ARID1B Syndrome

https://www.ncbi.nlm.nih.gov/books/NBK541502/

SummaryClinical 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.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.

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DiagnosisHeterozygous 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 FindingsARID1B 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 feetDevelopmental or cognitive delay of variable degreeTypical 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 eyelashesCentral hypotoniaHypertrichosis 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 regionsThough 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)ANDAny of the following features presenting in infancy or childhood:Generalized hypotonia of infancyInfant feeding difficultiesSpasticityEpilepsy (predominately tonic-clonic)Behavior problems, such as attention-deficit/hyperactivity disorder (ADHD) and autistic featuresCryptorchidismLaryngomalaciaMyopiaDelayed speech developmentSuggestive dysmorphic features (see Clinical Description)Establishing the DiagnosisThe 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

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Suggestive FindingsARID1B 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 feetDevelopmental or cognitive delay of variable degreeTypical 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 eyelashesCentral hypotoniaHypertrichosis 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 regionsThough 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)ANDAny of the following features presenting in infancy or childhood:Generalized hypotonia of infancyInfant feeding difficultiesSpasticityEpilepsy (predominately tonic-clonic)Behavior problems, such as attention-deficit/hyperactivity disorder (ADHD) and autistic featuresCryptorchidismLaryngomalaciaMyopiaDelayed speech developmentSuggestive dysmorphic features (see Clinical Description)

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

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 DiagnosisThe 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. 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Molecular Genetic Testing Used in ARID1B-Related Disorder

Gene 1PhenotypeMethodProportion of Probands with a Pathogenic Variant 2

Detectable by Method

ARID1B

Coffin-Siris syndromeSequence analysis 371/80 4Gene-targeted deletion/duplication analysis 59/80 6ARID1B intellectual disabilitySequence analysis 354/63 7, 8CMA 99/63 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]

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Clinical CharacteristicsClinical DescriptionMost 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.

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

Genetically Related (Allelic) DisordersNo 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 DiagnosisARID1B Coffin Siris Syndrome (ARID1B-CSS)Table 2. Other Disorders to Consider in the Differential Diagnosis of ARID1B Coffin-Siris Syndrome (CSS)View in own windowDifferential Diagnosis DisorderGene(s) /Genetic MechanismMOIClinical Features of Differential Diagnosis DisorderOverlapping w/ARID1B-CSSDistinguishing from ARID1B-CSSCoffin-Siris syndrome caused by genes other than ARID1B

ARID1A

DPF2

SMARCC2

SMARCA4

SMARCB1

SMARCE1

SOX11

ADFrequently clinically indistinguishable from ARID1B-CSSMicrocephaly seen more frequently in individuals w/a heterozygous pathogenic variant in SMARCB1 or SMARCE1

Nicolaides-Baraitser syndrome

SMARCA2

ADCharacteristic coarse facial featuresSparse scalp hairID

Prominence of interphalangeal joints & distal phalanges due to ↓ subcutaneous fatAbsence of 5th-digit nail / distal phalanx hypo/aplasia

Borjeson-Forssman-Lehmann syndrome(OMIM 301900)

PHF6

XLAffected females demonstrate some phenotypic overlap w/CSS, incl hypoplastic nails & fingers, sparse hair, & intellectual disability. 1, 2Other digital anomalies incl tapering of digits, hammer toes, syndactyly of toesDistinct facial gestalt incl prominent supraorbital ridges, deeply set eyes, prominent nasal bridge, short nose w/bulbous nasal tip

ARID2-ID(OMIM 617808)

ARID2

ADHypotoniaBehavior anomaliesVery mild hypoplasia of 5th fingernails & hypoplasia of 5th toenails in some individualsFacies: coarse features, flat nasal bridge, slightly broad nose, prominent philtrum, & large mouth w/thick lower vermilion 3ID

Birth defects not commonDOORS (deafness, onychodystrophy, osteodystrophy, mental retardation, & seizures) syndrome(See TBC1D24-Related Disorders.)

TBC1D24

ARHypoplastic terminal phalanges &/or nail anomaliesDeafnessNeurologic abnormalitiesID

OsteodystrophyProfound hearing loss (can occasionally occur in ARID1B-CSS)

Mabry syndrome(OMIM 239300)

PIGV

ARDelayed development & IDSeizuresCoarse facial featuresHypoplastic 5th digits

↑ serum concentrations of alkaline phosphatase

Cornelia de Lange syndrome

HDAC8

NIPBL

RAD21

SMC1A

SMC3

AD,XLLimb anomalies may incl 5th-finger hypoplasia.IDOther 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 deletionAD 1Curved, volar, 5th-digit nail that may resemble a hypoplastic distal phalanxID

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-linked1. 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 FeaturesBecause 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.

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ARDelayed development & IDSeizuresCoarse facial featuresHypoplastic 5th digits

↑ serum concentrations of alkaline phosphatase

Cornelia de Lange syndrome

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Distinctive craniofacial features (arched eyebrows, synophrys, upturned nose, small teeth, &

microcephaly)4q21 deletion syndrome(OMIM 613509)Contiguous-gene deletionAD 1Curved, volar, 5th-digit nail that may resemble a hypoplastic distal phalanxID

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-linked1. 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.

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

(CSS)View in own windowDifferential Diagnosis DisorderGene(s) /Genetic MechanismMOIClinical Features of Differential Diagnosis DisorderOverlapping w/ARID1B-CSSDistinguishing from ARID1B-CSSCoffin-Siris syndrome caused by genes other than ARID1B

ARID1A

DPF2

SMARCC2

SMARCA4

SMARCB1

SMARCE1

SOX11

ADFrequently clinically indistinguishable from ARID1B-CSSMicrocephaly seen more frequently in individuals w/a heterozygous pathogenic variant in SMARCB1 or SMARCE1

Nicolaides-Baraitser syndrome

SMARCA2

ADCharacteristic coarse facial featuresSparse scalp hairID

Prominence of interphalangeal joints & distal phalanges due to ↓ subcutaneous fatAbsence of 5th-digit nail / distal phalanx hypo/aplasia

Borjeson-Forssman-Lehmann syndrome(OMIM 301900)

PHF6

XLAffected females demonstrate some phenotypic overlap w/CSS, incl hypoplastic nails & fingers, sparse hair, & intellectual disability. 1, 2Other digital anomalies incl tapering of digits, hammer toes, syndactyly of toesDistinct facial gestalt incl prominent supraorbital ridges, deeply set eyes, prominent nasal bridge, short nose w/bulbous nasal tip

ARID2-ID(OMIM 617808)

ARID2

ADHypotoniaBehavior anomaliesVery mild hypoplasia of 5th fingernails & hypoplasia of 5th toenails in some individualsFacies: coarse features, flat nasal bridge, slightly broad nose, prominent philtrum, & large mouth w/thick lower vermilion 3ID

Birth defects not commonDOORS (deafness, onychodystrophy, osteodystrophy, mental retardation, & seizures) syndrome(See TBC1D24-Related Disorders.)

TBC1D24

ARHypoplastic terminal phalanges &/or nail anomaliesDeafnessNeurologic abnormalitiesID

OsteodystrophyProfound hearing loss (can occasionally occur in ARID1B-CSS)

Mabry syndrome(OMIM 239300)

PIGV

ARDelayed development & IDSeizuresCoarse facial featuresHypoplastic 5th digits

↑ serum concentrations of alkaline phosphatase

Cornelia de Lange syndrome

HDAC8

NIPBL

RAD21

SMC1A

SMC3

AD,XLLimb anomalies may incl 5th-finger hypoplasia.IDOther findings may incl cardiac defects, gastrointestinal anomalies, & genitourinary malformations.

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

Differential Diagnosis DisorderGene(s) /Genetic MechanismMOIClinical Features of Differential Diagnosis DisorderOverlapping w/ARID1B-CSSDistinguishing from ARID1B-CSSCoffin-Siris syndrome caused by genes other than ARID1B

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Absence of 5th-digit nail / distal phalanx hypo/aplasia

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

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

Hypoplastic terminal phalanges &/or nail anomalies

Deafness

Neurologic abnormalities

ID

Osteodystrophy

Profound hearing loss (can occasionally occur in ARID1B-CSS)

Delayed development & ID

Seizures

Coarse facial features

Hypoplastic 5th digits

Limb anomalies may incl 5th-finger hypoplasia.

ID

Other findings may incl cardiac defects, gastrointestinal anomalies, & genitourinary malformations.

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.

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

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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 FeaturesBecause 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.

ManagementEvaluations Following Initial Diagnosis of ARID1B-Related DisordersTo 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-RDView in own windowSystem/ConcernEvaluationComment

Eyes

Ophthalmologic evalAssess for myopia, astigmatism, & strabismus.

ENT

Audiologic evalAssess for hearing loss (even if newborn hearing screen is normal).

Cardiovascular

Cardiology evalARID1B-CSS: Echocardiogram to evaluate for structural cardiac defectsARID1B-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 presentRenal ultrasoundTo evaluate for occult renal malformations

Musculoskeletal

Clinical assessment for scoliosisConsider referral to orthopedist, if severe.

Neurologic

Neurologic evalIncl EEG & brain MRI, if indicated.

Psychiatric/

Behavioral

Neuropsychiatric evalScreen persons age >12 mos for behavior concerns incl ADHD &/or traits suggestive of ASD.

Miscellaneous/

Other

Consultation w/clinical geneticist or genetic counselorDevelopmental assessmentIncl evaluation of motor, speech/language, general cognitive, & vocational skills.ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder1. 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 ManifestationsTable 4. Treatment of Manifestations in Individuals with ARID1B-RDView in own windowManifestation/ConcernTreatmentConsiderations/Other

Abnormal vision &/or strabismus

Standard treatment(s) per ophthalmologist

Hearing loss

Standard therapy based on the type of hearing loss detectedSee Hereditary Hearing Loss and Deafness Overview.

Congenital heart defects

Standard treatment

Obstructive sleep apnea

Standard treatment

Feeding difficulties

Nasogastric or gastrostomy tube may be required.Eval by gastroenterologist &/or feeding specialistLow 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 neurologistMany different ASMs may be effective; none has been demonstrated effective specifically for this disorder.ASM = anti-seizure medication; GERD = gastroesophageal reflux disease1. 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 IssuesAges 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 DifficultiesChildren 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.SurveillanceTable 5. Recommended Surveillance for Individuals with ARID1B-RDView in own windowSystem/ConcernEvaluationFrequency

Constitutional

Growth parametersAt each visit

Eyes

Ophthalmologic evalAnnually

ENT

Audiologic evalAs required

Musculoskeletal

Clinical assessment for scoliosisAnnually, 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

Miscellaneous/Other

Monitor developmental progress & educational needs.Annually1. 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 RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Therapies Under InvestigationCelen 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.

Evaluations Following Initial Diagnosis of ARID1B-Related DisordersTo 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-RDView in own windowSystem/ConcernEvaluationComment

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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.

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Assess males for cryptorchidism.Urologic evaluation if cryptorchidism presentRenal ultrasoundTo evaluate for occult renal malformations

Musculoskeletal

Clinical assessment for scoliosisConsider referral to orthopedist, if severe.

Neurologic

Neurologic evalIncl EEG & brain MRI, if indicated.

Psychiatric/

Behavioral

Neuropsychiatric evalScreen persons age >12 mos for behavior concerns incl ADHD &/or traits suggestive of ASD.

Miscellaneous/

Other

Consultation w/clinical geneticist or genetic counselorDevelopmental assessmentIncl evaluation of motor, speech/language, general cognitive, & vocational skills.ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder1. 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.

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Recommended Evaluations Following Initial Diagnosis in Individuals with ARID1B-RD

System/ConcernEvaluationComment

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Treatment of ManifestationsTable 4. Treatment of Manifestations in Individuals with ARID1B-RDView in own windowManifestation/ConcernTreatmentConsiderations/Other

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Standard treatment(s) per ophthalmologist

Hearing loss

Standard therapy based on the type of hearing loss detectedSee Hereditary Hearing Loss and Deafness Overview.

Congenital heart defects

Standard treatment

Obstructive sleep apnea

Standard treatment

Feeding difficulties

Nasogastric or gastrostomy tube may be required.Eval by gastroenterologist &/or feeding specialistLow 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 neurologistMany different ASMs may be effective; none has been demonstrated effective specifically for this disorder.ASM = anti-seizure medication; GERD = gastroesophageal reflux disease1. 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 IssuesAges 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).

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Hearing loss

Standard therapy based on the type of hearing loss detectedSee Hereditary Hearing Loss and Deafness Overview.

Congenital heart defects

Standard treatment

Obstructive sleep apnea

Standard treatment

Feeding difficulties

Nasogastric or gastrostomy tube may be required.Eval by gastroenterologist &/or feeding specialistLow 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 neurologistMany different ASMs may be effective; none has been demonstrated effective specifically for this disorder.ASM = anti-seizure medication; GERD = gastroesophageal reflux disease1. 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.

Treatment of Manifestations in Individuals with ARID1B-RD

Manifestation/ConcernTreatmentConsiderations/Other

Abnormal vision &/or strabismus

Standard treatment(s) per ophthalmologist

Hearing loss

Standard therapy based on the type of hearing loss detectedSee Hereditary Hearing Loss and Deafness Overview.

Congenital heart defects

Standard treatment

Obstructive sleep apnea

Standard treatment

Feeding difficulties

Nasogastric or gastrostomy tube may be required.Eval by gastroenterologist &/or feeding specialistLow 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 neurologistMany different ASMs may be effective; none has been demonstrated effective specifically for this disorder.

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Developmental Delay / Intellectual Disability Management IssuesAges 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.

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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.

Physical therapy is recommended to maximize mobility.

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Social/Behavioral DifficultiesChildren 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.

SurveillanceTable 5. Recommended Surveillance for Individuals with ARID1B-RDView in own windowSystem/ConcernEvaluationFrequency

Constitutional

Growth parametersAt each visit

Eyes

Ophthalmologic evalAnnually

ENT

Audiologic evalAs required

Musculoskeletal

Clinical assessment for scoliosisAnnually, 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

Miscellaneous/Other

Monitor developmental progress & educational needs.Annually1. 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).

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

Therapies Under InvestigationCelen 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 InheritanceARID1B-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 TestingOnce 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.

Mode of InheritanceARID1B-related disorder (ARID1B-RD) is inherited in an autosomal dominant manner.

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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 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.ARID1B-Related Disorder: Genes and DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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) View in own window 135900COFFIN-SIRIS SYNDROME 1; CSS1

614556AT-RICH INTERACTION DOMAIN-CONTAINING PROTEIN 1B; ARID1BMolecular PathogenesisThe 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 GeneReviewView in own windowDNA Nucleotide ChangePredicted Protein ChangeReference Sequencesc.850C>Tp.Gln284Ter

NM_020732.3

NP_065783.3

c.1259delAp.Asn420IlefsTer10Variants 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 TumorsBoth 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.

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AT-rich interactive domain-containing protein 1B

ARID1B @ LOVD

ARID1B

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Table B.OMIM Entries for ARID1B-Related Disorder (View All in OMIM) View in own window

135900COFFIN-SIRIS SYNDROME 1; CSS1

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

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Chapter NotesAuthor NotesDr 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 gro.dkhc@onagreV.ahtnamaS.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 History23 May 2019 (ma) Review posted live26 July 2018 (sv, gs) Original submission

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