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ASXL3-Related Disorder

Synonym: Bainbridge-Ropers Syndrome (BRPS)

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Summary

Clinical characteristics

ASXL3-related disorder is characterized by developmental delay or intellectual disability, typically in the moderate to severe range, with speech and language delay and/or absent speech. Affected individuals may also display autistic features. There may be issues with feeding. While dysmorphic facial features have been described, they are typically nonspecific. Affected individuals may also have hypotonia that can transition to spasticity resulting in unusual posture with flexion contractions of the elbows, wrists, and fingers. Other findings may include poor postnatal growth, strabismus, seizures, sleep disturbance, and dental anomalies.

Diagnosis/testing

The diagnosis of *ASXL3*-related disorder is established in a proband by identification of a heterozygous pathogenic variant in *ASXL3* by molecular genetic testing.

Management

Treatment of manifestations: Feeding therapy; gastrostomy tube placement for those with persistent feeding issues; anti-reflux medication and/or fundoplication for those with gastroesophageal disease; standard treatment for epilepsy, joint contractures, sleep apnea, dental anomalies, strabismus and/or refractive error, and developmental delay / intellectual disability.

Surveillance: At each visit: Measurement of growth parameters and nutritional status; assessment of developmental progress, behavioral issues, new neurologic manifestations (change in tone, seizure onset and/or frequency), mobility and self-help skills, as well as signs and symptoms of sleep disturbance. Dental evaluation every six months after age three years or as clinically indicated. At least annual ophthalmology evaluation.

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Genetic counseling

ASXL3-related disorder is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Rarely, individuals diagnosed with *ASXL3*-related disorder have the disorder as the result of a pathogenic variant inherited from a parent. If the *ASXL3* pathogenic variant identified in the proband is not identified in either parent, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of parental germline mosaicism. Once the *ASXL3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Formal clinical diagnostic criteria for *ASXL3*-related disorder have not been established.

Suggestive Findings

ASXL-related disorder **should be considered** in individuals with the following clinical findings:

- Developmental delay (DD) or intellectual disability, typically in the moderate to severe range; AND
- Any of the following features presenting in infancy or childhood:
  - Speech and language delay and/or absent speech
  - Autism spectrum disorder or autistic traits
  - Dysmorphic facial features including prominent forehead; highly arched eyebrows; synophrys, widely spaced eyes; downslanted palpebral fissures; long, tubular nose with prominent nasal bridge; wide mouth with full, everted vermilion of the lower lip; and crowded teeth
  - Feeding difficulties
  - Hypotonia
  - Poor postnatal growth
  - Epilepsy including generalized tonic-clonic seizures and absence seizures
  - Vision impairment including strabismus
  - Skeletal findings such as Marfanoid habitus, pectus excavatum, scoliosis, arachnodactyly, and joint flexion with contractures

Establishing the Diagnosis

The diagnosis of *ASXL3*-related disorder **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *ASXL3* by molecular genetic testing (see Table 1).

Note: (1) Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *ASXL3* variant of uncertain significance does not establish or rule out a diagnosis of *ASXL3*-related disorder.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability typically begins with chromosomal microarray analysis (CMA). If CMA is not diagnostic, the next step is typically either a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *ASXL3*, followed by gene-targeted deletion/duplication analysis) is rarely useful due to the nonspecific nature of clinical presentation and typically NOT recommended.

Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *ASXL3*) that cannot be detected by sequence analysis.

An intellectual disability multigene panel that includes *ASXL3* 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*. (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, but **genome sequencing** may be performed, and yields results similar to an ID multigene panel with the additional advantage that exome and genome sequencing includes genes recently identified as causing ID, whereas some multigene panels may not.

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 *ASXL3*-Related Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ASXL3	Sequence analysis [3]	98%-99% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	1%-2% [7]
	CMA [8]	Rare [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. From Balasubramanian et al [2017], Kuechler et al [2017], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Most individuals so far reported with *ASXL3*-related disorder have truncating or splice site variants in *ASXL3*.
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.
7. At least two individuals in a cohort with typical *ASXL3*-related disorder have *ASXL3* deletions identified on chromosomal microarray (CMA) [Authors, personal observation]. Both individuals had deletions that included only *ASXL3* without deletion of adjacent genes.
8. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *ASXL3*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 18q12.1 region. CMA designs in current clinical use target the 18q12.1 region.

Clinical Characteristics

Clinical Description

To date, 44 individuals from 40 families have been identified with a pathogenic variant in *ASXL3* [Bainbridge et al 2013, Dinwiddie et al 2013, Hori et al 2016, Retterer et al 2016, Srivastava et al 2016, Balasubramanian et al

2017, Chinen et al 2017, Dad et al 2017, Kuechler et al 2017, Bacrot et al 2018, Contreras-Capetillo et al 2018, Koboldt et al 2018, Myers et al 2018a, Myers et al 2018b, Verhoeven et al 2018, Zhang et al 2018, Qiao et al 2019, Wayhelova et al 2019, Schirwani et al 2020]. The authors have collected clinical and molecular data on another 45 affected individuals in an additional cohort study that will be submitted for publication. The following description of the phenotypic features associated with this condition is based on these published reports and the additional cohort study (n=89 affected individuals).

Table 2. Select Features of *ASXL3*-Related Disorder

Feature	% of Persons w/Feature	Comment
Speech delay	100%	Most are nonverbal or have very limited speech.
Intellectual disability	99%	Typically moderate to severe
Facial dysmorphism	98%	See Suggestive Findings.
Hypotonia	86%	Central hypotonia can be assoc w/↑ tone in upper & lower limbs.
Behavioral concerns	78%	Incl autistic traits or an ASD diagnosis
Feeding difficulties	78%	Most patients in the early stages are referred w/feeding difficulties & failure to thrive.
Skeletal findings	74%	
Eyes	~50%	Strabismus is the most common finding.
Seizures	38%	GTCS & absence seizures; most have normal brain MRI imaging.

ASD = autism spectrum disorder; GTCS = generalized tonic-clonic seizures

Speech delay. All individuals with *ASXL3*-related disorder have delayed speech and language development. First word was achieved in 32% of affected individuals, at an average age of 28.8 months [Authors, personal observation].

- A majority of known individuals with *ASXL3*-related disorder are nonverbal.

  Use of communication devices with expert speech and language therapy input can often be helpful in these individuals to develop alternate modes of communication, as it appears that receptive language skills may be better than expressive language skills in persons with this disorder.

- Less commonly, communication through gesture, sounds, words, and sentences has been described.

Intellectual disability (ID). A majority of the individuals with *ASXL3*-related disorder have developmental delay and intellectual disability that is generally moderate to severe. However, a spectrum of intellectual capabilities has been described.

- Initial reports were of affected individuals with profound ID partly attributed to ascertainment bias; however, as more affected individuals have been identified, milder degrees of ID are being observed.
- The authors are aware of a father and son with a paternally inherited truncating *ASXL3* pathogenic variant, suggesting that a few individuals with *ASXL3*-related disorder may have normal cognition [Authors, personal observation].

Children with *ASXL3*-related disorder may be able to attend a mainstream school with dedicated support. However, so far, most individuals have required special educational provisions. The vast majority of adults described to date have required assisted living with some degree of independence.

Dysmorphic features. Individuals with *ASXL3*-related disorder have similar but typically nonspecific facial features (see Suggestive Findings) which are often recognized only after a diagnosis has been established.

Behavioral concerns. More than three-quarters of individuals with *ASXL3*-related disorder have significant behavioral, social, and communication difficulties with substantial impact on the affected individuals and their families.

- About half of affected individuals meet the formal clinical diagnostic criteria of an autism spectrum disorder (ASD), whereas others have autistic-like features. However, others are described as having a very friendly, placid personality.
- Other (more rarely) associated behaviors can include:
    - Hand flapping
    - Agitation
    - Motor and/or vocal tics (Tourette syndrome)
    - Hyperventilation episodes
    - Teeth grinding (bruxism)
    - Attention-deficit disorder (ADD)
    - Pica
    - Self-harm behaviors including self-biting, face scratching, and head banging

      Onset of self-injurious behavior can be as early as age two years; some individuals display this behavior later in life.

Growth. Most affected individuals display normal birth weight for gestational age but often experience poor postnatal growth as a result of feeding issues during infancy. During this time, growth may decline to 2 SD below the mean or more for age. Short stature is not a primary feature of *ASXL3*-related disorder and growth (both weight and length/height) typically stabilize or normalize after appropriate treatment of feeding issues (see following).

Feeding issues. Most individuals with *ASXL3*-related disorder, especially in the younger age groups, come to medical attention because of poor postnatal growth (see above) and ongoing feeding difficulties. They may display poor suck and swallow, recurrent vomiting, and gastroesophageal reflux disease.

- Swallow studies have shown impairment of oral stage of swallowing and oral sensorimotor feeding delay characterized by oral motor weakness, reduced mastication skills for age, and suspected oral hypersensitivity. This may result in delay in weaning and food refusal behavior. Affected individuals may also have a high arched palate.
- The severity of feeding difficulties varies considerably, with some affected children requiring long-term gastrostomy tube insertion while in others, feeding may be improved with the use of slow-flow nipples (see Treatment of Manifestations).
- Although initial feeding issues may resolve with age, there may be ongoing difficulties with feeding as a result of food aversion, sensitivity to different food textures, and behavioral issues that may affect eating.

Neurologic

- **Hypotonia** is a common feature in individuals with *ASXL3*-related disorder, especially during the neonatal period and in early infancy. Later in life, some children develop an unusual posture and contractures with elbow, wrist, and fingers held in the flexion position. This is likely because of spasticity that becomes apparent with age.

- **Seizures** occur in about one third of affected individuals and can range from generalized tonic-clonic seizures to absence seizures. Seizures typically respond to standard anti-seizure medications.
- **Imaging.** Most individuals with *ASXL3*-related disorder have normal brain imaging and do not have any characteristic brain findings.

Skeletal features. More than two thirds of individuals with *ASXL3*-related disorder have a skeletal abnormality. Findings may include:

- Marfanoid habitus
- Pectus excavatum
- Joint hypermobility
- Pes planus
- Digital abnormalities including arachnodactyly, syndactyly, clinodactyly, contractures, and tapering fingers
- Postural scoliosis (possibly due to hypotonia)
- Delayed bone age

Sleep. Sleep disturbance is a common finding, with some affected individuals reported to have sleep apnea, for which a sleep study and further evaluation to establish a cause is warranted. Some affected individuals have abnormal breathing patterns including apnea, breath-holding episodes, and irregular breathing patterns (particularly at night) that coincide with sleep disturbances.

Eyes. Strabismus has been described in more than half of affected individuals. It can be persistent or intermittent. Some affected individuals have myopia, hyperopia, and ptosis. Visual difficulties (including astigmatism) needing correction may also be seen.

Dental. Dental abnormalities, ranging from dental overcrowding, malocclusion, and large teeth to severe hypodontia, are present in nearly 50% of individuals.

Other

- Some affected individuals have problems with temperature regulation and are insensitive to cold/heat.
- Altered pain perception has been described in association with this condition but is not a consistent finding.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *ASXL3* have been identified.

Nomenclature

ASXL3-related disorder was first described by Bainbridge et al [2013] in four unrelated individuals with truncating variants in *ASXL3*; it is sometimes referred to as Bainbridge-Ropers syndrome.

Prevalence

The prevalence of *ASXL3*-related disorder is not known. However, to date *ASXL3* is one of the top ten genes in which pathogenic variants have been found in large-scale exome sequencing studies of individuals with ID [Fitzgerald et al 2015, Wright et al 2015].

Affected individuals have been reported from all ethnicities and most have been identified in countries that undertake genomic testing in individuals with ID.

Genetically Related (Allelic) Disorders

All heterozygous pathogenic variants so far reported in association with *ASXL3*-related disorder have been truncating and splicing variants; missense variants are not thought to be causative. However, biallelic missense *ASXL3* variants have been reported in four individuals with congenital heart defects (tetralogy of Fallot or transposition of the great arteries) from two families [Fu et al 2021]; further evidence is required to establish the role of biallelic missense *ASXL3* variants in the pathogenesis of congenital heart defects.

Sporadic tumors (including parathyroid adenomas and prostate and pancreatic cancers) occurring as single tumors in the absence of any other findings of *ASXL3*-related disorder may harbor somatic variants in *ASXL3* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information see Cancer and Benign Tumors.

Differential Diagnosis

Because the clinical presentation of *ASXL3*-related disorder is typically nonspecific global developmental delay, all disorders associated 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.

Note: Heterozygous pathogenic variants *ASXL1* and *ASXL2*, the other two genes in the ASXL gene family (see Molecular Pathogenesis), are associated with Bohring-Opitz syndrome (BOS) and Shashi-Pena syndrome, respectively. Both disorders are characterized by developmental delay but can be distinguished from *ASXL3*-related disorder by the characteristic facial dysmorphism associated with BOS, and by macrocephaly and abnormal brain imaging in Shashi-Pena syndrome.

Management

Consensus clinical management guidelines for *ASXL3*-related disorder have not been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ASXL3*-related disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *ASXL3*-Related Disorder

System/Concern	Evaluation	Comment
Development	Developmental assessment	To incl motor, adaptive, cognitive, & speech/language eval
		Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screen for behavior concerns incl sleep disturbances, ADD, &/or traits suggestive of ASD.
Constitutional	Measurement of growth parameters	To evaluate for growth deficiency
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	To incl eval of aspiration risk, GERD, & nutritional status
		Consider eval for gastric tube placement in those w/dysphagia &/or aspiration risk.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, pes planus, scoliosis & joint hypermobility • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Respiratory	Assessment for sleep disturbance &/or evidence of sleep apnea	
Dental	Age-appropriate dental eval	To assess for malocclusion & hypodontia
Eyes	Ophthalmologic eval	To assess for strabismus & ↓ vision
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support/resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADD = attention-deficit disorder; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *ASXL3*-Related Disorder

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain / Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
GERD	Anti-reflux medication; fundoplication or percutaneous endoscopic gastrostomy in severe situations	Consider consultation w/gastroenterology specialist in those w/severe disease.
Epilepsy	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]
Pes planus, joint contractures, scoliosis	Standard treatment per orthopedist	
Sleep apnea	Standard treatment per ENT / sleep specialist	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Malocclusion &/or hypodontia	Standard treatment per dentist/orthodontist	
Strabismus &/or refractive error	Standard treatment per ophthalmologist	
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; DD = developmental delay; GERD = gastroesophageal reflux disease; ID = intellectual disability; 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.

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 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, and hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, and 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

Table 5. Recommended Surveillance for Individuals with *ASXL3*-Related Disorder

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for attention & aggressive or self-injurious behavior	
Feeding	• Measurement of growth parameters • Eval of nutritional status & signs/symptoms of GERD or feeding aversion	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures & changes in tone.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Respiratory	Assess for signs/symptoms of sleep disturbance & sleep apnea.	
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, & other local resources) & care coordination.	
Dental	Eval by dentist	Every 6 mos after age 3 yrs or as clinically indicated
Eyes	Ophthalmology eval	Annually or as clinically indicated

GERD = gastroesophageal disease; 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

ASXL3-related disorder is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Parents of a proband

- To date, most individuals with *ASXL3*-related disorder whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo ASXL3* pathogenic variant.
- Rarely, individuals diagnosed with *ASXL3*-related disorder have the disorder as the result of a pathogenic variant inherited from a parent.

- Molecular genetic testing is recommended for the parents of a 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. Sib recurrence due to presumed parental germline mosaicism has been reported in three families [Koboldt et al 2018, Schirwani et al 2020]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.

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 heterozygous for the *ASXL3* pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
- If the *ASXL3* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Koboldt et al 2018, Schirwani et al 2020].

Offspring of a proband. Each child of an individual with *ASXL3*-related disorder has a 50% chance of inheriting the *ASXL3* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *ASXL3* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ASXL3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

Resources

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

- **ASXL Rare Research Endowment Foundation**

Email: info@arrefoundation.org
www.arrefoundation.org

- **ASXL3 Mutations & Bainbridge-Ropers Syndrome**
  www.asxl3.com
- **Unique: The Rare Chromosome Disorder Support Group**
  United Kingdom
  Phone: 44(0)1883 723356
  Email: info@rarechromo.org
  Bainbridge-Ropers syndrome
- **Simons Searchlight Registry**
  Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.
  Phone: 855-329-5638
  Fax: 570-214-7327
  Email: coordinator@simonssearchlight.org
  www.simonssearchlight.org

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. ASXL3-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ASXL3	18q12.1	Putative Polycomb group protein ASXL3	ASXL3	ASXL3

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 ASXL3-Related Disorder (View All in OMIM)

615115	ASXL TRANSCRIPTIONAL REGULATOR 3; ASXL3
615485	BAINBRIDGE-ROPERS SYNDROME; BRPS

Molecular Pathogenesis

ASXL1, *ASXL2*, and *ASXL3* are human homologs of the Drosophila additional sex combs (asx) genes that encode putative polycomb proteins and are likely to act as histone methyltransferases in complexes with other proteins [Katoh 2015]. Polycomb group proteins are implicated in embryogenesis and carcinogenesis through transcriptional regulation of target genes; *ASXL1* is thought to be one of the most frequently mutated genes in malignant myeloid diseases; ASXL is a scaffold protein interacting with methyltransferases and additional proteins of the epigenetic machinery [Fisher et al 2003, Duployez et al 2016].

Truncating pathogenic variants in *ASXL1* have been reported in association with Bohring-Opitz syndrome (BOS), which has phenotypic overlap with *ASXL3*-related disorder [Hoischen et al 2011]. More recently, truncating variants in *ASXL2* were reported in association with a newly recognizable clinical phenotype [Shashi et al 2016].

ASXL3 is expressed in similar tissues to *ASXL1* including brain, spinal cord, kidney, liver, and bone marrow, but at a lower level [Sahtoe et al 2016]. The high correlation of expression patterns between *ASXL1* and *ASXL3* may account for some of the shared phenotypic features.

Mechanism of disease causation. Loss of function

Cancer and Benign Tumors

Somatic missense variants in *ASXL3* have been identified in nonsyndromic parathyroid adenomas and may contribute to simplex (a single occurrence in a family) parathyroid tumorigenesis [Wei et al 2018]. Somatic truncating variants in *ASXL3* have been reported in pancreatic and prostate cancers [Micol & Abdel-Wahab 2016].

Chapter Notes

Author Notes

Dr Balasubramanian's web page: mellanbycentre.org/meena-balasubramanian

In the area of pediatric dysmorphology / genomic medicine, the author has led several studies focused on genotype-phenotype correlation in newly identified genes from next-generation sequencing studies such as the Deciphering Developmental Disorders study and has several first/senior author papers published in this area in large cohorts of individuals with new syndromal diagnoses. The author has published the largest cohort of people so far with *ASXL3*-related disorder and continued to gather phenotypic data on more than 70 individuals with *ASXL3*-related disorder. She has also written the Unique patient support group information leaflet on the condition along with Anna Pelling from Unique (www.rarechromo.org).

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