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Bryant-Li-Bhoj Neurodevelopmental Syndrome

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Summary

Clinical description

Bryant-Li-Bhoj neurodevelopmental syndrome (BRYLIB) is characterized by developmental delay / intellectual disability (typically in the severe range) and nonspecific craniofacial abnormalities. Many affected individuals do not achieve independent sitting, walking, or speaking, although there is a range of developmental outcomes. The presentation is highly variable and can include hypotonia, epilepsy, other neurologic findings (spasticity, loss of developmental milestones, worsening gait, and/or camptocormia – forward flexion of the spine when standing that resolves when lying down), growth abnormalities (most commonly poor growth), craniosynostosis (of any suture), and ocular involvement. Congenital anomalies are rare but can include congenital heart defects, brain malformations, and genitourinary abnormalities in males.

Diagnosis/testing

The diagnosis of BRYLIB is established in a proband with suggestive findings and a heterozygous pathogenic variant in either *H3-3A* (*H3F3A*) or *H3-3B* (*H3F3B*) identified by molecular genetic testing.

Management

Treatment of manifestations: Feeding issues and poor weight gain may benefit from feeding therapy; in individuals with persistent feeding issues, gastrostomy tube may be considered. Standard treatment for developmental delay / intellectual disability, attention-deficit/hyperactivity disorder, autism spectrum disorder, anxiety, epilepsy, spasticity, constipation, craniosynostosis, vision issues, hearing loss, congenital heart defects, undescended testes, and hypothyroidism.

Surveillance: At each visit: measure growth parameters; assess nutrition safety and oral intake; monitor for constipation; assess for new manifestations, such as seizures and changes in tone and/or gait; monitor developmental progress and educational needs; and assess for behavioral issues, such as mobility and self-help skills. Annually or as clinically indicated: ophthalmology evaluation, audiology evaluation, and thyroid function tests.

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Genetics counseling

BRYLIB is expressed in an autosomal dominant manner and typically caused by a *de novo H3-3A* (*H3F3A*) or *H3-3B* (*H3F3B*) pathogenic variant. Therefore, the risk to other family members is presumed to be low. Once an *H3-3A* (*H3F3A*) or *H3-3B* (*H3F3B*) pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Bryant-Li-Bhoj neurodevelopmental syndrome (BRYLIB) have been published.

Suggestive Findings

Bryant-Li-Bhoj neurodevelopmental syndrome (BRYLIB) **should be considered** in individuals with the following clinical and brain MRI findings and family history.

Clinical findings

- Mild-to-profound developmental delay (DD) or intellectual disability (ID), most commonly in the severe range

AND

- Any of the following features:
  - Hypotonia
  - Microcephaly or macrocephaly
  - Craniosynostosis (of any suture) or abnormal head shape, excluding positional plagiocephaly
  - Poor growth with short stature
  - Epilepsy, including generalized myoclonic and tonic seizures, complex partial seizures, and tonic-clonic seizures
  - Spasticity
  - Progressive neurologic features, particularly loss of developmental milestones, worsening seizures, or worsening gait in adulthood
  - Camptocormia (forward flexion of the spine when standing that resolves when lying down; "bent spine") developing in adulthood
  - Ophthalmologic involvement, particularly strabismus or nystagmus
  - Nonspecific dysmorphic features (See Clinical Description.)
  - Minor congenital heart defects, most commonly atrial septal defect
  - Genitourinary anomalies in males, particularly cryptorchidism or retractile testes

Brain MRI findings

- Cortical atrophy
- Small posterior fossa

Family history. Because BRYLIB is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family).

Establishing the Diagnosis

The diagnosis of BRYLIB **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *H3-3A* (*H3F3A*) or *H3-3B* (*H3F3B*), both of which encode histone H3.3, identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *H3-3A* or *H3-3B* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with **chromosomal microarray analysis (CMA)**. Other options include use of a **multigene panel** or **exome sequencing**. Note: Single-gene testing (sequence analysis of *H3-3A* or *H3-3B*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability multigene panel** that includes *H3-3A* or *H3-3B* 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 relative recent description (2020) and rarity of BRYLIB, some panels for intellectual disability may not include these genes. (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.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an intellectual disability multigene panel, with the additional advantage that exome sequencing includes genes recently identified as causing intellectual disability, whereas some multigene panels may not.

  Genome sequencing is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Bryant-Li-Bhoj Neurodevelopmental Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
H3-3A	Sequence analysis [3]	39/39 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

Table 1. continued from previous page.

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
H3-3B	Sequence analysis [3]	18/18 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

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. 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020], Bryant et al [2020], and Okur et al [2021]
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.

Clinical Characteristics

Clinical Description

Bryant-Li-Bhoj neurodevelopmental syndrome (BRYLIB) is characterized by developmental delay / intellectual disability and nonspecific craniofacial abnormalities. The presentation is highly variable and can include hypotonia, epilepsy, other neurologic findings (spasticity, loss of developmental milestones, worsening gait, and/or camptocormia), poor growth, and ocular involvement. Congenital anomalies are rare but can include congenital heart defects and genitourinary abnormalities in males.

To date, 57 unrelated individuals have been identified with a pathogenic variant in *H3-3A* (*H3F3A*) or *H3-3B* (*H3F3B*) [Maver et al 2019, Bryant et al 2020, Okur et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of Bryant-Li-Bhoj Neurodevelopmental Syndrome

Feature	# of Persons w/Feature	Comment
Developmental delay / intellectual disability	56/56 (100%)	Typically in severe range, w/many persons not achieving independent sitting, walking, or speaking
Dysmorphic facial features	50/57 (88%)	Typically nonspecific w/o recognizable pattern
Hypotonia	41/57 (72%)	Hypotonia in infancy is common but often resolves.
Oculomotor abnormalities	30/57 (53%)	Most commonly strabismus, but nystagmus or cortical visual impairment may be present in small minority of persons.
Seizures	27/57 (47%)	Seizures begin in childhood & are variable in type.
Short stature [1]	22/57 (39%)	Occasionally tall stature can be seen instead.
Microcephaly [2]	19/57 (33%)	Macrocephaly can be seen instead.
Craniosynostosis / abnormal head shape	18/57 (32%)	No particular suture
Congenital heart defects	11/57 (19%)	Atrial septal defect is the most common heart defect.
Spasticity	11/57 (19%)	Most commonly in the legs

Table 2. continued from previous page.

Feature	# of Persons w/Feature	Comment
Camptocormia developing in adulthood	3/3 (100%)	All reported adults had new subacute onset of motor issues in 3rd decade of life that generally remains stable after onset.

1. Defined as a length or height that is greater than two standard deviations below the mean for age and sex.
2. Defined as a head circumference that is greater than two standard deviations below the mean for age and sex.

Developmental delay (DD) and intellectual disability (ID). All individuals with BRYLIB have some degree of developmental delay or intellectual disability, typically in the severe range. Affected individuals usually experience delays in both gross motor skills and speech development, but some only experience one or the other. However, there is a wide range of developmental outcomes.

- About 78% of affected individuals have delayed independent sitting (achieved after age 8 months) or have not achieved independent sitting (older than age 8 months and still unable to sit independently). The delay can be profound. The oldest affected individual to achieve independent sitting began sitting independently at age seven years.
- About 93% of affected individuals were either delayed in achieving independent walking (achieved after age 16 months) or have not achieved that milestone (older than age 16 months and not walking independently). This milestone can be achieved very late. One affected individual began independently walking at age eight years.
- About 52% of affected individuals are nonverbal, with an additional 40% experiencing speech delay.

Developmental regression can occur in a minority of affected individuals. Regression is not continuous and is not always associated with seizures. Although developmental regression is typically mild, it can be severe, such that children who were previously able to walk and talk can lose those abilities.

Other neurodevelopmental features

- **Hypotonia** is common but may resolve in some individuals as they age. Occasionally hypotonia can evolve into hypertonia.
- **Infant feeding difficulties** have been described in about 25% of affected individuals. Most are treated with a nasogastric tube or gastrostomy tube.
- **Spasticity** typically involves the legs. Spasticity typically develops in childhood and is associated with either hypotonia or hypertonia. Hypertonia tends to be limited to limbs, while hypotonia can be seen in other parts of the body.
- **Camptocormia.** All reported adults have had a new subacute onset of motor issues in the third decade of life that generally remains stable after onset. This affects their ability to walk independently and has significant impact on their gait.

Epilepsy. About half of individuals with a heterozygous pathogenic variant in *HD-3A* or *H3-3B* have epilepsy.

- Onset is generally in infancy or childhood.
- The type of seizure disorder is variable and includes myoclonic and tonic epilepsy, partial or complex partial seizures, and tonic-clonic seizures.
- Seizure frequency is highly variable, with some individuals having relatively few seizures and others experiencing progressively more frequent seizures or status epilepticus.
- Some individuals with seizures are well controlled on medication while others are refractory to treatment (see Management).

Behavioral issues. Behavioral issues can include autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Happy demeanor and stereotypic flapping of hands has also been noted in some affected individuals.

Growth is impacted in about half of all affected individuals.

- **Weight**
  - Poor weight gain was reported in eight infants.
  - Weight is typically less affected than length/height, with only four individuals being more than two standard deviations below the mean for their age and sex in terms of weight.
  - However, six individuals were at least two standard deviations above the mean for their age and sex.
- **Length/height**
  - Short stature was observed in 22 individuals.
  - Tall stature was seen in three individuals.
- **Head circumference**
  - Congenital microcephaly was seen in 19 individuals.
  - Four individuals had congenital macrocephaly and two had relative macrocephaly.

Craniosynostosis / abnormal head shape (excluding positional plagiocephaly) has been described in about one third of affected individuals. The presentation is variable, and no specific sutures have been identified as being more likely to be involved. Brachycephaly, dolichocephaly, and sagittal craniosynostosis have all been observed.

Ophthalmologic involvement. Strabismus is present in slightly more than one third of affected individuals, and nystagmus is present in a small minority of affected individuals (7%). Difficulty or inability to fixate and/or track was seen in about 9% of affected individuals. Interestingly, 5% have cortical visual impairment.

Neuroimaging. The most common finding on brain MRI is small posterior fossa (72%) [Alves et al 2022], with the next most common finding being cortical malformations (44%), which can include diffuse dysgyria, anterior pachygyria, and/or simplified cortical appearance. Brain malformations do not appear to correlate with any other clinical features, including seizures or craniosynostosis.

- Malformation of the corpus callosum, including hypoplasia and agenesis, can also be seen (28%).
- About 25% of affected individuals show evidence of hypomyelination or delayed myelination.
- Chiari I malformations were seen in 4/18 (22%) of individuals imaged.

Genitourinary abnormalities in males. About 35% of affected males have cryptorchidism. Retractile testes have also been observed.

Other associated features

- **Cardiovascular abnormalities.** Atrial septal defect was seen in about 16% of individuals with BRYLIB.
- **Gastrointestinal issues.** Chronic constipation was reported in 26% of affected individuals.
- **Hearing loss.** A subset of affected individuals have been reported with mild-to-moderate congenital hearing loss. This is thought to be static.
- **Endocrinology.** Hypothyroidism has been reported in a subset of affected individuals.
- **Facial features.** No specific dysmorphic features have been observed. If present, dysmorphic features are nonspecific.

Prognosis. It is unknown whether life span in BRYLIB is abnormal. Based on current data, life span is not limited by this condition, as several adults have been reported. Data on possible progression of behavior abnormalities or neurologic findings are still limited.

Phenotype Correlations by Gene

There is no difference in the phenotype regardless of whether the pathogenic variant is in *H3-3A* or *H3-3B*.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified for either *H3-3A* or *H3-3B*.

Prevalence

Germline pathogenic variants in *H3-3A* and *H3-3B* are rare and have been reported in 57 individuals to date. There are no specific populations with increased risk for these pathogenic variants.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *H3-3A* (*H3F3A*) or *H3-3B* (*H3F3B*).

Sporadic tumors (including giant cell tumor of bone, chondroblastoma, and brain tumors such as glioma and medulloblastoma) occurring as single tumors in the absence of any other findings of Bryant-Li-Bhoj neurodevelopmental syndrome frequently contain a somatic pathogenic variant in *H3-3A* [van der Heijden et al 2022] or *H3-3B* [Behjati et al 2013] that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. Tumors have not been reported in individuals with germline pathogenic variants, including the five adults described in the literature.

Differential Diagnosis

The phenotypic features associated with Bryant-Li-Bhoj neurodevelopmental syndrome are not sufficient to diagnose this condition clinically; all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

No clinical practice guidelines for Bryant-Li-Bhoj neurodevelopmental syndrome (BRYLIB) have been published.

Evaluations Following Initial Diagnosis

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

Table 3. Bryant-Li-Bhoj Neurodevelopmental Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length/height, & head circumference	To evaluate for poor growth, short stature, &/or microcephaly [1]
Neurologic	Neurologic eval, to incl assessment of tone & gait, if ambulatory	• To incl brain MRI • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl ADHD &/or findings suggestive of ASD

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	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)
	Assess for head shape & sutural ridging that would suggest craniosynostosis.	Consider obtaining a head CT w/3D reconstruction to evaluate for craniosynostosis in those w/abnormal head shape.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk. • Assess for signs & symptoms of constipation.
Eyes	Ophthalmology eval	To assess for strabismus, abnormal ocular movement, best corrected visual acuity, refractive errors, & reduced vision that may require referral for subspecialty care &/or low vision services
Ears	Audiology eval	To assess for hearing loss
Cardiovascular	Echocardiogram	To assess for unrecognized congenital heart disease, specifically atrial septal defects
Genitourinary	Testicular exam in males	To assess for cryptorchidism & retractile testes
Endocrine	Thyroid function tests, which may incl TSH, T_4 &/or free T_4	To screen for hypothyroidism
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of BRYLIB to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; BRYLIB = Bryant-Li-Bhoj neurodevelopmental syndrome; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; TSH = thyroid-stimulating hormone; T_4 = thyroxine

1. Some affected individuals may have increased weight, tall stature, or macrocephaly.

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for BRYLIB.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. Bryant-Li-Bhoj Neurodevelopmental Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Some affected persons are refractory to treatment. • Education of parents/caregivers [1]
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Camptocormia	Treatment per PT	Consider eval by neurologist.
Poor weight gain	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Craniosynostosis	Standard treatment per craniofacial specialist	Abnormal head shape in absence of craniosynostosis may benefit from helmet therapy.
Ophthalmologic involvement	By ophthalmologist	Treatment of refractive errors &/or strabismus
	Low vision services	• Children: through early intervention programs &/or school district • Adults: referral to low vision clinic &/or community vision services
Hearing	Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district
Congenital heart defects	Standard treatment per cardiologist	
Undescended testes	Standard treatment per urologist	
Hypothyroidism	Standard treatment per endocrinologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy/therapist; PT = physical therapy/therapist
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.

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 as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

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 for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US 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 and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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 should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory

illnesses or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

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 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 attention-deficit/hyperactivity disorder, when necessary.

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

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with Bryant-Li-Bhoj Neurodevelopmental Syndrome

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for constipation.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures & changes in tone &/or gait, if ambulatory.	
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Behavioral assessment for anxiety, ADHD, & ASD	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	
Eyes/Vision	Ophthalmology eval	Annually, or as clinically indicated

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Ears	Audiology eval	As clinically indicated
Endocrine	Thyroid function tests [1]	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy
1. Which may include thyroid-stimulating hormone, thyroxine (T_4), and/or free T_4

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

Bryant-Li-Bhoj neurodevelopmental syndrome (BRYLIB) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with BRYLIB whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo H3-3A* (*H3F3A*) or *H3-3B* (*H3F3B*) pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - 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 *H3-3A* or *H3-3B* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%. However, to date all known cases have been *de novo*.

- If the *H3-3A* or *H3-3B* 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 BRYLIB are not known to reproduce; however, many are not yet of reproductive age.

Other family members. Given that all probands with BRYLIB reported to date have the disorder as a result of a *de novo H3-3A* or *H3-3B* 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

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo H3-3A* or *H3-3B* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal and preimplantation genetic testing may be considered.

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. Bryant-Li-Bhoj Neurodevelopmental Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
H3-3A	1q42.12	Histone H3.3	H3-3A	H3-3A

Table A. continued from previous page.

H3-3B	17q25.1	Histone H3.3	H3-3B	H3-3B

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 Bryant-Li-Bhoj Neurodevelopmental Syndrome (View All in OMIM)

601058	H3 HISTONE, FAMILY 3B; H3F3B
601128	H3 HISTONE, FAMILY 3A; H3F3A
619720	BRYANT-LI-BHOJ NEURODEVELOPMENTAL SYNDROME 1; BRYLIB1
619721	BRYANT-LI-BHOJ NEURODEVELOPMENTAL SYNDROME 2; BRYLIB2

Molecular Pathogenesis

Histone H3.3 plays an important role in both development (stem cells) and in postmitotic cells, such as neurons [Cox et al 2012, Funk et al 2022]. H3.3 is the only replication-independent form of H3 and therefore is the main form of H3 in postmitotic cells. Histone H3.3 is incorporated into the nucleosome, where it helps provide structure to chromatin and regulate gene expression [Jang et al 2015, Shi et al 2017]. While all reported pathogenic variants in *H3-3A* and *H3-3B* result in the same phenotype, the specific way in which individual pathogenic variants alter H3.3 function varies [Bryant et al 2020, Okur et al 2021]. Pathogenic missense variants can completely abolish binding to chaperone proteins or alter post-translational modifications [Elsässer et al 2012, Trovato et al 2020].

Mechanism of disease causation. The mechanism of disease causation is currently unknown.

***H3-3A* (*H3F3A*)- or *H3-3B* (*H3F3B*)-specific laboratory technical considerations.** Most literature describing variants in *H3-3A* and *H3-3B* or orthologous genes in other organisms do not include the initiating methionine when indicating amino acid changes. This includes Bryant et al [2020]. Care should be taken when using primary literature to determine which numbering nomenclature is being used.

Chapter Notes

Author Notes

Dr Bryant's work focuses on studying the pathogenic mechanism of missense variants in *H3-3A* (*H3F3A*) and *H3-3B* (*H3F3B*). Dr Bhoj's research is focused on discovering new human disease genes, their pathogenic mechanism, and potential treatments.

Revision History

- 28 September 2023 (ma) Review posted live
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