disability with or without nonspecific dysmorphic features (*ARID1B*-ID) from those with *ARID1B* Coffin-Siris syndrome (*ARID1B*-CSS).

Prevalence

This condition is estimated to occur in approximately 1:10,000 to 1:100,000 individuals [Hoyer et al 2012].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ARID1B*.

Sporadic tumors (including predisposition to childhood neuroblastoma) occurring as single tumors in the absence of any other findings of *ARID1B*-RD frequently harbor somatic variants in *ARID1B* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information see Cancer and Benign Tumors.

Differential Diagnosis

ARID1B Coffin Siris Syndrome (*ARID1B*-CSS)

Table 2. Other Disorders to Consider in the Differential Diagnosis of *ARID1B* Coffin-Siris Syndrome (CSS)

Differential Diagnosis Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*ARID1B*-CSS	Distinguishing from *ARID1B*-CSS
Coffin-Siris syndrome caused by genes other than *ARID1B*	*ARID1A* *DPF2* *SMARCC2* *SMARCA4* *SMARCB1* *SMARCE1* *SOX11*	AD	Frequently clinically indistinguishable from *ARID1B*-CSS	Microcephaly seen more frequently in individuals w/a heterozygous pathogenic variant in *SMARCB1* or *SMARCE1*
Nicolaides-Baraitser syndrome	*SMARCA2*	AD	• Characteristic coarse facial features • Sparse scalp hair • ID	• Prominence of interphalangeal joints & distal phalanges due to ↓ subcutaneous fat • Absence of 5th-digit nail / distal phalanx hypo/aplasia
Borjeson-Forssman-Lehmann syndrome (OMIM 301900)	*PHF6*	XL	Affected females demonstrate some phenotypic overlap w/CSS, incl hypoplastic nails & fingers, sparse hair, & intellectual disability. [1, 2]	• Other digital anomalies incl tapering of digits, hammer toes, syndactyly of toes • Distinct facial gestalt incl prominent supraorbital ridges, deeply set eyes, prominent nasal bridge, short nose w/bulbous nasal tip
ARID2-ID (OMIM 617808)	*ARID2*	AD	• Hypotonia • Behavior anomalies • Very mild hypoplasia of 5th fingernails & hypoplasia of 5th toenails in some individuals • Facies: coarse features, flat nasal bridge, slightly broad nose, prominent philtrum, & large mouth w/thick lower vermilion [3] • ID	Birth defects not common
DOORS (*d*eafness, *o*nychodystrophy, *o*steodystrophy, mental *r*etardation, & *s*eizures) syndrome (See *TBC1D24*-Related Disorders.)	*TBC1D24*	AR	• Hypoplastic terminal phalanges &/or nail anomalies • Deafness • Neurologic abnormalities • ID	• Osteodystrophy • Profound hearing loss (can occasionally occur in *ARID1B*-CSS)

Table 2. continued from previous page.

Differential Diagnosis Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*ARID1B*-CSS	Distinguishing from *ARID1B*-CSS
Mabry syndrome (OMIM 239300)	*PIGV*	AR	• Delayed development & ID • Seizures • Coarse facial features • Hypoplastic 5th digits	↑ serum concentrations of alkaline phosphatase
Cornelia de Lange syndrome	*HDAC8* *NIPBL* *RAD21* *SMC1A* *SMC3*	AD, XL	• Limb anomalies may incl 5th-finger hypoplasia. • ID • Other findings may incl cardiac defects, gastrointestinal anomalies, & genitourinary malformations.	Distinctive craniofacial features (arched eyebrows, synophrys, upturned nose, small teeth, & microcephaly)
4q21 deletion syndrome (OMIM 613509)	Contiguous-gene deletion	AD [1]	• Curved, volar, 5th-digit nail that may resemble a hypoplastic distal phalanx • ID	• Facial gestalt may incl broad forehead, widely spaced eyes, & frontal bossing. • Postnatal growth restriction may be severe.

AD = autosomal dominant; AR = autosomal recessive; CSS = Coffin-Siris syndrome; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. To date, all reported probands have had the disorder as the result of a *de novo* deletion.

2. Zweier et al [2014]

3. While some of these features demonstrate overlap with CSS, an assessment of a larger cohort of individuals with *ARID2* pathogenic variants will be needed to determine whether it is clinically similar to or distinct from CSS.

The following genetic and teratogenic disorders may also be considered in the differential diagnosis of *ARID1B*-CSS:

- **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.
- **Fetal alcohol syndrome (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.

ARID1B Intellectual Disability with or without Nonspecific Dysmorphic Features

Because the phenotypic features associated with *ARID1B*-ID are not sufficiently distinctive to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

Evaluations Following Initial Diagnosis of *ARID1B*-Related Disorders

To establish the extent of disease and needs in an individual diagnosed with *ARID1B*-RD, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to diagnosis) are recommended. Note that some evaluations depend on whether the clinician thinks that the affected individual has *ARID1B*-CCS or *ARID1B*-ID.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *ARID1B*-RD

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	Assess for myopia, astigmatism, & strabismus.
ENT	Audiologic eval	Assess for hearing loss (even if newborn hearing screen is normal).
Cardiovascular	Cardiology eval	• *ARID1B*-CSS: Echocardiogram to evaluate for structural cardiac defects • *ARID1B*-ID: Consider an echocardiogram in infancy. [1, 2]
Respiratory	Assess for signs & symptoms of obstructive sleep apnea.	If present, consider ENT or sleep clinic evaluation &/or polysomnography.
Gastrointestinal/ Feeding	Assess growth parameters.	Consider bone age studies or other hormonal assessments if person has short stature ↓ predicted mid-parental height.
	Assess feeding & nutritional status.	Refer to gastroenterologist or feeding specialist, as needed, for persistent feeding issues.
Genitourinary	Assess males for cryptorchidism.	Urologic evaluation if cryptorchidism present
	Renal ultrasound	To evaluate for occult renal malformations
Musculoskeletal	Clinical assessment for scoliosis	Consider referral to orthopedist, if severe.
Neurologic	Neurologic eval	Incl EEG & brain MRI, if indicated.
Psychiatric/ Behavioral	Neuropsychiatric eval	Screen persons age >12 mos for behavior concerns incl ADHD &/or traits suggestive of ASD.
Miscellaneous/ Other	Consultation w/clinical geneticist or genetic counselor	
	Developmental assessment	Incl evaluation of motor, speech/language, general cognitive, & vocational skills.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder

1. An echocardiogram is recommended for those individuals with *ARID1B*-CSS. Although cardiac anomalies have not been described in individuals with *ARID1B*-ID, they can be a component of mild *ARID1B*-CSS and therefore a cardiology evaluation should be considered [Mannino et al 2018].

2. Echocardiogram may not be warranted in older children without obvious cardiovascular signs or symptoms based on exam.

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *ARID1B*-RD

Manifestation/Concern	Treatment	Considerations/Other
Abnormal vision &/or strabismus	Standard treatment(s) per ophthalmologist	
Hearing loss	Standard therapy based on the type of hearing loss detected	See Hereditary Hearing Loss and Deafness Overview.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Congenital heart defects	Standard treatment	
Obstructive sleep apnea	Standard treatment	
Feeding difficulties	Nasogastric or gastrostomy tube may be required.	Eval by gastroenterologist &/or feeding specialist
		Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia or feeding aversion
Constipation &/or GERD	Standard therapy	
Cryptorchidism / Renal anomalies	Standard treatment per urologist/ nephrologist, as appropriate	
Scoliosis	Bracing or casting as indicated by orthopedist	
Seizures [1]	Standardized treatment w/ASMs by experienced neurologist	Many different ASMs may be effective; none has been demonstrated effective specifically for this disorder.

ASM = anti-seizure medication; GERD = gastroesophageal reflux disease

1. Education of parents regarding common seizure presentations is appropriate. For additional information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Developmental Delay / Intellectual Disability Management Issues

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed. Before entering school, a neuropsychiatric evaluation may be of benefit to identify additional barriers to learning and other opportunities for assistance (i.e., identification of attention-deficit/hyperactivity disorder [ADHD] or autism spectrum traits).

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility.
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers/standers or gait trainers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction. If the individual is safe to eat by mouth, feeding therapy, typically from an occupational or speech therapist, is recommended for affected individuals who have difficulty feeding due to poor oral motor control. A swallow study may be necessary prior to initiation of oral feeds to evaluate for aspiration.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

Social/Behavioral Difficulties

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat ADHD, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with *ARID1B*-RD

System/Concern	Evaluation	Frequency
Constitutional	Growth parameters	At each visit
Eyes	Ophthalmologic eval	Annually
ENT	Audiologic eval	As required
Musculoskeletal	Clinical assessment for scoliosis	Annually, until growth is complete
Neurologic	Monitor those w/seizures as clinically indicated.	As needed
Psychiatric	Behavior assessment for anxiety, attention, & aggressive or self-injurious behavior	
Endocrine	Hormonal eval [1] &/or bone age studies	

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Miscellaneous/Other	Monitor developmental progress & educational needs.	Annually

1. To assess for poor growth velocity and/or short stature; specific hormonal evaluations depend on the clinical scenario but could include thyroid function tests and evaluation of growth-specific factors (e.g., IGF1 and IGFBP3 levels).

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Celen et al [2017] demonstrated potential response to growth hormone in *ARID1B*-haploinsufficient mice, although there have not been sufficient studies in humans with pathogenic *ARID1B* variants who are receiving growth hormone clinically to determine if this therapy is of benefit in increasing final adult height and improving muscle tone.

Search 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.

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 Inheritance

ARID1B-related disorder (*ARID1B*-RD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most probands reported to date with *ARID1B*-RD whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo ARID1B* pathogenic variant.
- Parental transmission of *ARID1B* pathogenic variants has been reported in two families in which the phenotype in the proband and the transmitting parent was consistent with *ARID1B*-RD; in both families, the transmitting parent was mildly affected [Mignot et al 2016, Smith et al 2016].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *ARID1B* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism (parental germline mosaicism has been reported [Ben-Salem et al 2016]).
- The family history of some individuals diagnosed with *ARID1B*-RD may appear to be negative because of failure to recognize the disorder in family members; given the variability in the *ARID1B*-RD phenotype, a parent may be heterozygous for an *ARID1B* pathogenic variant while being only mildly affected [Santen,

personal observation]. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.
- Theoretically, if the parent is the individual in whom the *ARID1B* pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *ARID1B* pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
- If the *ARID1B* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is approximately 1%-2%, and therefore greater than that of the general population because of the possibility of parental germline mosaicism [Ben-Salem et al 2016].

Offspring of a proband. Each child of an individual with *ARID1B*-RD has a 50% chance of inheriting the *ARID1B* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *ARID1B* pathogenic variant, the parent's 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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ARID1B* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

No specific resources for *ARID1B*-Related Disorder have been identified by *GeneReviews* staff.

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. ARID1B-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

ARID1B	6q25.3	AT-rich interactive domain-containing protein 1B	ARID1B @ LOVD	ARID1B	ARID1B

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 ARID1B-Related Disorder (View All in OMIM)

135900	COFFIN-SIRIS SYNDROME 1; CSS1
614556	AT-RICH INTERACTION DOMAIN-CONTAINING PROTEIN 1B; ARID1B

Molecular Pathogenesis

The ARID1B protein serves the largest alternating subunit of the SWI/SNF complex, along with ARID1A. It functions as a primary chromatin remodeler, regulating gene transcription and protein-protein interactions, and acts as a tumor suppressor [Santen et al 2012, Bögershausen & Wollnik 2018]. Despite this fact, no increased incidence above the general population risk of tumor development has been found in individuals with *ARID1B*-related disorder and no tumor screening protocols are currently recommended (see Genetically Related Disorders and Cancer and Benign Tumors).

Gene structure. *ARID1B* encodes a 20-exon gene.

See Table A, **Gene** for a detailed summary of gene and protein information.

Benign variants. Exon 3 is a small (14-amino acid), in-frame exon that is present in transcript NM_020732.3 but not NM_017519.2. Loss-of-function variants have not been reported in this exon and may be benign; therefore, caution must be used in interpreting variants in this exon [Santen, personal communication].

Pathogenic variants. The vast majority of reported pathogenic variants are truncating (nonsense, frameshift, splice site, single-exon, multiexon, and whole-gene deletions).

A c.1259delA maternally inherited deletion has been reported in two probands – one *de novo* and one maternally inherited [Smith et al 2016].

Loss-of-function variants associated with CSS are rarely seen at the 5' end of *ARID1B*. The most 5' pathogenic variant described is a *de novo* nonsense variant, c.850C>T (p.Gln284Ter), in exon 1 [Santen, personal communication].

In addition, microdeletions and nonsense variants have been reported in several individuals with nonspecific intellectual disability. However, evaluation of several of these subjects revealed some mild overlap with CSS features suggesting a range of clinical features for individuals with haploinsufficiency of ARID1B [Hoyer et al 2012, Santen et al 2014]. Other than subjects with large microdeletions including additional genes having additional phenotypes, there is currently no clear genotype-phenotype correlation, suggesting the involvement of other phenotypic modifiers.

Table 6. Pathogenic *ARID1B* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.850C>T	p.Gln284Ter	NM_020732.3 NP_065783.3
c.1259delA	p.Asn420IlefsTer10	

Variants 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.

Normal gene product. The ARID1B protein contains 2,249 amino acids (NP_065783.3) and is a component of the SWI/SNF chromatin remodeling complex, possibly playing a role in cell-cycle activation. ARID1B is similar to ARID1A, and the two proteins function as alternative, mutually exclusive ARID subunits of the SWI/SNF complex. The associated complexes play opposing roles in some contexts.

Abnormal gene product. Loss of *ARID1B* expression appears to result in aberrant chromatin remodeling, causing downstream dysregulation of further genes and resulting in the *ARID1B*-RD or CSS phenotype.

Cancer and Benign Tumors

Both somatic deletions and mutations of *ARID1B* have been reported in a small number of cases of childhood neuroblastoma in individuals without features of *ARID1B*-RD [Sausen et al 2013]. However, no individuals with germline pathogenic *ARID1B* variants are known to have neuroblastoma; therefore, there are currently no screening recommendations.

Chapter Notes

Author Notes

Dr Samantha Schrier Vergano is a clinical geneticist at the Children's Hospital of The King's Daughters in Norfolk, Virginia. Her primary research interest is Coffin-Siris syndrome. She runs an international IRB-approved registry for the condition. For more information, please visit www.coffinsiris.org or email her at Samantha.Vergano@chkd.org.

Dr Gijs Santen is a clinical geneticist at the Leiden University Medical Center striving to improve clinical delineation of Coffin-Siris syndrome. He has a registry for individuals with pathogenic variants in *ARID1B* (humandiseasegenes.nl/arid1b) and runs a CSS clinic in The Netherlands.

Revision History

- 23 May 2019 (ma) Review posted live
- 26 July 2018 (sv, gs) Original submission

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