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Spinal Muscular Atrophy, X-Linked Infantile

Synonyms: SMAX2, XL-SMA

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Summary

Clinical characteristics

X-linked infantile spinal muscular atrophy (XL-SMA) is characterized by congenital hypotonia, areflexia, and evidence of degeneration and loss of anterior horn cells (i.e., lower motor neurons) in the spinal cord and brain stem. Often congenital contractures and/or fractures are present. Intellect is normal. Life span is significantly shortened because of progressive ventilatory insufficiency resulting from chest muscle involvement.

Diagnosis/testing

The diagnosis of X-linked infantile spinal muscular atrophy is established in a male proband with suggestive clinical features and a hemizygous pathogenic variant in *UBA1* identified by molecular genetic testing.

Management

Treatment of manifestations: Assure adequate caloric intake by caloric supplementation and/or gastrostomy feedings; manage constipation with diet or medication; provide rigorous airway clearance techniques, secretion management, and, ideally, noninvasive ventilatory support, although tracheostomy with permanent mechanical ventilation can be considered; discuss "do not attempt to resuscitate" status with the family before respiratory failure occurs. Orthopedic consultation and physical and occupational therapy to manage contractures and progressive scoliosis. Standard treatment for gastroesophageal reflux disease.

Surveillance: Affected children should be followed at least monthly until the severity and disease course are more clearly delineated. Routine evaluations by a multidisciplinary team, including neurology, pulmonology, orthopedics, physical and occupational therapy, nutrition, and gastroenterology, as needed. Measurement of

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growth parameters, neurologic evaluation, nutrition/feeding assessment, evaluation of respiratory status, and physical examination for kyphosis/scoliosis at each visit.

Genetic counseling

By definition, XL-SMA is inherited in an X-linked manner. Heterozygous females have a 50% chance of transmitting the pathogenic variant with each pregnancy. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and will usually not be affected. Once the *UBA1* pathogenic variant has been identified in an affected family member, carrier testing for at risk female relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

While suggestive diagnostic criteria were proposed by Dressman et al [2007] as part of inclusion criteria for a research study on this condition, no consensus clinical diagnostic criteria for X-linked infantile spinal muscular atrophy have been published.

Suggestive Findings

X-linked infantile spinal muscular atrophy **should be suspected** in an individual with the following clinical, imaging, electrophysiologic, supportive laboratory, and family history findings.

Clinical features

- Congenital hypotonia and areflexia on physical examination
- Congenital contractures and/or fractures
- Digital contractures at birth. These usually remain throughout the individual's life.

Neuroimaging. Spinal MRI demonstrating evidence of degeneration and loss of anterior horn cells (i.e., lower motor neurons) in the spinal cord and brain stem

Electrophysiology. Electromyogram (EMG) demonstrating denervation

Supportive laboratory findings. Normal *SMN1* molecular genetic testing for autosomal recessive spinal muscular atrophy

Family history. A simplex case involving a male (i.e., a single occurrence in a family) or X-linked pattern of inheritance (e.g., no male-to-male transmission) in families with more than one affected individual is consistent with XL-SMA.

Establishing the Diagnosis

The diagnosis of X-linked infantile spinal muscular atrophy **is established in a male proband** with suggestive clinical features and a hemizygous pathogenic (or likely pathogenic) variant in *UBA1* identified by molecular genetic testing (see Table 1).

Note: (1) Female carriers of XL-SMA are usually unaffected. (2) 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 *GeneReview* is understood to include likely pathogenic variants. (3) Identification of a hemizygous *UBA1* variant of uncertain significance does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of X-linked infantile spinal muscular atrophy is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with infantile hypotonia and/or arthrogryposis are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of X-linked infantile spinal muscular atrophy, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *UBA1* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions. To date, only missense and synonymous variants in exon 15 have been identified.

  Note: Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis. However, no deletions or duplications involving this gene have been reported as a cause of X-linked infantile SMA and some studies suggest that deletion of this gene in a male may be embryonic lethal.

- **A neuromuscular or arthrogryposis multigene panel** that includes *UBA1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of X-linked infantile spinal muscular atrophy some panels for hypotonia, neuromuscular conditions, and/or arthrogryposis may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by hypotonia, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **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 X-Linked Infantile Spinal Muscular Atrophy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
UBA1	Sequence analysis [3]	9/9 [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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. To date, eight families and one simplex individual have been detected with *UBA1* pathogenic variants [Dressman et al 2007, Ramser et al 2008, Dlamini et al 2013, Jędrzejowska et al 2015, Shaughnessy et al 2020, Wang et al 2020].
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. To date, all pathogenic variants reported have been missense variants [Balak et al 2017].

Clinical Characteristics

Clinical Description

Males

X-linked infantile spinal muscular atrophy (XL-SMA) is characterized by severe hypotonia and areflexia with loss of anterior horn cells in the spinal cord (i.e., lower motor neurons). The disease course is similar to that of the most severe forms of classic autosomal recessive SMA (when supportive care only is given) caused by biallelic pathogenic variants in *SMN1*: SMA type 0 (SMA0) and SMA type I (SMA1) (see Spinal Muscular Atrophy). In SMA0, prenatal onset of weakness and poor intrauterine movement results in congenital contractures. In SMA1, motor skills regress before age six months in those receiving supportive care only; affected children who do not receive targeted therapies are never able to sit independently.

Neuromuscular. The weakness of XL-SMA is often prenatal in onset, manifest as polyhydramnios and poor movement in utero that results in congenital contractures. (Note: The term "arthrogryposis" is used to describe the presence of multiple congenital contractures of any cause.) Some neonates with XL-SMA are born with fractures that are perhaps related to poor fetal movement and subsequent bone fragility.

- The most consistent features of XL-SMA are anterior horn cell disease and contractures (especially digital contractures) with or without fractures.
- The weakness in XL-SMA is progressive. Affected infants may achieve some early motor milestones, but the extent varies among families.

Cognitive ability. Observed during an often-limited life span, cognition appears to be normal in those with molecularly confirmed XL-SMA.

Respiratory. The greatest morbidity in XL-SMA may be restrictive lung disease, which is usually in proportion to the child's weakness and can be further complicated by aspiration and infection [Iannaccone 2007].

- Most children affected with XL-SMA have severe respiratory issues, due to weakness of muscles in the respiratory system.
- The majority of children have succumbed due to complications of upper respiratory tract infections or pneumonia, and thus it is advisable to consider noninvasive ventilation and/or tracheostomy shortly after

birth (see Management). Such an intervention has been proven to extend life span [Authors, personal observation]; however, the ethical implications of invasive treatment for those who are severely affected must also be considered.

Gastrointestinal/feeding issues are a frequent problem.

- During the neonatal period, affected individuals typically have poor suck-and-swallow responses.
- Placement of a gastrostomy tube to avoid aspiration and to provide proper nutrition is often necessary (see Management).

Other features of XL-SMA that are variably present:

- Mild micrognathia
- Kyphosis
- Scoliosis
- Cryptorchidism

Prognosis. Children with XL-SMA usually die from respiratory failure by age two years; however, the age at death ranges from the neonatal period to adolescence, the latter representing those exceptional cases in which extensive respiratory and medical support are provided. The two longest living known affected individuals received both mechanical ventilatory support and a gastrostomy tube.

Note: Individuals with a clinical picture consistent with SMA type II or type III have not been tested for pathogenic variants in *UBA1*; thus, it is not yet known if individuals with milder SMA phenotypes have *UBA1* pathogenic variants.

Females

Female carriers of XL-SMA are usually unaffected.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

XL-SMA has also been called:

- X-linked lethal infantile SMA
- Infantile X-linked SMA
- X-linked arthrogryposis multiplex congenita
- Distal X-linked AMC
- X-linked arthrogryposis type I, AMCX1

Note: SMAX1 is Kennedy disease (spinal and bulbar muscular atrophy), an unrelated X-linked, adult-onset disease.

Prevalence

The prevalence of XL-SMA is unknown. To date, 14 multigenerational families with affected family members have been identified throughout North America, Europe, Mexico, and Thailand [Author, personal observation]. This includes the family described by Greenberg et al [1988].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *UBA1*.

Somatic (i.e., mosaic or postzygotic) *UBA1* pathogenic variants in hematopoietic stem cells are associated with **VEXAS syndrome** (*v*acuoles, *E*1 enzyme, *X*-linked, *a*utoinflammatory, *s*omatic syndrome) [Beck et al 2020]. VEXAS syndrome is a late adult-onset inflammatory disorder seen in males only.

Differential Diagnosis

The differential diagnosis of X-linked infantile spinal muscular atrophy (XL-SMA) caused by mutation of *UBA1* includes other disorders associated with spinal muscular atrophy and/or arthrogryposis (see Table 2).

Table 2. Disorders with Spinal Muscular Atrophy and/or Contractures in the Differential Diagnosis of X-Linked Infantile Spinal Muscular Atrophy

MOI	Gene	Disorder [1]	Age of Onset	Multiple Contractures [2]	Fractures	Hypotonia	Muscle Weakness	Motor Regression	Absent Tendon Reflexes	Myopathic Facies	Neurogenic Atrophy	Denervation (by EMG)	AHC Loss
XL	*UBA1*	XL-SMA (topic of this *GeneReview*; incl for comparison)	Neonatal-infantile	+	+	±	+	+	+	±	±	+	+
	ATP7A	Occipital horn syndrome (See *ATP7A*-Related Copper Transport Disorders.)	Neonatal	+ [3]	NR	+	+	NR	NR	+	NR	NR	NR
	ZC4H2	Wieacker-Wolff syndrome (OMIM 314580)	Neonatal	+	NR	+	+	+	+	+	+ (Distal)	NR	±
AD	*BICD2*	Lower extremity-predominant SMA 2A (OMIM 615290)	Neonatal-infantile	+	NR	+	+	Delayed motor development	+	NR	+	+	+
		Lower extremity-predominant SMA 2B (OMIM 618291)	In utero [4]	+	+	+	+	Delayed motor development		NR	+	+	-
	TRPV4	Scapuloperoneal SMA (See Autosomal Dominant *TRPV4* Disorders.)	Neonatal	NR	NR	+	+	Delayed motor development	+	+	+	NR	NR
AR	*ASCC1*	SMA w/ congenital bone fractures 2 (OMIM 616867)	Prenatal	+	+	+	+	NA	+	+	+	+	+
	CHRND	See footnote 5.	Neonatal [6]										

Table 2. continued from previous page.

MOI	Gene	Disorder [1]	Age of Onset	Multiple Contractures [2]	Fractures	Hypotonia	Muscle Weakness	Motor Regression	Absent Tendon Reflexes	Myopathic Facies	Neurogenic Atrophy	Denervation (by EMG)	AHC Loss
	DNM2	Lethal congenital contracture syndrome 5 (OMIM 615368)	Prenatal	+	NR	+	+	NA	+	NR	+	+	+
	ERBB3	Lethal congenital contractural syndrome 2 (OMIM 607598)	Neonatal	+	NR	NA	NA	NA	NA	Micrognathia	+	NA	+
	EXOSC3	*EXOSC3* pontocerebellar hypoplasia	Neonatal [6]	+	NR	+	+	Delayed motor development	NR	NR	+	+	+
	GLE1	Congenital arthrogryposis w/ anterior horn cell disease (OMIM 611890)	Neonatal	+	NR	+	+	+	+	+	+	+	+
		Lethal congenital contracture syndrome 1 [7] (OMIM 253310)	Neonatal death	+	+	NA	+	NA	NA	NA	+	NA	+
	IGHMBP2	SMA w/ respiratory distress type 1 (OMIM 604320)	Early infancy	+	±	+	+	NR	+	+	NR	+	+
	RARS2	Pontocerebellar hypoplasia type 6 (OMIM 611523)	Neonatal [6]	+	NR	+	NA	±	+	+	+	NR	NR
	SMN1	SMA 0	Prenatal	+	±	+	+	±	+	±	+	+	+
		SMA 1	Infancy (<6 mos)	NR	NR	+	±	NR	+	NR	+	+	+

Table 2. continued from previous page.

MOI	Gene	Disorder [1]	Age of Onset	Multiple Contractures [2]	Fractures	Hypotonia	Muscle Weakness	Motor Regression	Absent Tendon Reflexes	Myopathic Facies	Neurogenic Atrophy	Denervation (by EMG)	AHC Loss
	TRIP4	SMA w/ congenital bone fractures 1 (OMIM 616866)	Prenatal	+	+	+	+	NA	+	+	+	+	+
	TSEN54	*TSEN54* pontocerebellar hypoplasia type 2A	Neonatal [6]	+	NR	NR	NR	NR	+	NR	NR	NR	NR
	VRK1	Pontocerebellar hypoplasia type 1A (OMIM 607596)	Prenatal-neonatal [6]	+	NR	+	+	+	NR	NR	+	+	+

+ = feature that is present in persons with this disorder; ± = feature that may or may not be present in persons with this disorder AD = autosomal dominant; AHC= anterior horn cell loss; AR = autosomal recessive; EMG = electromyogram; MOI = mode of inheritance; NA= not applicable or not available; NR = feature not reported in persons with this disorder; SMA = spinal muscular atrophy: XL = X-linked

1. Following XL-SMA, disorders are ordered alphabetically by gene within inheritance groups.

2. See following Note on arthrogryposis.

3. Hyperextensibility of finger joints is often found, despite reports of limited elbow and knee extensions.

4. Often associated with prenatal death

5. Two boys with clinical findings identical to those associated with XL-SMA were found to have biallelic *CHRND* pathogenic variants (the mother and father were confirmed to be heterozygous for the *CHRND* pathogenic variants) [Authors, unpublished data]. See OMIM 100720 for other phenotypes associated with pathogenic variants in *CHRND*.

6. Most die of respiratory failure in the first year of life. Survivors have failure to thrive and intellectual disability.

7. The highest prevalence is in Finland (OMIM 253310).

Note: Arthrogryposis (defined as multiple congenital contractures in multiple body areas) is etiologically heterogeneous: underlying etiologies include central nervous system causes, neurogenic effects, fetal constraint, and intrauterine vascular disruption (e.g., amyoplasia). Congenital myasthenic syndromes (disorders of the neuromuscular junction) may also present with arthrogryposis. Many genetic disorders are associated with arthrogryposis (see Hall [2021]). Of these disorders, the subset with the greatest phenotypic overlap with XL-SMA are included in Table 2.

For a detailed review of X-linked syndromes with arthrogryposis or early contractures, see Hunter et al [2015].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with X-linked infantile spinal muscular atrophy (XL-SMA), 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 X-Linked Infantile Spinal Muscular Atrophy

System	Evaluation	Comment
Neurologic	Assessment of muscle tone & strength (if possible)	To guide supportive management [1]
Nutrition/ Feeding	Gastroenterology, nutrition, feeding team eval [2]	• To incl eval of aspiration risk, fatigue during feeding, GERD, & nutritional status • Consider eval for gastrostomy tube placement in those w/ dysphagia &/or aspiration risk &/or poor oral intake.
Respiratory/ Cardiovascular	Assessment of respiratory rate, work of breathing, presence of paradoxic breathing, chest wall shape, & skin perfusion	
	Baseline pulmonary studies	To determine extent of restrictive airway disease & cough efficiency
	Baseline polysomnogram [2]	To assess for sleep-disordered breathing, nocturnal hypoventilation, & oxygen desaturation
Skeletal	Clinical eval for joint contractures & scoliosis	Consider referral to: • Orthopedist; • PT for flexion contractures.
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.

GERD = gastroesophageal reflux disease; PT = physical therapist

1. Iannaccone [2007]

2. Wang et al [2007]

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with X-Linked Infantile Spinal Muscular Atrophy

Manifestation/ Concern	Treatment	Considerations/Other
Weak suck → poor weight gain	Placement of a gastrostomy tube & nutritional supplementation [1]	• For affected males who survive newborn period • Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia &/or weak suck
GERD	Standard treatment	
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	If diet & ↑ water content are insufficient
Respiratory insufficiency/ failure options [2, 3]	Palliative care &/or no respiratory support [4]	May be an option, depending on family preference
	Airway clearance techniques & secretion mgmt [5]	• Incl mechanical in-exsufflator in conjunction w/ suctioning & chest physiotherapy, esp during acute illness. • Use of mechanical in-exsufflation in treatment of children w/neuromuscular diseases (incl those w/XL-SMA) appears to ↓ pulmonary complications.
	Noninvasive ventilation [5] (e.g., BiPAP)	• For hypoventilation as demonstrated by ↓ oxygen saturation by pulse oximetry or by obstructive sleep apnea • BiPAP may improve chest wall & lung development, which may ↓ lung infections & pulmonary comorbidity.
	Tracheostomy w/permanent mechanical ventilation	Ethical considerations re use of invasive ventilation in severely affected infants w/XL-SMA must be addressed.
Joint contractures	PT, OT	
	Consider surgical intervention.	For severe contractures
Progressive scoliosis	Standard surgical intervention per orthopedist	For severe scoliosis
Family/ Community	Ensure appropriate social work involvement to connect families w/local resources, respite, & support.	Ongoing assessment of need for palliative care involvement &/or home nursing
	Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	

GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy

1. Including higher-calorie feeds and fat supplementation

2. Options should be discussed with the parents/care providers before respiratory failure occurs.

3. The type of respiratory support is dependent on the individual's respiratory status, quality-of-life goals, and reduction in respiratory complications.

4. Discuss "do not attempt to resuscitate" status with the family before respiratory failure occurs. This discussion may begin early but is appropriate when abdominal breathing is present and/or the forced vital capacity is less than 30%.

5. Noninvasive pulmonary intervention should be incorporated into the management of all affected individuals.

Surveillance

Individuals with XL-SMA should be followed regularly by a physician familiar with this condition (e.g., a clinical geneticist). Other subspecialists involved in ongoing care include a neurologist, pulmonologist, orthopedist, physical and occupational therapists, nutritionist, and gastroenterologist as needed.

Affected children should be followed at least monthly until the severity and disease course are more clearly delineated. Affected children frequently die in infancy or early childhood; their clinical status should be followed closely to optimize management, and to assure that the family has a good understanding of the progression and can make informed decisions.

Table 5. Recommended Surveillance for Individuals with X-Linked Infantile Spinal Muscular Atrophy

System	Evaluation	Frequency
Growth	Measurement of growth parameters	At each visit
Neurologic	Neurologic assessment	
Nutrition/ Feeding	Monitor for symptoms of swallowing dysfunction, incl coughing, choking, &/or recurrent pneumonia.	
Respiratory [1]	Assessment of respiratory status	
Skeletal	Assessment for kyphosis and/or scoliosis	

Wang et al [2007]
1. Referral to a pulmonologist is recommended.

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. 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

By definition, X-linked infantile spinal muscular atrophy (XL-SMA) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *UBA1* pathogenic variant.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the

UBA1 pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the affected male may have a *de novo* pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *UBA1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and will usually not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *UBA1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is unknown but presumed to be low, although greater than that of the general population because of the possibility of maternal germline mosaicism.

Offspring of a male proband

- Males with a severe phenotype do not generally survive.
- Males with milder phenotypes transmit the *UBA1* pathogenic variant to:
  - All of their daughters, who will be heterozygotes and will usually not be affected;
  - None of their sons.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes, and the aunts' offspring, depending on their sex, may be at risk of being heterozygotes or of being affected.

Heterozygote (Carrier) Detection

Carrier testing for at risk female relatives requires prior identification of the *UBA1* pathogenic variant in the family.

Note: Females who are heterozygous for this X-linked disorder will usually not be affected.

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 young adults who are affected, are heterozygotes, or are at risk of being heterozygotes.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *UBA1* pathogenic variant has been identified in the family, prenatal and preimplantation genetic testing for XL-SMA 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.

- **Cure SMA**
  Phone: 800-886-1762
  Email: info@curesma.org
  curesma.org
- **National Organization for Rare Disorders (NORD)**
  Spinal Muscular Atrophy
- **AMCSI: Arthrogryposis Multiplex Congenita Support, Inc.**
  P.O. Box 6291
  Spartanburg SC 29304
  Phone: 805-55-AMCSI (1-805-552-6274)
  Email: bod@amcsupport.org
  www.amcsupport.org
- **Compassionate Friends**
  Supporting Family After a Child Dies
  Phone: 877-969-0010
  compassionatefriends.org
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  Email: ResourceCenter@mdausa.org
  mda.org
- **National Rehabilitation Information Center (NARIC)**
  8201 Corporate Drive
  Suite 600
  Landover MD 20785
  Phone: 800-346-2742 (toll-free); 301-459-5984 (TTY); 301-459-5900
  Fax: 301-459-4263
  Email: naricinfo@heitechservices.com
  www.naric.com

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. Spinal Muscular Atrophy, X-Linked Infantile: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
UBA1	Xp11.3	Ubiquitin-like modifier-activating enzyme 1	UBA1 @ LOVD	UBA1	UBA1

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 Spinal Muscular Atrophy, X-Linked Infantile (View All in OMIM)

301830	SPINAL MUSCULAR ATROPHY, X-LINKED 2; SMAX2
314370	UBIQUITIN-LIKE MODIFIER-ACTIVATING ENZYME 1; UBA1

Molecular Pathogenesis

UBA1 encodes ubiquitin-like modifier activating enzyme 1. The UBA1 enzyme is at the pinnacle of the ubiquitin proteasome system (UPS) ubiquitination cascade, initiating a series of complex and well-regulated steps that is common to all known processes that involve conjugating ubiquitin to itself or other proteins, including the essential function of tagging proteins to be targeted by the 26s proteasome. Protein degradation is as important as synthesis for protein homeostasis, and UBA1 is essential in all living cells from yeast to human. Complete loss of *UBA1* is thought to be lethal, as no in vivo models of *Uba1* knockout have been successfully created.

Mechanism of disease causation. Unknown; all pathogenic variants reported to date have been either missense variants or synonymous variants contained within exon 15; there is speculation that these variants may affect gene methylation.

Chapter Notes

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Revision History

- 9 May 2024 (ma) Revision: VEXAS syndrome added to Genetically Related Disorders
- 29 July 2021 (ma) Comprehensive update posted live
- 13 September 2012 (me) Comprehensive update posted live
- 30 October 2008 (me) Review posted live
- 10 July 2008 (lbr) Original submission

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