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BCL11A-Related Intellectual Disability

Synonyms: Dias-Logan Syndrome, Intellectual Developmental Disorder with Persistence of Fetal Hemoglobin

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Summary

Clinical characteristics

BCL11A-related intellectual disability (*BCL11A*-ID) is characterized by developmental delay / intellectual disability of variable degree, neonatal hypotonia, microcephaly, distinctive but variable facial characteristics, behavior problems, and asymptomatic persistence of fetal hemoglobin. Growth delay, seizures, and autism spectrum disorder have also been reported in some affected individuals.

Diagnosis/testing

The diagnosis of *BCL11A*-ID is established in a proband with suggestive clinical and laboratory findings and a heterozygous pathogenic variant in *BCL11A* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment is primarily supportive and dictated by symptoms. Standard anti-seizure medication for seizure disorder; standard treatment for abnormal vision and/or strabismus, sleep disturbance, scoliosis, joint laxity, gastroesophageal reflux disease (GERD), constipation, and developmental issues.

Surveillance: Assessment of growth parameters, feeding difficulties, GERD, constipation, scoliosis, developmental progress, and behavior at each visit. Monitor seizures as clinically indicated. Assessment of vision and eye alignment as needed.

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Genetic counseling

BCL11A-ID is inherited in an autosomal dominant manner; however, most affected individuals have the disorder as the result of a *de novo BCL11A* pathogenic variant. Once the *BCL11A* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Formal clinical diagnostic criteria for *BCL11A*-related intellectual disability (*BCL11A*-ID) have not been established.

Suggestive Findings

BCL11A-ID **should be considered** in individuals presenting with the following clinical, laboratory, and neuroimaging findings.

Clinical findings

- Mild-to-severe developmental delay or intellectual disability; AND
- Any of the following features presenting in infancy or childhood:
  - Microcephaly
  - Craniofacial features including flat midface, small nares, thin vermilion of the upper lip and everted vermilion of the lower lip [Dias et al 2016] (see Figure 1)
  - External ear anomalies
  - Strabismus
  - Blue sclerae in infancy
  - Generalized hypotonia of infancy
  - Infant feeding difficulties
  - Language delay and/or dyspraxia
  - Joint laxity
  - Behavioral concerns (repetitive behavior, autism spectrum disorder)
  - Sleep disturbance
  - Seizures

Laboratory findings. Persistence of fetal hemoglobin detected by standardized laboratory methods, such as hemoglobin HPLC (high-performance liquid chromatography) or hemoglobin electrophoresis

Nonspecific brain MRI findings. Hypoplasia of the corpus callosum, hypoplasia of the cerebellar vermis, or white matter abnormalities

Establishing the Diagnosis

The diagnosis of *BCL11A*-ID **is established** in a proband with suggestive findings by identification of a heterozygous pathogenic (or likely pathogenic) variant in *BCL11A* on 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 in a child with developmental delay or an older individual with intellectual disability typically begins with chromosomal microarray analysis (CMA). If CMA is not diagnostic, the next step is typically either a multigene panel or exome sequencing.

Note: Single-gene testing (sequence analysis of *BCL11A*, followed by gene-targeted deletion/duplication analysis) may be considered in individuals with nonfamilial persistence of fetal hemoglobin identified by hematologic assays.

CMA uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *BCL11A*) that cannot be detected by sequence analysis. See Genetically Related Disorders for discussion of individuals who have larger deletions or duplications of the 2p15-p16.1 region, which includes *BCL11A* and surrounding genes.

An intellectual disability (ID) multigene panel that includes *BCL11A* 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*. Of note, given the rarity of *BCL11A*-ID, some panels for ID may not include this gene. (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.

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 the advantage that all rare genes recently identified as causing ID are represented, while some newly identified ID genes may not be included on a multigene panel.

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 *BCL11A*-Related Intellectual Disability

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
BCL11A	Sequence analysis [3]	21/27 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]
	CMA [7, 8]	6/27 [9]

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. Firth et al [2009], De Rubeis et al [2014], Iossifov et al [2014], Dias el al [2016], Cai et al [2017], Landrum et al [2018], Peron et al [2018], Soblet et al [2018], Yoshida et al [2018]
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. No data on detection rate of gene-targeted deletion/duplication analysis are available.
7. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *BCL11A*) 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 2p15-p16.1 region. CMA designs in current clinical use target the 2p15-p16.2 region.
8. Includes partial or whole-gene deletions of *BCL11A* without disrupting other protein-coding genes (excludes contiguous gene deletion syndromes, namely 2p15-16.1 microdeletion syndrome).
9. Firth et al [2009], Peter et al [2014], Balci et al [2015], Peron et al [2018]

Clinical Characteristics

Clinical Description

BCL11A-related intellectual disability (*BCL11A*-ID) is characterized by developmental delay / intellectual disability of variable degree (from mild to severe, but most frequently in the moderate range), neonatal hypotonia, microcephaly, distinctive but variable facial characteristics, behavior problems, and asymptomatic persistence of fetal hemoglobin (HbF). Growth delay, seizures, and autism spectrum disorder have also been reported in some affected individuals.

To date, 27 individuals have been reported with a pathogenic (or likely pathogenic) variant in *BCL11A* [Firth et al 2009, De Rubeis et al 2014, Iossifov et al 2014, Peter et al 2014, Balci et al 2015, Deciphering Developmental Disorders Study Group 2015, Dias et al 2016, Cai et al 2017, Landrum et al 2018, Peron et al 2018, Soblet et al 2018, Yoshida et al 2018]; the authors are aware of additional affected individuals. The following description of the phenotypic features associated with this condition is based on the reported cases and the authors' experience.

Developmental delay (DD) and intellectual disability (ID). All individuals with *BCL11A*-ID present with DD. Speech delay is always present, and gross and fine motor delays are usually seen as well. All affected individuals have ID, with variable levels ranging from mild to severe.

Other neurodevelopmental features:

- Neonatal hypotonia is seen in the majority of affected individuals, and may result in delayed acquisition of motor milestones (average age at walking: ~30 months). Hypotonia may resolve in childhood, though in some it persists into adolescence.
- Infant feeding difficulties are occasionally present and thought to be associated with central hypotonia as opposed to primary dysphagia.

- Ataxia and/or broad-based gait has been reported in three affected individuals.

Epilepsy has been reported in 5/25 affected individuals [Cai et al 2017, Peron et al 2018, Yoshida et al 2018].

- Various types of seizures have been described (including myoclonic, tonic, and atonic seizures; absence seizures; and spasms) without a common electroclinical pattern.
- Age at seizure onset among individuals reported in the literature varied from two months to three years.
- Seizures are usually controlled with single or combined (2) anti-seizure medication(s). Three reported individuals had seizures that were drug resistant [Peron et al 2018, Yoshida et al 2018] (see also Genetically Related Disorders).

Behavior problems. Most individuals reported have presented with behavior problems [Dias et al 2016].

- Autism spectrum disorder has been described in a subset of affected individuals [De Rubeis et al 2014, Iossifov et al 2014, Dias et al 2016, Cai et al 2017].
- Others exhibit autistic-like traits, such as repetitive behaviors.
- Other behavior problems:
  - Attention deficit and self-injurious behaviors have been reported in one person each.
  - Sleep disturbances have been reported in three people.

Hematologic. A key manifestation of *BCL11A*-ID is the persistence of fetal hemoglobin (HbF) in affected individuals. In individuals from the general population, HbF is high in the second and third trimester of gestation and in the neonatal period, physiologically decreasing after birth and within the first 12 months of life (with a transition to adult hemoglobin). Therefore, age-specific reference values for hemoglobin variants should be used up to age 24 months.

- Elevated HbF (% of total hemoglobin) has been identified in all affected individuals who have been tested [Dias et al 2016, Cai et al 2017, Peron et al 2018, Soblet et al 2018, Yoshida et al 2018].
- Persistence of HbF is not known to cause symptoms, and no affected individuals with hematologic problems have been reported thus far.

Growth. Intrauterine growth restriction (IUGR) and postnatal growth delay are occasionally present [Dias et al 2016, Cai et al 2017, Yoshida et al 2018], but more than half of the affected individuals have normal growth parameters.

Microcephaly (-2 to -3.5 SD) is seen in approximately half of affected individuals [Dias et al 2016, Cai et al 2017, Soblet et al 2018, Yoshida et al 2018].

Eyes. Strabismus has been reported in 10/21 affected individuals [Dias et al 2016, Cai et al 2017, Peron et al 2018] but no other vision or hearing impairments have been documented. Some affected children with pathogenic loss-of-function variants exhibit blue sclerae in infancy (see Genotype-Phenotype Correlations) [Dias et al 2016].

Neuroimaging. Brain MRI is normal in only a minority of affected individuals; however, most abnormal brain MRI findings are mild and/or nonspecific.

- Structural anomalies of the central nervous system can be present, including hypoplasia of the corpus callosum and/or cerebellar vermis [Dias et al 2016, Peron et al 2018].
- White matter abnormalities, including reduced white matter volume, have been reported [Dias et al 2016].

Other associated features

- **Musculoskeletal features**
  - Joint hypermobility is a common finding (>80%) in individuals with *BCL11A*-ID.

- Scoliosis has occasionally been reported [Dias et al 2016, Cai et al 2017].
- **Gastrointestinal problems.** Infantile feeding problems with poor weight gain, gastroesophageal reflux disease (GERD), and constipation have occasionally been reported [Dias et al 2016].
- **Craniofacial features.** No specific dysmorphic features have been observed. If present, dysmorphic features are nonspecific.
  - Affected individuals frequently have flat midface, full cheeks, small nares, thin vermilion of the upper lip, and full or everted vermilion of the lower lip [Dias et al 2016, Peron et al 2018].
  - A subset of individuals have external ear anomalies, including overfolded helix, everted ears, and small earlobe [Liang et al 2009, Dias et al 2016, Soblet et al 2018].

Prognosis. *BCL11A*-ID is a congenital disorder without known regression of skills. Life span and typical cause of death are unknown due to the limited number of individuals reported to date and ascertainment bias toward diagnosis in childhood. However, the lack of life-limiting congenital anomalies in affected individuals suggests a favorable long-term prognosis with appropriate support. The authors are aware of two affected individuals who are alive and well at 19 and 23 years, respectively [Authors, personal observation], 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

With the limited number of affected individuals reported to date, no statistically significant genotype-phenotype correlations can be made. However, certain features described to date have been seen only in individuals with loss-of-function (nonsense and frameshift) variants [Dias et al 2016, Yoshida et al 2018]:

- Blue sclerae in infancy
- Epicanthal folds
- Micrognathia or retrognathia
- Short stature (mild)

Prevalence

The prevalence of *BCL11A*-ID is unknown. To date, 27 affected individuals have been reported in the literature.

Genetically Related (Allelic) Disorders

No disease phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *BCL11A*.

2p15p16.1 deletion syndrome was first reported by Rajcan-Separovic et al [2007] in individuals with intellectual disability, autism spectrum disorder, progressive microcephaly, brain anomalies, renal anomalies, visual defects, neuromotor deficits, and distinctive dysmorphic features. Subsequent reports of individuals with variably sized deletions and shared features have led to the delineation of the contiguous gene deletion syndrome. Reports of people with speech impairment and/or intellectual disability with deletions encompassing *BCL11A* only [Peter et al 2014] or including only adjacent non-protein coding genes [Balci et al 2015] suggest that *BCL11A* has an essential role in the phenotype.

Individuals with larger deletions of 2p15p16.1 encompassing *BCL11A* and multiple adjacent genes typically display a more severe phenotype compared to those with deletions encompassing *BCL11A* and only non-protein-coding adjacent regions.

- Those with larger deletions typically have more severe structural brain defects, including cortical dysplasia and/or atrophy [Rajcan-Separovic et al 2007, Bagheri et al 2016, Lévy et al 2017], abnormalities of the

corpus callosum [Hucthagowder et al 2012, Piccione et al 2012, Florisson et al 2013, Jorgez et al 2014, Bagheri et al 2016, Shimbo et al 2017], cerebellar and/or pontine hypoplasia [Florisson et al 2013, Balci et al 2015, Shimbo et al 2017], and optic nerve anomalies [Rajcan-Separovic et al 2007, de Leeuw et al 2008, Liang et al 2009].

- Congenital malformations (genitourinary anomalies and/or congenital heart defects) have only been identified in individuals with contiguous gene deletions involving *BCL11A* and adjacent genes [de Leeuw et al 2008, Hucthagowder et al 2012, Piccione et al 2012, Jorgez et al 2014, Bagheri et al 2016].
- One affected individual with a 2.5-Mb deletion of 2p15p16.1 encompassing multiple adjacent genes was reported to have intractable epilepsy [Hucthagowder et al 2012].

2p16.1p15 duplication encompassing *BCL11A* may result in delayed developmental milestones, attention deficit, and motor dyspraxia. Height and head circumference were within normal range [Mimouni-Bloch et al 2015, Pavone et al 2019].

Sporadic tumors (including ovarian clear cell carcinoma, lung cancer, melanoma, and hematologic malignancies [Kadoch et al 2013]) occurring as single tumors in the absence of any other findings of *BCL11A*-related intellectual disability (*BCL11A*-ID) frequently harbor somatic variants in *BCL11A* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. Currently there is no evidence that individuals with *BCL11A*-ID are at increased risk of developing cancer, and no specific cancer screening guidelines for individuals with *BCL11A*-ID have been published.

Differential Diagnosis

Table 2 describes specific conditions that may have features that overlap with *BCL11A*-related intellectual disability (*BCL11A*-ID).

Note: The phenotypic features associated with *BCL11A*-ID are generally not sufficient 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.

Table 2. Selected Disorders to Consider in the Differential Diagnosis of *BCL11A*-Related Intellectual Disability

DiffDx Disorder	Gene(s)	MOI	Key Clinical Features of DiffDx Disorder	
			Overlapping w/*BCL11A*-ID	Distinguishing from *BCL11A*-ID
KANSL1-related intellectual disability syndrome	*KANSL1*	AD	ID, infant hypotonia, joint hypermobility, everted lower lip, strabismus	• Facial features incl blepharophimosis & bulbous or tubular nose • More frequent congenital anomalies (renal & urogenital anomalies, heart defects)
Alpha-thalassemia X-linked intellectual disability syndrome (ATRX)	*ATRX*	XL	• ID, hypotonia, small head circumference, everted lower lip, short nose, short stature • Facial gestalt in a subset of those w/*BCL11A*-ID resembles that of ATRX. [1]	• Craniofacial features (telecanthus, tented vermilion of upper lip, progressive coarsening of facial features), genital abnormalities, & skeletal abnormalities • ID is typically severe to profound in boys (heterozygous females w/craniofacial features, ID, & growth restriction have been described). [2] • Alpha-thalassemia (in ~85% of individuals)

AD = autosomal dominant; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Peron et al [2018]
2. Badens et al [2006]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *BCL11A*-ID, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *BCL11A*-Related Intellectual Disability

System/Concern	Evaluation	Comment
Neurologic	Assessment for hypotonia & signs/symptoms of seizures	• EEG if seizures suspected • Consider brain MRI to detect brain abnormalities.
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >18 mos: screen for behavior problems incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Constitutional	Weight, length/height, & head circumference	Assess for evidence of short stature, failure to thrive, microcephaly.
Eyes	Ophthalmologic eval	Assess for strabismus, visual acuity.
Musculoskeletal	Clinical eval for scoliosis	Consider radiographic scoliosis survey based on clinical suspicion & referral to orthopedic surgeon as appropriate.
	Clinical eval for joint laxity	Consider referral to rehab specialist & OT.
Gastrointestinal/ Feeding	Assessment of feeding problems in infancy & for GERD at any age	Referral to feeding therapist if feeding problems identified
Hematologic	Hemoglobin HPLC or hemoglobin electrophoresis	Expect ↑ HbF.
Miscellaneous/ Other	Developmental assessment	• Incl eval of motor, speech &language, general cognitive, & vocational skills • Refer to speech & rehab therapy, PT, & OT as appropriate.
	Consultation w/clinical geneticist &/or genetic counselor	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disorder; HbF = fetal hemoglobin; HPLC = high-performance liquid chromatography; OT = occupational therapist; PT = physical therapist

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *BCL11A*-Related Intellectual Disability

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASMs by experienced neurologist [1]	Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.
Sleep disturbances	Standard mgmt	Consider melatonin.
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	
Scoliosis	Standard mgmt as recommended by orthopedist	
Joint laxity	PT &/or OT	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
GERD &/or constipation	Referral to (pediatric) gastroenterologist	Symptomatic mgmt to enhance nutritional intake & hydration

ASM = anti-seizure medication; GERD = gastroesophageal reflux disorder; OT = occupational therapy; PT = physical therapy
1. Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

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.

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.

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, guardianship, 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, 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. Assuming that 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 as a result of poor oral motor control.

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 Concerns

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 and/or a psychiatrist may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

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

Surveillance

Table 5. Recommended Surveillance for Individuals with *BCL11A*-Related Intellectual Disability

System/Concern	Evaluation	Frequency
Neurologic	Monitor those w/seizures as clinically indicated.	As clinically indicated
Psychiatric	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	Monitor clinically at each visit; refer for eval as indicated.
Constitutional	Weight, length/height, & head circumference measurements plotted on standard growth chart	At each visit
Eyes	Ophthalmologic eval	As clinically indicated
Musculoskeletal	Monitor for scoliosis. Orthopedic eval as indicated.	Monitor clinically at each visit.
Gastrointestinal	Assessment of feeding difficulties, GERD, constipation	At each visit (particularly in infancy)
Miscellaneous/ Other	Monitor developmental progress & educational needs.	At each visit

GERD = gastroesophageal reflux disorder

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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

BCL11A-related intellectual disability (*BCL11A*-ID) is inherited in an autosomal dominant manner and is typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Almost all probands reported to date with *BCL11A*-ID whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo BCL11A* pathogenic variant.
- One individual diagnosed with *BCL11A*-ID inherited a pathogenic variant from a heterozygous parent; the clinical status of the heterozygous parent is unknown [Firth et al 2009].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *BCL11A* 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. Although theoretically possible, no instances of germline mosaicism have been reported to date.
- Theoretically, if the parent is the individual in whom the *BCL11A* 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 is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%. It is not possible to reliably predict clinical severity in sibs who inherit the pathogenic variant.
- If the *BCL11A* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with a *BCL11A*-ID has a 50% chance of inheriting the *BCL11A* pathogenic variant. It is not possible to reliably predict clinical severity in offspring who inherit the 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 *BCL11A* pathogenic variant, the parent's family members may be at risk. However, given that almost all probands with *BCL11A*-ID reported to date have the disorder as a result of a *de novo BCL11A* pathogenic variant, the risk to other family members is presumed to be low.

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 *BCL11A* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

Resources

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

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **MedlinePlus**
  Intellectual Disability
- **Rare Disease Foundation (RDF)**
  4500 Oak Street
  Room C234
  Vancouver British Columbia V6H 3N1
  Canada
  Phone: 866-348-6677
  Email: families@rarediseasefoundation.org
  www.rarediseasefoundation.org
- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  rarechromo.org
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net
- **Human Disease Gene Website Series - Registry**
  BCL11A

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. BCL11A-Related Intellectual Disability: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BCL11A	2p16.1	B-cell lymphoma/ leukemia 11A	BCL11A @ LOVD	BCL11A	BCL11A

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 BCL11A-Related Intellectual Disability (View All in OMIM)

606557	BAF CHROMATIN REMODELING COMPLEX SUBUNIT BCL11A; BCL11A
617101	INTELLECTUAL DEVELOPMENTAL DISORDER WITH PERSISTENCE OF FETAL HEMOGLOBIN

Molecular Pathogenesis

BCL11A is a COUP-TF-interacting transcription factor that associates with the *B*RG1- and BRM-*a*ssociated *f*actor (BAF) swi/snf chromatin remodeling complex [Kadoch et al 2013]. Pathogenic variants in genes encoding the BAF complex are a recurrent cause of intellectual disability [Kosho et al 2014]. BCL11A is highly expressed in developing mouse brain and in postnatal cortex, hippocampus and caudate nucleus, and in B-lymphocytes. BCL11A is expressed in fetal brain [Nowakowski et al 2017], and in adult brain is restricted to neurons [Uhlén et al 2015]. In addition, BCL11A is a transcriptional repressor of fetal hemoglobin (HbF), playing an important role in globin switching [Bauer & Orkin 2011, Liu et al 2018]. In humans, BCL11A is highly expressed in hematopoietic cells, particularly in B lymphoid and erythroid lineages.

Multiple alternatively spliced transcript variants encoding different isoforms have been identified for *BCL11A*. BCL11A isoforms share a conserved N terminus and at least one Krüppel C2H2-type zinc finger. The three major BCL11A isoforms, -XL, -L, and -S, encode 835, 773, and 243 amino acid peptides, respectively.

Mechanism of disease causation. *BCL11A* causes disease through a loss-of-function (LOF) mechanism [Dias et al 2016]. Nonsense and frameshift variants as well as partial or whole-gene deletions have been reported. All LOF variants are predicted to undergo nonsense-mediated decay with loss of isoforms X and XL.

Pathogenic missense variants cluster in the N-terminal region of BCL11A. This region is required for localization to the nucleus, via two C2H2 zinc finger domains. N-terminal missense variants affecting BCL11A localization, dimerization, and transcriptional activity, with putative hypomorphic function, also result in a loss-of-function phenotype.

Heterozygous knockout mice have decreased brain size and aberrant brain transcriptional profiles; they present impaired social memory and decreased social interaction [Dias et al 2016]. BCL11A is associated with neocortical development, specifically the neuronal switch from multipolar to bipolar morphology. BCL11A-deficient neurons have been demonstrated to show impaired radial migration and overexpression of Semac3c [Wiegreffe et al 2015].

BCL11A interacts with calcium/calmodulin-dependent serine kinase (*CASK*), a gene implicated in X-linked intellectual disability (see *CASK*-Related Disorders). In a cultured model of hippocampal neurons, CASK enhanced the ability of BCL11A to restrict axon outgrowth and branching [Kuo et al 2010]. CASK interacts with the TBR1 transcription factor, which is also highly expressed in deep layers of cortex and is co-located with BCL11A. Heterozygous variants cause intellectual developmental disorder with autism and speech delay (OMIM 604616). BCL11A regulates the expression of TBR1 in the cortex with residues 629-773 appearing crucial in the interaction between TBR1 and BCL11A [Cánovas et al 2015].

***BCL11A*-specific laboratory considerations.** Individuals with *BCL11A*-related intellectual disability demonstrate persistence of HbF, with significantly higher levels of HbF than age-matched controls. HbF measurement may be performed to assist in the interpretation of variants of unknown significance.

Chapter Notes

Author Notes

The authors of this *GeneReview* clinically follow individuals with *BCL11A*-related intellectual disability and study the condition.

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