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Bohring-Opitz Syndrome

Synonym: Oberklaid-Danks Syndrome

Bianca Russell, MD,[1] Wen-Hann Tan, BMBS,[2] and John M Graham, Jr, MD, ScD[3]

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Summary

Clinical characteristics

Bohring-Opitz syndrome (BOS) is characterized by distinctive facial features and posture, growth failure, variable but usually severe intellectual disability, and variable anomalies. The facial features may include microcephaly or trigonocephaly / prominent (but not fused) metopic ridge, hypotonic facies with full cheeks, synophrys, glabellar and eyelid nevus flammeus (simplex), prominent globes, widely set eyes, palate anomalies, and micrognathia. The BOS posture, which is most striking in early childhood and often becomes less apparent with age, is characterized by flexion at the elbows with ulnar deviation and flexion of the wrists and metacarpophalangeal joints. Feeding difficulties in early childhood, including cyclic vomiting, have a significant impact on overall health; feeding tends to improve with age. Seizures are common and typically responsive to standard epileptic medications. Minor cardiac anomalies and transient bradycardia and apnea may be present. Affected individuals may experience recurrent infections, which also tend to improve with age. Isolated case reports suggest that individuals with BOS are at greater risk for Wilms tumor than the general population, but large-scale epidemiologic studies have not been conducted.

Diagnosis/testing

The diagnosis of Bohring-Opitz syndrome (BOS) is established in a proband with suggestive clinical features and/or the identification of a constitutional heterozygous pathogenic variant in *ASXL1* by molecular genetic testing.

Management

Treatment of manifestations. Cyclic vomiting may be managed by identification and avoidance of triggers, daily maintenance medication, and early abortive treatment; G-tubes or GJ-tubes may decrease aspiration and improve nutrition. Due to the prevalence of obstructive sleep apnea, polysomnography should be considered. Referral to a craniofacial team should be considered for those with palatal abnormalities, micrognathia, or

Author Affiliations: 1 Cincinnati Children's Hospital, Cincinnati, Ohio; Email: bianca.russell@cchmc.org. 2 Boston Children's Hospital, Boston, Massachusetts; Email: wen-hann.tan@childrens.harvard.edu. 3 Cedars Sinai Medical Center Department of Pediatrics, Harbor-UCLA Medical Center, Emeritus Professor of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, California; Email: john.graham@cshs.org.

obstructive sleep apnea. Tracheostomy may be considered for those with recurrent aspiration who develop secondary lung disease, or in those with severe sleep apnea that is not adequately treated with noninvasive pressure support (e.g., CPAP, BiPAP) or surgical intervention (e.g., mandibular distraction). Standard management is indicated for seizures, congenital heart defects, intellectual disability, myopia, urinary tract infections, urinary retention, and renal stones.

Prevention of primary manifestations. Adequate treatment of severe emesis can decrease hospitalizations, infectious exposures, and ascending aspiration.

Surveillance: Renal ultrasound every three months from birth to age eight to screen for the development of Wilms tumor; frequent monitoring of growth and development; close monitoring of feeding intolerance with a gastroenterology specialist; regular follow up for vision optimization.

Agents/circumstances to avoid. Triggers for vomiting should be avoided and managed with prophylactic antiemetics prior to the exposure.

Genetic counseling

Bohring-Opitz syndrome (BOS) is typically the result of a *de novo* pathogenic variant in *ASXL1*. When BOS results from a *de novo* variant, the risk to the sibs of a proband is small. No individuals with BOS have been reported to reproduce. Although the vast majority of BOS occurs as the result of a *de novo* variant in *ASXL1*, molecular genetic testing can be used to evaluate a pregnancy at theoretically increased risk as a result of constitutional and/or germline mosaicism for an *ASXL1* pathogenic variant in a clinically unaffected parent.

Diagnosis

Prior to the identification of the molecular cause of Bohring-Opitz syndrome (BOS), Hastings et al [2011] had proposed clinical diagnostic criteria for the condition. Ultimately, only five individuals used to develop these clinical diagnostic criteria were molecularly confirmed to have BOS. Therefore, the specificity of these diagnostic criteria is unclear.

Suggestive Findings

Bohring-Opitz syndrome **should be suspected** in individuals with the following clinical features [Bohring et al 1999, Bohring et al 2006, Hastings et al 2011, Magini et al 2012, Russell et al 2015].

Craniofacial appearance (Figure 1)

- Microcephaly or trigonocephaly / prominent (but not necessarily fused) metopic ridge
- Glabellar and eyelid nevus flammeus (simplex) that fades with age
- Prominent globes
- Cleft lip
- Palatal anomalies: cleft palate, high arched palate, or prominent palatine ridges
- Micrognathia and/or retrognathia

Growth and feeding

- Intrauterine growth restriction
- Severe feeding difficulties with chronic emesis that typically improves with age
- Poor postnatal weight gain and linear growth, often exacerbated by severe feeding intolerance

Neurologic

- Developmental delay or intellectual disability in the severe-to-profound range with minimal or complete lack of expressive language
- Seizures

Respiratory. Recurrent infections (commonly respiratory) in early childhood that improve with age

Sleep

- Sleep disturbance
- Obstructive sleep apnea

Ophthalmologic

- High myopia presenting in infancy that may worsen over the first years of life
- Variable optic nerve and retinal anomalies

BOS posture (Figure 2)

- Flexion at the elbows with ulnar deviation and flexion of the wrists and metacarpophalangeal joints; most noticeable in early childhood and usually less obvious with age
- Truncal hypotonia with hypertonia of the extremities

Establishing the Diagnosis

The diagnosis of Bohring-Opitz syndrome **is established** in a proband with suggestive clinical features (see Suggestive Findings) and/or by identification of a constitutional heterozygous pathogenic variant in *ASXL1* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, or **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *ASXL1* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **A multigene panel** that includes *ASXL1* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if single-gene testing (and/or use of a multigene panel that includes *ASXL1*) fails to confirm a diagnosis in an individual with features of Bohring-Opitz syndrome. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

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

Figure 1. Facial features of individuals with BOS at varying ages

A-B. 2 years

C. 18 months

D. 2 years

E-F. Infant and 12 years

Facial features include glabellar and eyelid nevus flammeus (simplex) that fades with age, synophrys, facial hypotonia with full cheeks, prominent globes, widely spaced eyes (hypertelorism), depressed and wide nasal bridge, anteverted nares, palatal anomalies (cleft palate, high arched palate or prominent palatine ridges), cleft lip, micrognathia and/or retrognathia, low-set ears with increased posterior angulation, variable trigonocephaly, microcephaly, or normocephaly.

From Russell et al [2015]. Republished with permission.

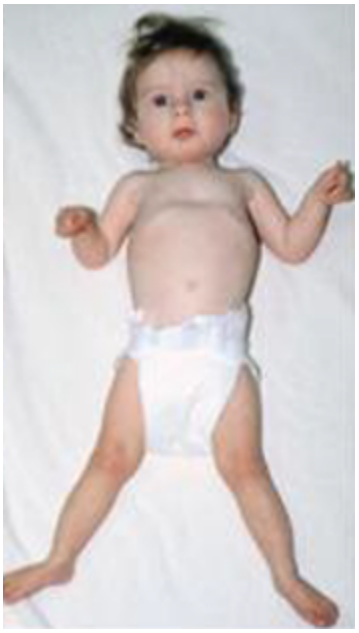

Figure 2. Typical BOS posture with flexion at the elbows, ulnar deviation, flexion of the wrists and metacarpophalangeal joints, and hypertonic extremities with central hypotonia

From Hastings et al [2011]. Republished with permission.

Table 1. Molecular Genetic Testing Used in Bohring-Opitz Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ASXL1	Sequence analysis [3]	20/24 (83%) [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [7]
Unknown [8]	NA	

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. The denominator represents only those individuals in the literature who have undergone sequence analysis of *ASXL1*; some clinically diagnosed individuals whose information has been published have not undergone molecular genetic testing.
5. Somatic mosaicism for *ASXL1* variants, including BOS-associated variants, may be found in the elderly or in other non-BOS cohorts (i.e., cohorts of individuals with cancer); such variants may be reported in reference databases, leading to misclassification of potentially pathogenic variants [Carlston et al 2017]. See Molecular Genetics.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.
8. In four individuals with features suggestive of BOS molecular genetic testing of *ASXL1* failed to identify a pathogenic variant [Brunner et al 2000, Hastings et al 2010, Hastings et al 2011, Hoischen et al 2011]. It is unclear if these individuals have a different genetic syndrome with clinical features overlapping those of BOS. Greenhalgh et al [2003] reported two sibs with clinical features of BOS in whom a different diagnosis was subsequently confirmed [Bruel et al 2017].

Clinical Characteristics

Clinical Description

Bohring-Opitz syndrome (BOS) is a rare condition characterized by distinctive facial features and posture, variable but usually severe intellectual disability, growth failure, and variable anomalies. Feeding difficulties have a significant impact on overall health in early childhood; feeding tends to improve with age. This section summarizes clinical data from numerous case reports and case series; see Russell et al [2015] and references therein, Dangiolo et al [2015], and Suggested Reading. Additional references are cited where appropriate.

Craniofacial. Individuals with BOS have a characteristic facial appearance (see Suggestive Findings), although significant variability is observed. The most striking and consistent features are a prominent glabellar nevus flammeus (simplex) that fades with age, synophrys that becomes more prominent with age, hypotonic facies with full cheeks, and prominent or proptotic eyes. The majority of affected individuals also have hypertrichosis with rapidly growing hair and nails.

Other features widely, but variably, reported include cleft lip with or without cleft palate, high arched palate, widely spaced eyes (hypertelorism), depressed and wide nasal bridge, anteverted nares, and low-set ears with increased posterior angulation.

Growth. Mild intrauterine growth restriction has been noted, but many infants are products of healthy pregnancies with average or low-average birth weights. Poor growth is typically noted in the first year of life and is often clinically attributed to chronic emesis and feeding intolerance. Adequate nutrition does play a role in early growth, but even those without feeding intolerance typically display poor long-term growth.

Feeding. Most children have had feeding issues beginning in infancy and generally improving or resolving in early childhood. Historically, feeding issues have been presumed to be secondary to severe gastroesophageal reflux, but initial case reports did not produce diagnostic evidence of gastroesophageal reflux or demonstrate improvement on traditional antireflux therapies. Recent publications have suggested a neurogenic etiology, including cyclic vomiting with possible poor gastric motility, as the underlying cause of the chronic emesis [Russell et al 2015]. Given the frequency of emesis, there is a high risk for aspiration and dehydration, typically resulting in multiple hospitalizations.

Development and behavior. All affected individuals reported in the literature have severe-to-profound intellectual disability. Few are able to speak, but many have been able to express basic needs using augmentative and alternative communication (AAC) devices as well as gestures with associated basic vocalizations. Individuals with BOS often have a happy and pleasant demeanor [Russell et al 2015]. Typically, they are able to recognize caregivers and have a social, interactive nature. Most are unable to walk independently, but some have had success using walkers and braces in late childhood. Given the recent increase in rate of diagnosis due to genomic testing, it is expected that affected individuals with a milder phenotype may be reported in the future.

Neurologic. Seizures are common in individuals with BOS and are typically responsive to standard antiepileptic medications. Affected individuals have also been described to have truncal hypotonia with hypertonia of the extremities. A wide range of primary brain anomalies have been reported. Corpus callosum defects are the most common and range from hypoplastic to absent. Dandy-Walker malformation, delayed myelination, and enlarged ventricles have also been described.

Cardiovascular. Idiopathic and transient bradycardia as well as apnea were widely reported in the initial literature that predated the identification of the genetic cause of BOS. Cardiovascular deaths associated with bradycardia and apnea account for four (33%) of the 12 deaths published in the literature (although none of those individuals had a molecular confirmation of BOS). Other minor cardiac anomalies including septal defects and cardiac hypertrophy have also been described in a small number of affected individuals.

Respiratory. In addition to apnea and bradycardia, respiratory infections are common in infancy and account for about 42% of deaths (5/12). When chronic emesis is treated or improves with age, the rate of respiratory infections decreases [Russell et al 2015]. Tracheostomies have been necessary for some (see Management).

Sleep. Obstructive sleep apnea and sleep disturbances, including difficulty falling asleep and staying asleep, are frequently reported. Affected individuals with micrognathia may also exhibit tongue-based airway obstruction.

Ophthalmologic. Myopia, often severe, is common in individuals with BOS. Most affected individuals require corrective lenses in infancy. Retinal and optic nerve abnormalities including colobomas, retinal and optic nerve atrophy, and abnormal coloration of the retinas are also frequently reported.

Immunologic. Recurrent infections may be frequent in early life, although immunodeficiency has not been reported in the literature. The frequency of infections typically declines with age.

Urologic. Urinary retention and recurrent urinary tract infections have been reported in individuals with BOS [Russell et al 2015]. There also appears to be an increased risk for renal stones [Author, personal observation].

Skeletal. The typical BOS posture (see Suggestive Findings) is most notable in early childhood and usually becomes less obvious with age. Congenital contractures, dislocations, and pectus excavatum have also been reported.

Malignancy. Isolated case reports suggest that children with BOS are at greater risk for Wilms tumor than the general population; large-scale epidemiologic studies have not been conducted due to the limited number of individuals diagnosed with BOS. Of three individuals with a clinical diagnosis of BOS and renal neoplasia, two had documented pathogenic variants in *ASXL1* and bilateral Wilms tumor; Wilms tumor was diagnosed in one at age two years and in the other at age six years [Russell et al 2015]. Another individual with BOS had nephroblastomatosis on autopsy at age five months. This infant later underwent molecular genetic testing of *ASXL1*; no pathogenic variant was identified [Brunner et al 2000, Hoischen et al 2011]. Overall, Wilms tumor appears to affect about 7% of individuals with BOS. This risk estimate is based on a very small number of reported cases and thus is likely to change over time as larger cohorts of children and adults with BOS are investigated.

The only other neoplastic process reported was medulloblastoma in a child age five years with clinical features of BOS in whom a pathogenic *ASXL1* variant was not identified [Hastings et al 2010, Hoischen et al 2011].

Other

- Annular pancreas has been described in some affected individuals.
- Gallstones have been reported in several affected individuals [Author, personal observation].
- Historically, this condition had been associated with high infant mortality (27% based on data published before 2015), but the current survival rate is likely to be much better due to advances in pediatric care and more aggressive interventions [Russell et al 2015].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported to date, but the total number of individuals in whom *ASXL1* pathogenic variants have been identified is limited.

Nomenclature

BOS is occasionally known as Oberklaid-Danks syndrome after F Oberklaid and DM Danks, who described one of the early cases of BOS [Oberklaid & Danks 1975]. BOS is the more commonly used term.

Prevalence

The prevalence of BOS is unknown; out of 46 clinically diagnosed individuals reported in the literature, 20 had the diagnosis molecularly confirmed.

Note: Not all clinically diagnosed individuals reported in the literature have undergone molecular genetic testing of *ASXL1*.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ASXL1*.

Sporadic malignancies (including myelodysplastic syndrome) occurring in the absence of any other findings of Bohring-Opitz syndrome frequently harbor somatic variants in *ASXL1* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more details see Cancer and Benign Tumors.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of Bohring-Opitz Syndrome (BOS)

Disorder	Gene(s)	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/BOS	Distinguishing from BOS
C syndrome (Opitz trigonocephaly syndrome) [1] (OMIM 211750)	*CD96*	AD	• Severe DD/ID • Microcephaly • Trigonocephaly • Upslanting palpebral fissures • Retrognathia • Low-set ears	Common in BOS, not in C syndrome: • Nevus flammeus (simplex) over glabella • BOS posture • Poor linear growth • Feeding difficulties • High myopia
Shashi-Pena syndrome (*ASXL2* syndrome) [2] (OMIM 617190)	*ASXL2*	AD	• DD • Hypotonia • Feeding difficulties in infancy • Nevus flammeus (simplex) over the glabella • Facial characteristics (particularly widely spaced eyes, prominent globes, & low-set or posteriorly rotated ears) • Hypertrichosis (2 of 6 reported cases)	Common in BOS: • Severe to profound ID • Microcephaly • BOS posture Common in Shashi-Pena syndrome: • Variable ID (borderline to severe) • Macrocephaly • Lesser feeding difficulties & normal weight gain • Episodic hypoglycemia of unknown etiology

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/BOS	Distinguishing from BOS
Bainbridge-Ropers syndrome (*ASXL3*-related disorder) [3]	*ASXL3*	AD	• Severe DD/ID w/minimal speech • Hypotonia • Feeding difficulties • Poor linear growth & weight gain • Microcephaly	Common in BOS; not typical in Bainbridge-Ropers syndrome: • IUGR • Nevus flammeus (simplex) over the glabella • Prominent globes • Typical BOS posture
Cornelia de Lange syndrome (CdLS)	*HDAC8* *NIPBL* *RAD21* *SMC1A* *SMC3*	AD XL [4]	• DD/ID • Prenatal and postnatal growth restriction • Microcephaly • Hypertrichosis • Small feet • In *HDAC8*-related CdLS, nevus flammeus (simplex) over the glabella & widely spaced eyes [5]	Common in BOS: • More severe feeding intolerance • High myopia • BOS posture • Prominent globes Common in CdLS: • Small hands & feet sometimes w/upper-limb reduction defects

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/BOS	Distinguishing from BOS
KLHL7-associated syndrome [6]	*KLHL7*	AR	• DD/ID • Feeding difficulties • IUGR • Seizures • Microcephaly • Hypoplastic corpus callosum • Facial characteristics: prominent eyes, anteverted nares • Facial nevus flammeus (simplex) • Hypertrichosis • Joint contractures • BOS posture	In *KLHL7*-associated syndrome: • Absence of high myopia & retinal/optic nerve atrophy • Retinitis pigmentosa in childhood • Hyperthermia • Oropharyngeal muscle contraction

AD = autosomal dominant; AR = autosomal recessive; DD/ID = developmental delay / intellectual disability; IUGR = intrauterine growth restriction; MOI = mode of inheritance; XL = X-linked

1. The phenotypic spectrum of C syndrome is not well defined, apart from the reportedly more common features. The mode of inheritance is also unclear since the molecular etiology remains elusive. A Japanese individual with a clinical diagnosis of C syndrome had a chromosomal translocation that disrupted *CD96* (also known as *TACTILE*), and another Japanese individual with a clinical diagnosis of C syndrome had a heterozygous missense variant in *CD96* [Kaname et al 2007]. However, these findings have not been replicated since 2007, so it remains unclear whether pathogenic variants in *CD96* could result in C syndrome. More recently, compound heterozygous pathogenic variants in *IFT140* were found in an individual with a clinical diagnosis of C syndrome – along with clinical features suggestive of a ciliopathy, which had not been previously reported in C syndrome [Peña-Padilla et al 2017]. Thus, it is unclear whether this is distinct from "classic" C syndrome.

2. Shashi et al [2016]

3. Balasubramanian et al [2017], Kuechler et al [2017]

4. NIPBL-, *RAD21-*, and *SMC3*-related CdLS are inherited in an autosomal dominant manner; *HDAC8-* and *SMC1A*-related CdLS are inherited in an X-linked manner.

5. Pathogenic variants in *HDAC8* result in an X-linked subtype of CdLS that is more severe in males and bears facial resemblance to BOS, with features not typically seen in "classic" CdLS: nevus flammeus (simplex) over the glabella and widely spaced eyes [Kaiser et al 2014, Parenti et al 2016].

6. Angius et al [2016], Bruel et al [2017]

Management

Evaluations Following Initial Diagnosis

To establish the spectrum of manifestations and medical needs in an individual diagnosed with Bohring-Opitz syndrome (BOS), the following evaluations are recommended if they have not already been completed.

Table 3. Recommended Evaluations Following Initial Diagnosis of Bohring-Opitz Syndrome

System/Concern	Evaluation	Comment
Growth	Weight, length/height, & head circumference measurements plotted on standard growth chart	• Goal: normal weight-for-length or body mass index • Expected final adult height: <2nd centile

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
ENT/Mouth	Craniofacial evaluation if cleft lip/palate, micrognathia, or obstructive sleep apnea is present	If mainly due to tongue-based airway obstruction, severe obstructive sleep apnea may be treatable by adenoidectomy or mandibular distraction.
Gastrointestinal	• Feeding evaluation (w/consideration of swallowing study) to assess for chronic emesis & aspiration risk • Consideration of gastric emptying time to assess for poor gastric motility	
Neurologic	Assessment for signs/symptoms of seizures	If present, consider neurology evaluation & head MRI.
	Evaluation by developmental specialists incl speech, occupational, & physical therapists	
Cardiovascular	Echocardiogram for cardiac anatomy	
Respiratory	Assessment for apnea/bradycardia (more common in younger individuals)	Consider sleep study if sleep apnea is a concern.
Eyes	Ophthalmology evaluation	For high myopia & retinal/optic nerve defects
Genitourinary	Baseline renal ultrasound	To assess renal structure & screen for Wilms tumor
Musculoskeletal	Orthopedic evaluation if bony anomalies noted	
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with BOS

Manifestation/Concern	Treatment	Considerations/Other
Poor growth & feeding due to chronic severe emesis [1]	• For cyclic vomiting: identification & avoidance of triggers, [2] daily maintenance medication, [3] & early abortive treatment at episode onset [4] • G-tubes or GJ-tubes often decrease aspiration & improve nutrition; [5] consider thickened feeds.	Fundoplication & traditional antireflux management w/acid blockers are typically not beneficial if gastroesophageal reflux is not the underlying etiology.
Cleft lip &/or palate	• Primary closure of cleft lip along standard timeline • Consider leaving cleft palates unrepaired when speech is lacking. • Palate repair in a child at risk for obstructive apnea may ↑ risk.	• Assess language & mobility to determine plan for palate closure & alveolar bone grafting. • Palate repair may be warranted in individuals w/language skills.
Frequent infections &/or aspiration pneumonia [4]	Aggressive management of chronic emesis	
Fever or increase in emesis	• Urinalysis & urine culture for possible urinary tract infection • Evaluation for other possible sources of infection, pain, or exposure	
Seizures	Standard antiepileptic medications	Most individuals respond to monotherapy.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Congenital heart defects	Standard management	
Respiratory symptoms	Tracheostomy may be effective in: • Creating a safe airway • Treating aspiration → lung disease • Treating severe obstructive sleep apnea not controlled by noninvasive pressure support (e.g., CPAP, BiPAP) or surgical management (e.g., adenoidectomy, mandibular distraction) Aspiration may also be amenable to treatment w/ postpyloric feedings (e.g., by gastrojejunostomy).	• Inhaled albuterol & inhaled steroids have improved respiratory status in some, although typical findings for reactive airway disease were lacking [Russell et al 2015]. • Descending aspiration of saliva can often be managed w/glycopyrrolate or salivary Botox injections.
Sleep disturbances	Melatonin, treatment of anemia	
Myopia	Corrective lenses, often first prescribed in infancy	
Urinary retention, urinary tract infections, renal stones	Standard treatments	Appropriate management of these conditions can improve emesis & hospitalization rate.

1. If vomiting is well controlled, growth typically improves, hospitalizations for dehydration and aspiration decrease, and overall health and well-being improve, although the rate of linear growth and weight gain remains poor. Lifelong feeding interventions may not be required, so periodic reexamination is appropriate.
2. Triggers such as vaccines, infections, and anesthesia have been reported, although this is not a reason to avoid vaccination and anesthesia: all children with BOS should receive the full course of standard vaccinations as recommended by the local authorities.
3. Cyproheptadine has been used for daily maintenance therapy.
4. Prophylactic treatment prior to a trigger exposure with antiemetics has been beneficial. Abortive treatment includes lorazepam, ondansetron, and acetaminophen or some combination of an antiemetic, pain reliever, and sedative.
5. Most affected individuals with feeding difficulties require a permanent feeding tube (G-tube or GJ-tube). Thickened feeds can help with emesis, and while G-tubes often do not stop emesis completely, they can limit the amount of nutrition lost through vomiting.

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.

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 due to 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.

Prevention of Primary Manifestations

Adequate treatment of severe emesis can decrease hospitalizations, infectious exposures, and aspiration.

Surveillance

The following are appropriate:

- Renal ultrasound every three months from birth to age eight years to screen for the development of Wilms tumor [Russell et al 2015]
- Frequent monitoring of growth and development with interventions as needed (see Treatment of Manifestations)
- Close management of feeding intolerance with a gastroenterology specialist
- Regular follow up with an ophthalmologist for vision optimization

Agents/Circumstances to Avoid

Triggers for vomiting should be avoided and managed with prophylactic antiemetics prior to the exposure (see Treatment of Manifestations).

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 information on clinical studies for a wide range of diseases and conditions.

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

Bohring-Opitz syndrome (BOS) is inherited in an autosomal dominant manner.

Note: A previously published sib pair identified as having BOS (which could have implied either autosomal recessive inheritance or germline mosaicism in a parent) have subsequently been identified as having another genetic condition [Greenhalgh et al 2003, Bruel et al 2017].

Risk to Family Members

Parents of a proband

- Most probands with BOS reported to date have the disorder as a result of a *de novo ASXL1* pathogenic variant.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo ASXL1* pathogenic variant include molecular genetic testing.

Sibs of a proband

- Most affected individuals reported to date have had a *de novo ASXL1* pathogenic variant, suggesting a low risk to sibs.
- If the *ASXL1* 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 BOS are not known to reproduce.

Other family members. Given that most probands with BOS reported to date have the disorder as a result of a *de novo ASXL1* 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ASXL1* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

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.

- **ASXL Rare Research Endowment Foundation**
  Email: info@arrefoundation.org
  www.arrefoundation.org
- **Bohring-Opitz Syndrome**
  A worldwide exchange of information and awareness.
  www.bohring-opitz.org
- **Bohring-Opitz Syndrome Foundation**
  Email: info@bos-foundation.org
  www.bos-foundation.org
- **Bohring-Opitz Syndrome & ASXL Related Disorders Registry**
  Email: ASXL-CHROMATIN-REGISTRY@mednet.ucla.edu
  BOS & ASXL REGISTRY

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. Bohring-Opitz Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ASXL1	20q11.21	Polycomb group protein ASXL1	ASXL1 @ LOVD	ASXL1	ASXL1

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 Bohring-Opitz Syndrome (View All in OMIM)

605039	BOHRING-OPITZ SYNDROME; BOPS
612990	ASXL TRANSCRIPTIONAL REGULATOR 1; ASXL1

Molecular Pathogenesis

ASXL1 is one of the human orthologs of the additional sex combs gene (Asx), which is an atypical polycomb group (PcG) protein that in *Drosophila* regulates gene expression by binding to chromatin and by regulating

ubiquitination of specific histones (e.g., histone H2A) through activation of specific deubiquitinases. In humans, *ASXL1*, *ASXL2*, and *ASXL3* (Table 2) code for putative PcG proteins (for *ASXL1* see www.uniprot.org/uniprot/Q8IXJ9) that regulate transcription through various mechanisms, including recruitment of histone H3 in specific cell types and deubiquitination of specific histone H2A. See Russell & Graham [2013] and references therein for insights into conditions associated with members of the ASXL family.

Gene structure. NM_015338 is the longest *ASXL1* transcript variant; it is composed of 13 exons. Alternatively spliced transcripts have been reported. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. In one report, *de novo* heterozygous inactivating pathogenic variants were detected in 50% of individuals who had features consistent with a diagnosis of BOS [Dangiolo et al 2015]. See Table A, **LSDB** and **HGMD**.

NOTE: *ASXL1* variants, including BOS-associated variants, have been identified in the elderly or in cohorts of individuals with cancer; such variants can be found in reference population databases. However, these variants are thought to result from hematopoiectic somatic mosaicism as opposed to BOS-associated germline variants [Carlston et al 2017 and references therein]. Failure to consider somatic mosaicism may lead to the misclassification of potentially pathogenic variants. See Cancer and Benign Tumors.

Normal gene product. The transcript NM_015338 encodes the protein isoform NP_056153 (isoform 1) with 1,541 amino acid residues known as putative polycomb group protein ASXL1.

Abnormal gene product. The *de novo* frameshift and nonsense *ASXL1* pathogenic variants suggest a loss-of-function mechanism as a cause of BOS [Hoischen et al 2011, Dangiolo et al 2015].

Cancer and Benign Tumors

Sporadic malignancies (including myelodysplastic syndrome) occurring in the absence of any other findings of BOS frequently harbor somatic variants in *ASXL1* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable.

Somatic *ASXL1* pathogenic variants are known to be associated with a worse prognosis in persons with myeloid leukemia [Abdel-Wahab et al 2012]. Mice with somatic pathogenic *Asxl* variants are at high risk for myelodysplastic conditions [Abdel-Wahab et al 2013], but constitutive *Asxl1* loss does not produce long-term cell line dysfunction [Fisher et al 2010a, Fisher et al 2010b]. Leukemias have not been reported in individuals with *ASXL1*-related BOS.

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Chapter Notes

Author Notes

Dr Bianca Russell is a clinical geneticist at Cincinnati Children's Hospital who has been studying and caring for patients with Bohring-Opitz Syndrome since meeting two patients with the condition in 2012. She met these patients while under the mentorship of Dr John Graham at Cedars Sinai Medical Center. Dr Graham has been a leader in the field of clinical dysmorphology for decades and an outstanding mentor. Dr Wen-Hann Tan is a clinical geneticist at Boston Children's Hospital who cares for several patients with BOS and was an integral part of their 2015 publication on clinical management of BOS.

Dr Russell and Dr Tan are continuing their work with the BOS community through a registry for disorders caused by pathogenic variants in the *ASXL* family of genes.

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