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Primrose Syndrome

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Summary

Clinical characteristics

Primrose syndrome is characterized by macrocephaly, hypotonia, developmental delay, intellectual disability with expressive speech delay, behavioral issues, a recognizable facial phenotype, radiographic features, and altered glucose metabolism. Additional features seen in adults: sparse body hair, distal muscle wasting, and contractures. Characteristic craniofacial features include brachycephaly, high anterior hairline, deeply set eyes, ptosis, downslanted palpebral fissures, high palate with torus palatinus, broad jaw, and large ears with small or absent lobes. Radiographic features include calcification of the external ear cartilage, multiple wormian bones, platybasia, bathrocephaly, slender bones with exaggerated metaphyseal flaring, mild epiphyseal dysplasia, and spondylar dysplasia. Additional features include hearing impairment, ocular anomalies, cryptorchidism, and nonspecific findings on brain MRI.

Diagnosis/testing

The diagnosis of Primrose syndrome is established in a proband with characteristic features and a heterozygous pathogenic variant in *ZBTB20* identified on molecular genetic testing.

Management

Treatment: Individualized educational program, speech therapy, physical therapy, and occupational therapy as indicated; treatment of behavioral concerns; applied behavioral analysis for autism; standard treatment for seizures, musculoskeletal issues, hearing loss, and thyroid dysfunction; oral hypoglycemics or insulin as needed for diabetes.

Surveillance: Monitor growth and development every six months; speech and developmental assessment every six months; assess for behavioral issues, seizures, and musculoskeletal complications at each visit; brain stem

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evoked response audiometry annually; annual fasting and postprandial blood glucose, hemoglobin A1c, and assessment for signs and symptoms of thyroid dysfunction.

Genetic counseling

Primrose syndrome is an autosomal dominant disorder. All probands reported to date with Primrose syndrome whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo ZBTB20* pathogenic variant. If a parent of the proband is known to have the *ZBTB20* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%. Once the *ZBTB20* 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

No consensus clinical diagnostic criteria for Primrose syndrome have been published.

Suggestive Findings

Primrose syndrome **should be suspected** in individuals with the following clinical, laboratory, and imaging findings.

Clinical findings

- Developmental delay with speech delay
- Intellectual disability
- Behavioral issues (e.g., autism spectrum disorder, attention-deficit/hyperactivity disorder)
- Typically postnatal-onset macrocephaly (macrocephaly at birth in <50%)
- Characteristic craniofacial features (brachycephaly, high anterior hairline, sparse eyebrows, deeply set eyes, downslanted palpebral fissures, ptosis, high palate, torus palatinus, broad jaw, and large ears with small or absent lobes; see Figure 1)
- Hearing loss
- Ocular anomalies (e.g., cataracts, strabismus, glaucoma)
- Cryptorchidism
- Distal muscle atrophy and contractures
- Sparse body hair

Laboratory findings

- Abnormal plasma acylcarnitine profile (increased levels of C2, C4OH, C5OH, C6OH, C14, and C14:2).
- Abnormal urine organic acids (mildly elevated dicarboxylic acids (adipic, sebacic, and/or suberic acid); elevated ethylmalonic acid and glutaric acid)
- Abnormal glucose metabolic profile (e.g., elevated fasting glucose, hemoglobin A1c, and glucose levels on oral glucose tolerance testing)
- Increased serum alphafeto protein levels

Imaging findings

- Calcification of the external ear cartilage on head CT; cerebral calcification (mainly of the basal ganglia) may also occur.
- Radiographs show unique skeletal manifestations: multiple wormian bones, platybasia, bathrocephaly, bitemporal bossing, slender bones with exaggerated metaphyseal flaring, mild epiphyseal dysplasia, and spondylar dysplasia.

- Brain MRI may show agenesis/dysgenesis of the corpus callosum, mild cerebral atrophy, and delayed myelination.

Establishing the Diagnosis

The diagnosis of Primrose syndrome **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *ZBTB20* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP 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 [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *ZBTB20* variant of uncertain significance does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in suggestive findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with developmental delay and/or macrocephaly are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic, laboratory, and imaging findings suggest the diagnosis of Primrose syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ZBTB20* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **An intellectual disability multigene panel** that includes *ZBTB20* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by developmental delay and macrocephaly, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Figure 1. Male age two years with Primrose syndrome

Note macrocephaly, high anterior hairline, sparse eyebrows, deeply set eyes, large prominent ears, and genu valgum.

Modified from Arora et al [2020], Figure 1

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 Primrose Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
ZBTB20	Sequence analysis [4]	>99% [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Additional individuals [Juven et al 2020] with contiguous gene deletions (not included in these calculations) have been reported (see Genetically Related Disorders).
4. 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.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. 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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Juven et al [2020]) may not be detected by these methods.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Primrose syndrome is a rare disorder characterized by macrocephaly with developmental delay, intellectual disability, behavioral issues, a recognizable facial phenotype, altered glucose metabolism, hearing loss, ocular

anomalies, cryptorchidism, and unique imaging findings including calcification of the ear cartilage [Arora et al 2020, Melis et al 2020].

To date, 52 individuals have been identified with a pathogenic variant in *ZBTB20* [Arora et al 2020, Melis et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Primrose Syndrome: Frequency of Select Features

Feature		# (%) of Persons w/Feature
Characteristic facial features	High anterior hairline	25/32 (78%)
	Ptosis	23/31 (74%)
	Large ears	27/39 (69%)
	Downslanted palpebral fissures	21/37 (57%)
	High palate	12/26 (46%)
	Broad jaw	19/31 (61%)
	Torus palatinus	10/30 (33%)
Neurologic manifestations	Intellectual disability	52/52 (100%)
	Hearing loss	36/43 (83%)
	Hypotonia	28/37 (76%)
	Autism	29/39 (74%)
	Dysgenesis of the corpus callosum	17/37 (46%)
	Flexion contractures	15/34 (44%)
	Ataxia	10/26 (38%)
	Distal muscle wasting	14/36 (38%)
	Seizures	7/32 (22%)
	Delayed myelination	6/37 (16%)
	Brain calcification	5/37 (14%)
Miscellaneous	Sparse body hair	14/15 (93%)
	Diabetes	11/28 (39%)
	Delayed puberty	5/14 (36%)
	Strabismus	12/34 (35%)
	Cataract	7/33 (21%)

Growth. Although historically described as an overgrowth syndrome, length at birth >+2SD was only reported in 1/22 newborns, height was >+2SD in 3/25 children (12%), and height was >+2SD in 0/9 adults [Melis et al 2020].

The majority of affected individuals have macrocephaly. Head circumference >+2SD at birth was seen in 9/22 newborns, 21/26 children (81%), and 8/12 adults (67%).

Characteristic craniofacial features become evident in early childhood and include brachycephaly, high anterior hairline, deeply set eyes, ptosis, downslanted palpebral fissures, high palate with torus palatinus, broad jaw, and large ears with small or absent lobes.

Motor development is impaired by childhood hypotonia, but almost all individuals achieve independent walking by age two to three years. Delayed motor development is found in almost all individuals [Cleaver et al 2019].

Cognitive development. Intellectual disability (ID) has been reported in all individuals. Most individuals have moderate-to-severe ID, while approximately 15% have mild ID. Severe expressive speech delay is common with minimal development of expressive speech in most individuals. Most individuals have better receptive language development; thus, sign language or use of pictograms is of value to many affected individuals [Battisti et al 2002, Carvalho & Speck-Martins 2011, Melis et al 2020].

Behavior abnormalities include attention-deficit/hyperactivity disorder, temper tantrums, self-injurious behavior, sleep disturbances, and autism spectrum disorder [Stellacci et al 2018, Melis et al 2020].

Seizures have been identified in 22% of individuals. Focal seizures were clinically described in two individuals and were controlled with anti-seizure medication. In the remaining individuals with seizures, the type of seizure was not reported.

Progressive musculoskeletal and motor involvement. Distal muscle wasting is a common feature with lower limbs more affected than the upper limbs. Flexion contractures are seen in the knees and the elbows. Genu valgum and/or genu varum have been reported. Dysplastic hips were also reported by Melis et al [2020]. This results in difficultly walking and eventually wheelchair dependence. Progressive ataxia is rare and is associated with spasticity.

Hearing loss is common (21/27 children and 12/13 adults) and is prelingual. Hearing loss is generally mild to moderate sensorineural hearing loss, although a mixed type of hearing loss was reported in one individual who had recurrent ear infections.

Brain imaging findings include agenesis/dysgenesis of the corpus callosum, mild cerebral atrophy, delayed myelination, and cerebral calcification (mainly involving the basal ganglia).

Endocrine manifestations

- Individuals with Primrose syndrome have disrupted glucose metabolism and may develop diabetes mellitus requiring oral hypoglycemics and/or insulin therapy in adulthood.
- Rarely, congenital hypothyroidism has been reported [Mattioli et al 2016]. Three instances of childhood-onset hypothyroidism have also been reported.
- Growth hormone deficiency (2 individuals)
- Delayed puberty (average onset of puberty: age 16 years)
- Sparse body hair is present in both males and females

Cryptorchidism also has been reported in half of all affected males [Melis et al 2020].

Ocular anomalies. Cataracts may be congenital or may appear later in adulthood; strabismus and glaucoma are also seen. Microphthalmia was reported in two individuals.

Other

- Pulmonary artery stenosis was described in an adult [Melis et al 2020].
- IgG2 deficiency with recurrent otitis media and testicular cancer was diagnosed at age 27 years in one individual [Yamamoto-Shimojima et al 2020].

Life expectancy. Longitudinal data are insufficient to determine life expectancy; the oldest reported individual is age 53 years [Dalal et al 2010].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

The penetrance is 100%.

Nomenclature

The authors of this *GeneReview* suggest the term "intellectual disability-cataracts-calcified pinnae-macrocephaly syndrome" as an alternative name for Primrose syndrome.

Prevalence

To date, approximately 52 individuals with Primrose syndrome have been identified.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with a heterozygous germline pathogenic variant in *ZBTB20*.

3q13.31 contiguous deletions that include *ZBTB20* have been reported in several individuals [Shuvarikov et al 2013, Wiśniowiecka-Kowalnik et al 2013, Rasmussen et al 2014, Juven et al 2020]. See Table 3 for overlapping and distinguishing features with Primrose syndrome.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Primrose Syndrome

Gene(s) / Genetic Mechanism	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/Primrose syndrome	Distinguishing from Primrose syndrome
1.5- to 1.8-Mb duplication at 7q11.23	7q11.23 duplication syndrome	AD	Behavioral & facial phenotype, DD	Congenital malformations, cardiovascular disease, GI issues
3q13.31 deletion [1]	3q13.31 deletion syndrome [2] (OMIM 615433) (See also Genetically Related Disorders.)	AD	Autism; macrocephaly; ear cartilage calcification; diabetes	Distinct facial gestalt; feeding difficulties, ataxia, neuropsychiatric manifestations
FMR1	Fragile X syndrome (See *FMR1* Disorders.)	XL	Autism, DD	Less prominent macrocephaly; distinctive facial features
GPC3 *GPC4*	Simpson-Golabi-Behmel syndrome type 1	XL	Macrocephaly, variable ID	Predominantly affects males; polydactyly, supernumerary nipples, diastasis recti, pectus excavatum; facial gestalt differs
NSD1	Sotos syndrome	AD	Autism, macrocephaly	Prenatal onset of overgrowth; characteristic facial features

Table 3. continued from previous page.

Gene(s) / Genetic Mechanism	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/Primrose syndrome	Distinguishing from Primrose syndrome
PTEN	Cowden syndrome (See *PTEN* Hamartoma Tumor Syndrome.)	AD	Autism, macrocephaly	Vascular malformations, hamartomatous polyps, freckling of glans penis, lipomas, ↑ risk of thyroid & breast cancer
SHANK3 [3]	Phelan-McDermid syndrome	AD [3]	Autism, DD	Large fleshy hands, dysplastic toenails, hyperextensibility, full brow, normal head circumference

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; GI = gastrointestinal; ID = intellectual disability; MOI = mode of inheritance; PDA = patent ductus arteriosus; XL = X-linked

1. Contiguous gene deletion involving *DRD3*, *LSAMP*, and *ZBTB20* (See Genetically Related Disorders.)

2. Juven et al [2020]

3. Phelan-McDermid syndrome, caused by a deletion of 22q13.3 that includes at least a part of *SHANK3* or a pathogenic variant in *SHANK3*, is inherited in an autosomal dominant manner. The deletion may be *de novo* or the result of a balanced translocation in one of the parents; pathogenic variants in *SHANK3* are almost always *de novo*.

Management

No clinical practice guidelines for Primrose syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Primrose syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Primrose Syndrome

System/ Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Speech development	Speech therapy eval	Delayed speech is a major concern & should be addressed early.
Motor development	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Psychiatric/ Behavioral	Neuropsychiatric eval	Persons age >12 mos: screen for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Skeletal	Skeletal survey	To detect genu varus & valgus deformity & plan early correction
Hearing	Brain stem evoked response audiometry pure tone audiogram	

Table 4. continued from previous page.

System/ Concern	Evaluation	Comment
Endocrine	• Blood glucose level incl fasting & post-prandial • Hemoglobin A1c • Oral glucose tolerance test • Serum TSH & free T4	Beginning at age 7 yrs; earlier if clinically indicated
Eyes	Ophthalmology exam for cataract, ptosis, strabismus	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of Primrose syndrome to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent, Facebook; • Social work involvement for parental support; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Primrose Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
DDD/ID	Ages 3-5 yrs: • Developmental preschool w/IEP • Speech therapy, PT, &/or OT for speech & motor delays	All ages: • Consultation w/a developmental pediatrician to ensure involvement of appropriate community, state, & educational agencies & to support parents in maximizing quality of life • Developmental pediatricians can provide assistance w/transition to adulthood.
	Ages 5-21 yrs: • Continue IEP & therapies w/modifications as needed. • Discussion of transition plans incl financial, vocation/employment, & medical arrangements should begin at age 12 yrs.	
ADHD	Therapy as recommended by developmental pediatrician	Most children are hyperactive & medications should be reserved for severe manifestations.
Autism	Standard treatment of ASD, incl applied behavior analysis (ABA) therapy.	ABA therapy is targeted to individual child's behavioral, social, & adaptive strengths & weaknesses; typically performed one on one w/board-certified behavior analyst.
Other behavior disorders	• Supportive therapies as needed • Aggressive, hyperactive & destructive behaviors should be managed by child developmental team & child psychiatrist.	Specific recommendations re type of therapy per developmental pediatrician

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Skeletal	Refer to an orthopedist for surgical correction of deformities as indicated.	
Muscle wasting / Contractures / Ataxia	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Hearing loss	Consider hearing aids & referral to otolaryngologist.	Community hearing services through early intervention or school district
Diabetes	Consider insulin/oral hypoglycemics in consultation w/ endocrinologist.	
Thyroid dysfunction	Treatment per endocrinologist	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ASM = anti-seizure medication; DD/ID = developmental delay / intellectual disability; IEP = individualized education program; OT = occupational therapy; PT = physical therapy

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

Surveillance

Table 6. Recommended Surveillance for Individuals with Primrose Syndrome

System/Concern	Evaluation	Frequency
Growth	Anthropometry, clinical exam	Every 6 mos
Speech & development	• Developmental assessment • Monitor educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	At each visit
Seizures	Monitor those w/seizures as clinically indicated & assess for new seizures.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Hearing	Brain stem evoked response audiometry	Annually or as indicated
Endocrine	• Fasting & postprandial blood glucose • Hemoglobin A1c • Assess for signs/symptoms of thyroid dysfunction.	Annually, starting at age 7 yrs or earlier if indicated

OT = occupational therapy; PT = physical therapy

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

Primrose syndrome is an autosomal dominant disorder.

Risk to Family Members

Parents of a proband

- All probands reported to date with Primrose syndrome whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo ZBTB20* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

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 known to have the *ZBTB20* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *ZBTB20* 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. Individuals with Primrose syndrome are not known to reproduce; however, many are not yet of reproductive age.

Other family members. Given that all probands with Primrose syndrome reported to date have the disorder as a result of a *de novo ZBTB20* 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 *ZBTB20* 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. 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
  aaidd.org
- **MedlinePlus**
  Intellectual Disability

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. Primrose Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ZBTB20	3q13.31	Zinc finger and BTB domain-containing protein 20	ZBTB20	ZBTB20

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 Primrose Syndrome (View All in OMIM)

259050	PRIMROSE SYNDROME; PRIMS
606025	ZINC FINGER- AND BTB DOMAIN-CONTAINING PROTEIN 20; ZBTB20

Molecular Pathogenesis

Primrose syndrome is caused by functional dysregulation of *ZBTB20*, a transcriptional repressor controlling energetic metabolism and developmental programs. *ZBTB20* is a transcriptional repressor involved in the control of brain development and glucose metabolism [Sutherland et al 2009]. This protein belongs to the Broad-complex, Tramtrack, and Bric-a-brac zinc finger (BTB-ZF) family of transcription factors [Zhang et al 2015]. The

N-terminal BTB domain participates in protein-protein interaction, whereas five C2H2 zinc fingers at the C terminus mediate binding to promoters of target genes.

Mechanism of disease causation. A dominant-negative mechanism has been proposed [Stellacci et al 2018].

Chapter Notes

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- 17 June 2021 (ma) Revision: modifications to Suggestive Findings; Clinical Description (Table 2)
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