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Alpha-Thalassemia X-Linked Intellectual Disability Syndrome

Synonym: ATR-X Syndrome

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Summary

Clinical characteristics

Alpha-thalassemia X-linked intellectual disability (ATR-X) syndrome is characterized by distinctive craniofacial features, genital anomalies, hypotonia, and mild-to-profound developmental delay / intellectual disability (DD/ID). Craniofacial abnormalities include small head circumference, telecanthus or widely spaced eyes, short triangular nose, tented upper lip, and thick or everted lower lip with coarsening of the facial features over time. While all affected individuals have a normal 46,XY karyotype, genital anomalies comprise a range from hypospadias and undescended testicles, to severe hypospadias and ambiguous genitalia, to normal-appearing female external genitalia. Alpha-thalassemia, observed in about 75% of affected individuals, is mild and typically does not require treatment. Osteosarcoma has been reported in a few males with germline pathogenic variants.

Diagnosis/testing

The diagnosis of ATR-X syndrome is established in a proband with suggestive findings, a 46,XY karyotype, and a hemizygous pathogenic variant in *ATRX* identified by molecular genetic testing.

Management

Treatment of manifestations: DD/ID, seizures, gastrointestinal manifestations and feeding difficulties, excessive drooling, and genital anomalies are managed per standard of care.

Surveillance: Regular assessment of growth and developmental progress in infancy and childhood.

Genetic counseling

ATR-X syndrome is inherited in an X-linked manner. The mother of a proband may be heterozygous (i.e., a carrier) or the affected individual may have a *de novo* pathogenic variant. If the mother of the proband has an *ATRX* pathogenic variant, the chance of transmitting it in each pregnancy is 50%: sibs with a 46,XY karyotype

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who inherit the pathogenic variant will be affected; sibs with a 46,XX karyotype who inherit the pathogenic variant will be heterozygous and will rarely show clinical manifestations. Affected males do not reproduce. Once the *ATRX* pathogenic variant in the family has been identified, carrier testing for at-risk females, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Alpha-thalassemia X-linked intellectual disability (ATR-X) syndrome **should be suspected** in individuals with the following clinical findings, hematologic findings, and family history.

Clinical findings

- A recognizable pattern of craniofacial findings including small head circumference, upsweep of the frontal hair, telecanthus or widely spaced eyes, short triangular nose, tented upper lip, thick or everted lower lip, and open mouth. Irregular anatomy of the pinnae, widely spaced teeth, and protruding tongue are supplemental findings, the latter two adding to a coarseness of the facial appearance, particularly after the first few years of life.
- Growth impairment including microcephaly and short stature, usually present at birth
- Genital anomalies (in an individual with a 46,XY karyotype) that can range from hypospadias and undescended testes to ambiguous genitalia to normal external female genitalia
- Developmental delay / intellectual disability, typically in the severe-to-profound range

Hematologic findings. Hematologic studies show evidence of alpha-thalassemia in approximately 75% of males with ATR-X syndrome [Gibbons et al 2008].

- **HbH inclusions** (β-globin tetramers) in erythrocytes can be demonstrated following incubation of fresh blood smears with 1% brilliant cresyl blue. The proportion of cells with HbH inclusions ranges from 0.01% to 30% [Gibbons et al 1995a]. HbH inclusions may be demonstrated readily in some individuals, found only in an occasional erythrocyte in some, or observed only after repeated testing in others. The absence of HbH inclusions in one fourth of affected individuals and the rarity of inclusions (≤1% of erythrocytes) in an additional 40% of affected individuals diminish the utility of this testing in most clinical settings.
- **Red blood cell indices.** A microcytic hypochromic anemia characteristic of alpha-thalassemia may be seen in some affected individuals, but many have red cell indices in the normal range [Gibbons et al 1995b].
- **Newborn screening.** In rare instances, ATR-X syndrome has been identified through the detection of HgH on newborn screening for hemoglobinopathies.

Family history is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of ATR-X syndrome **is established** in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *ATRX* identified by molecular genetic testing (see Table 1).

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

Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype. **Gene-targeted testing** requires that the clinician determine which gene(s) are likely involved, whereas **genomic testing** does not.

Single-gene testing. Sequence analysis of *ATRX* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

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

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

Comprehensive genomic testing. This approach does not require the clinician to determine which genes are likely involved. **Exome sequencing** is commonly used; **genome sequencing** is becoming possible in some laboratories.

If exome sequencing is not diagnostic, **exome array** should be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 ATR-X Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ATRX	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Based on data from the subscription-based professional view of Human Gene Mutation Database [Stenson 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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, of note: whole-gene duplications but not deletions have been reported. Breakpoints of large duplications and/or duplication of adjacent genes (e.g., those described by Honda et al [2012], Isrie et al [2012], and Lugtenberg et al [2009]) may not be detected by these methods.

Other Testing

Epigenetic signature analysis / methylation microarray. A characteristic methylation signature identified on epigenetic signature analysis of leukocytes in individuals with ATR-X syndrome [Schenkel et al 2017] may be useful as a first-tier screening test in an individual with an atypical phenotype or as a second-tier test when molecular genetic testing identifies an *ATRX* variant of uncertain significance.

Clinical Characteristics

Clinical Description

A more or less distinctive phenotype is characteristic of alpha-thalassemia X-linked intellectual disability (ATR-X) syndrome. Craniofacial, genital, and developmental manifestations are prominent among the most severely affected individuals [Gibbons et al 1995b, Badens et al 2006a, Stevenson et al 2012].

As additional individuals/families have been evaluated using molecular genetic testing, the range of phenotypic variability has broadened, particularly on the mild end of the spectrum. Affected males may have mild, moderate, or profound intellectual disability (ID), even within the same family. Adults in the family described by Yntema et al [2002] appeared to have nonsyndromic X-linked ID (XLID), although childhood photographs showed evidence of facial hypotonia. Basehore et al [2015] reported 25 affected males in five families with the p.Arg37Ter variant who had variable but overall milder phenotypes (see Genotype-Phenotype Correlations).

Table 2. Selected Features of Alpha-thalassemia X-linked Intellectual Disability Syndrome

Feature	% of Persons with Feature	Comments
Developmental delay	100%	A minority never speak or have meaningful speech.
Intellectual disability	100%	Variable severity, from mild to profound

Table 2. continued from previous page.

Feature		% of Persons with Feature	Comments
Characteristic facies • Hypertelorism/telecanthus • Small nose • Tented upper lip • Open mouth • Prominent lips		90%	Usually present from birth, but may persist or become less distinctive in adult life. W/age, face may also coarsen w/open mouth, spaced teeth, & prominent lips.
Microcephaly		75%-85%	Usually present at birth; head size of those w/out microcephaly usually in lower centiles
Short stature		60%-70%	Usually present at birth
Gastrointestinal dysfunction		70%-80%	A major morbidity; incl: early feeding difficulty, vomiting, reflux, abdominal distention, obstruction, pain, & constipation
Genital anomalies		70%-80%	Wide range, from minimal hypospadias or undescended testes to normal-appearing female external genitalia
Neurologic	Hypotonia	80%-90%	Contributes to facial phenotype
	Seizures	30%-40%	

Developmental Impairment / Intellectual Disability

Severe developmental impairment and intellectual disability are the most important clinical manifestations. From the outset, developmental milestones are globally and markedly delayed. Speech and ambulation occur late in childhood. Some affected individuals never walk independently or develop significant speech.

Growth Impairment

Growth impairment with microcephaly and short stature occurs in most individuals with ATR-X syndrome and is often present at birth. Stature is typically short (>2 SD below the mean in 67% of individuals using standard growth charts; syndrome-specific growth charts are not available). Growth above average is exceptional.

Gastrointestinal Manifestations

Gastrointestinal manifestations, present in the majority of individuals, contribute significantly to morbidity. Approximately three fourths have gastroesophageal reflux and one third have chronic constipation. Gastric pseudo-obstruction can result from abnormal suspension of the stomach and constipation can result from colon hypoganglionosis [Martucciello et al 2006]. Aspiration, presumably related to gastroesophageal reflux, has been a fatal complication in some.

Genital Anomalies

Genital anomalies are often minor, including first-degree hypospadias, undescended testes, and underdevelopment of the scrotum. Although all individuals with ATR-X syndrome have a normal 46,XY karyotype, gonadal dysgenesis resulting in inadequate testosterone production can cause more severe defects that can include second- and third-degree hypospadias, small penis, ambiguous genitalia, or even normal-appearing female external genitalia. Although all individuals with ATR-X syndrome have a normal 46,XY karyotype, occasionally gonadal dysgenesis results in inadequate testosterone production and ambiguous genitalia. Although the spectrum of possible genital anomalies in ATR-X syndrome is broad, the type of genital anomaly appears to be consistent within a family.

Hypotonia

Hypotonia, a hallmark of ATR-X syndrome, contributes to the facial manifestations, drooling, developmental delay, and possibly to the gastrointestinal manifestations.

Seizures

Seizures of various types occur in about one third of individuals with ATR-X syndrome but are not a defining manifestation of the syndrome [Gibbons et al 1995b, Stevenson et al 2012, Giacomini et al 2019]. Brain atrophy and white matter abnormalities have been found on MRI and CT imaging [Wada et al 2013].

Other

The **neurobehavioral phenotype** has not been extensively delineated; however, most individuals appear affable, but some are emotionally labile with tantrums and bouts of prolonged crying or laughing.

Minor skeletal anomalies (brachydactyly, clinodactyly, tapered digits, joint contractures, pectus carinatum, kyphosis, scoliosis, dimples over the lower spine, varus and valgus foot deformation, and *pes planus*) occur, but do not contribute significantly to morbidity.

Major malformations are not common, but ocular coloboma, cleft palate, cardiac defects, inguinal hernia, heterotaxy, and asplenia [Leahy et al 2005] have been reported.

Although **predisposition to tumor development** has not been confirmed in individuals with germline *ATRX* pathogenic variants, four children with ATR-X syndrome have developed osteosarcoma [Ji et al 2017, Masliah-Planchon et al 2018], a finding that contrasts with the well-recognized tumor association of somatic *ATRX* pathogenic variants (see Cancer and Benign Tumors). Masliah-Planchon et al [2018] provide clinical, histologic, and genetic data supporting the possibility of tumor predisposition associated with germline *ATRX* pathogenic variants in their report of three instances of osteosarcoma in two males:

- One individual with two metachronous osteosarcomas, the first (of the tibia) diagnosed and successfully treated at age nine years, and the second (of the humerus) diagnosed and successfully treated ten years later at age 20 years
- One child, diagnosed with osteosarcoma of the femur with pulmonary nodules at age four years, who succumbed 18 months later

Heterozygous Females

Heterozygous females rarely show clinical manifestations. Typically, carrier females have marked skewing of X-chromosome inactivation (>90:10) with preferential inactivation of the X chromosome with the *ATRX* pathogenic variant. Rare exceptions have been reported, including the following:

- A five-generation pedigree in which three females had signs of ATR-X syndrome [Christensen et al 1999]
- Moderate ID without other phenotypic features of ATR-X syndrome in a female carrier with random X-chromosome inactivation [Wada et al 2005]
- A girl conceived by in vitro fertilization (IVF) who had craniofacial features, growth restriction, and developmental impairment typical of ATR-X syndrome [Badens et al 2006b]. Leukocyte studies showed marked skewing of X-chromosome inactivation with her pathogenic variant-bearing X chromosome being the active X chromosome. The role of IVF in this unique case of female expression is not known.

Genotype-Phenotype Correlations

Pathogenic variants that affect the ATRX zinc finger domain produce severe psychomotor impairment and urogenital anomalies, whereas pathogenic variants in the helicase domains cause milder phenotypes [Badens et al 2006a].

More severe genital anomalies occur with variants in the plant homeodomain-like domain.

A nonsense variant in exon 2 (p.Arg37Ter) appears to be a common pathogenic variant that results in an overall milder phenotype [Basehore et al 2015] (see Table 7).

Nomenclature

"Alpha-thalassemia X-linked intellectual disability syndrome" and "ATR-X syndrome" are the preferred designations for this disorder.

ATRX pathogenic variants have been found in several named XLID syndromes (Carpenter-Waziri syndrome, Holmes-Gang syndrome, Chudley-Lowry syndrome, XLID-arch fingerprints – hypotonia), in XLID with spastic paraplegia, in XLID with epilepsy, and in nonsyndromic XLID [Lossi et al 1999, Stevenson 2000, Stevenson et al 2000, Yntema et al 2002, Stevenson et al 2012]. These entities should be considered to be in the phenotypic spectrum of ATR-X syndrome; there are no compelling reasons to maintain the syndromic names.

Note: A family considered to have Juberg-Marsidi syndrome had an *ATRX* pathogenic variant [Villard et al 1996]. Subsequently, the original family reported with Juberg-Marsidi syndrome was found to have a *HUWE1* pathogenic variant, indicating that the family studied by Villard et al [1996] represented a misdiagnosis [Friez et al 2016].

Although two families considered to have Smith-Fineman-Myers syndrome have *ATRX* pathogenic variants, the original family with Smith-Fineman-Myers has not been restudied. Hence, the relationship of ATR-X syndrome and Smith-Fineman-Myers syndrome is unclear [Villard et al 1999a, Li et al 2020].

Prevalence

The prevalence is not known. More than 200 affected individuals are known to the laboratories conducting molecular genetic testing; substantial underascertainment, especially of those with milder phenotypes, is probable.

No racial or ethnic concentration of individuals has been reported.

Genetically Related (Allelic) Disorders

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

See also Cancer and Benign Tumors.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Alpha-Thalassemia X-Linked Intellectual Disability Syndrome

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/ATR-X syndrome	Not observed in ATR-X syndrome
HBA1 *HBA2*	Hemoglobin H (HbH) disease (See Alpha-Thalassemia.)	AR [1]	Microcytic hypochromic hemolytic anemia, hepatosplenomegaly, mild jaundice, & sometimes thalassemia-like bone changes	• Persons w/ATR-X syndrome have normal α-globin genotype (αα/αα); those w/HbH disease have deletion or dysfunction of 3 of 4 α-globin alleles. • ID is not a component of alpha-thalassemia involving α-globin production.
MECP2 + adjacent genes in Xq28	*MECP2* duplication syndrome	XL	• Severe ID, spasticity, infantile hypotonia, absent or limited speech, seizures, & recurrent respiratory infections • Autistic behaviors & GI dysfunction observed in several affected boys • 50% of affected males die by early adulthood.	• Face is not characteristically hypotonic as in ATR-X syndrome. • Microcephaly is less common. • Downslanted palpebral fissures
RPS6KA3	Coffin-Lowry syndrome	XL	• Severe-to-profound ID in males • Large open mouth & prominent lips • Short stature, microcephaly, & dental anomalies common • Childhood-onset kyphoscoliosis (often progressive) • Life span ↓ in some persons	• Short, soft, fleshy hands, often w/ hyperextensible & tapering fingers • Childhood-onset SIDAs in ~20% of persons [2] • Carrier females often have fullness of face & lips, fleshy & hyperextensible fingers, & learning difficulties.

AR = autosomal recessive; DiffDx = differential diagnosis; GI = gastrointestinal; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Alpha-thalassemia is usually inherited in an autosomal recessive manner.

2. Childhood-onset SIDAs (*s*timulus-*i*nduced *d*rop *a*ttacks) refers to a brief collapse (but no loss of consciousness) triggered by unexpected tactile or auditory stimuli or excitement.

Alpha-thalassemia intellectual disability, chromosome 16-related (ATR-16 syndrome; OMIM 141750) is the association of alpha-thalassemia and intellectual disability in individuals with a contiguous gene deletion involving the distal short arm of chromosome 16. Such deletions produce alpha-thalassemia by deleting the two genes in *cis* configuration at 16p13 that encode α-globin chains. Because the chromosome deletions and rearrangements giving rise to ATR-16 are large and variable, no specific clinical phenotype is observed in ATR-16; this is in contrast to ATR-X syndrome, in which the phenotype is more predictable.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with alpha-thalassemia X-linked intellectual disability (ATR-X) syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with ATR-X Syndrome

System/Concern	Evaluation	Comment
Growth	Assess height, weight, head circumference	In infants & children
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / speech therapy / PT & OT / special education
Neurologic	Neurologic eval	• To assess muscle tone, evidence for spasticity (↑ reflexes, Babinski response) • To incl EEG & MRI if seizures a concern
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	For: • Nutritional status • Swallowing difficulties & aspiration risk • GERD &/or recurrent vomiting • Gastric pseudo-obstruction • Constipation
Genital abnormalities	Physical exam for evidence of a disorder of genital development such as cryptorchidism, hypospadias, ambiguous genitalia, normal female external genitalia in 46,XY individuals	Consultation w/pediatric urologist if surgical intervention required
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Mobility & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Congenital heart defects	Pediatric cardiologist	Septal defects require eval re possible intervention.
Ophthalmologic involvement	Ophthalmologic exam	Assess for strabismus, ↓ visual acuity, structural eye defects (e.g., coloboma).
Genetic counseling	By genetics professionals [1]	To inform affected individuals & their families re nature, MOI, & implications of ATR-X syndrome in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Use of community or online resources such as Parent to Parent; • Social work involvement for parental support.	

GERD = gastroesophageal reflux disease; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with ATR-X Syndrome

Manifestation/Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none demonstrated effective specifically for this disorder • Education of parents/caregivers [1]
Gastrointestinal/ Feeding	Feeding therapy; calorie-dense formula; gastrostomy tube placement as needed for persistent feeding issues	• Usual treatment for GERD, constipation • Treatment for gastric pseudo-obstruction per treating gastroenterologist/pediatric surgeon
Drooling	Anticholinergics, botulinum toxin type A injection of salivary glands &/or surgical redirecting of submandibular ducts	Options when drooling is a serious problem
Genital abnormalities	Per treating urologist	
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT	Use of durable medical equipment & positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers)
Congenital heart defects	Per treating cardiologist	
Ophthalmologic involvement	Per treating ophthalmologist	

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

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 if any changes are needed.
  - As required by special education law, children should be in the least restrictive environment feasible at school and included in general education as much as possible and when appropriate.
  - 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.

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

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 6. Recommended Surveillance for Individuals with ATR-X Syndrome

System/Concern	Evaluation	Frequency
Growth	Height, weight, head circumference	At each visit in infancy & childhood
Development	Monitor developmental progress & educational needs.	
Gastrointestinal/ Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake • Monitor for excessive vomiting, GERD, abdominal distention & pain, constipation.	
Genital abnormalities	Follow up w/treating urologist as needed.	At initial visit in infancy
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, movement disorders.	At each visit
Congenital heart defects	Per treating cardiologist	Per treating cardiologist
Ophthalmologic involvement	Per treating ophthalmologist	Per treating ophthalmologist

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

Alpha-thalassemia X-linked intellectual disability (ATR-X) syndrome is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected individual with a 46,XY karyotype will not have the disorder nor will he be hemizygous for the *ATRX* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected individual with a 46,XY karyotype is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *ATRX* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If an affected individual with a 46,XY karyotype is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected individual may have a *de novo ATRX* pathogenic variant, in which case the mother is not a carrier. Only a minority (10%-20% of affected males) have a *de novo* pathogenic variant [Gibbons & Higgs 2000, Badens et al 2006a].

Sibs of a proband. The risk to sibs of a proband with a 46,XY karyotype depends on the genetic status of the mother:

- If the mother of the proband has an *ATRX* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Sibs with a 46,XY karyotype who inherit the pathogenic variant will be affected; sibs with a 46,XX karyotype who inherit the pathogenic variant will be heterozygous and will rarely show clinical manifestations (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *ATRX* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism. Maternal mosaicism (somatic and germline) for a pathogenic variant of *ATRX* has resulted in recurrent ATR-X syndrome in two brothers [Shimbo et al 2014]; presumed maternal mosaicism has been reported in two families [Bachoo & Gibbons 1999].

Offspring of a proband. No affected individual has reproduced.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the pathogenic variant and the aunts' offspring, depending on their karyotype, may be at risk of being heterozygotes (carriers) for the pathogenic variant or of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Carrier Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *ATRX* pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous for this X-linked disorder rarely show clinical manifestations of ATR-X syndrome (see Clinical Description, Heterozygous Females). (2) Identification of female heterozygotes requires either (a) prior identification of the *ATRX* pathogenic variant in the family or (b) if an affected individual with a 46,XY karyotype is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, 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 carriers, or are at risk of being carriers.

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 *ATRX* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk for ATR-X syndrome (i.e., an XY fetus) and preimplantation genetic testing are possible.

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

Resources

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

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **MedlinePlus**

Intellectual Disability

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Alpha-Thalassemia X-Linked Intellectual Disability Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATRX	Xq21.1	Transcriptional regulator ATRX	ATRX @ LOVD	ATRX	ATRX

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 Alpha-Thalassemia X-Linked Intellectual Disability Syndrome (View All in OMIM)

300032	ATRX CHROMATIN REMODELER; ATRX
301040	ALPHA-THALASSEMIA/IMPAIRED INTELLECTUAL DEVELOPMENT SYNDROME, X-LINKED; ATRX
309580	INTELLECTUAL DISABILITY-HYPOTONIC FACIES SYNDROME, X-LINKED, 1; MRXHF1

Molecular Pathogenesis

ATRX encodes ATRX, a transcription factor containing a zinc finger domain, which binds to DNA, and a helicase domain, which functions in the transcription process opening double-stranded DNA. In combination with other chromatin-associated proteins, the ATRX protein plays a role in chromatin remodeling, possibly silencing gene expression during development [Ausió et al 2003, Xue et al 2003, Tang et al 2004a, Tang et al 2004b, Kernohan et al 2010].

Mechanism of disease causation. Loss of function. While deletions, insertions, intragenic duplications, and nonsense and splice variants have been reported, a disproportionate number of variants are missense variants, and more than 90% of those reported are in regions encoding the zinc finger and helicase domains [Villard et al 1999b, Villard & Fontes 2002, Borgione et al 2003, Badens et al 2006a, Argentaro et al 2007, Thienpont et al 2007].

The abnormal ATRX protein downregulates the α-globin locus, resulting in thalassemia, and probably suppresses expression of other genes by disturbances in transcription and chromatin structure, leading to malformations and intellectual disability [Tang et al 2004a, Tang et al 2004b, Argentaro et al 2007, Nan et al 2007, Ritchie et al 2008, Kernohan et al 2010].

***ATRX*-specific laboratory technical considerations.** Pathogenic variants in *ATRX* are concentrated in the ADD (ATRX-DNMT3-DNMT3L) domain near the N-terminus and a cluster of helicase domains near the C terminus [Argentaro et al 2007].

Table 7. Notable *ATRX* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000489.4 NP_000480.3	c.109C>T	p.Arg37Ter	A common pathogenic variant that results in a milder phenotype [Basehore et al 2015]

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

Somatic *ATRX* variants associated with malignancy, summarized by Masliah-Planchon et al [2018], are truncating variants (frameshift and nonsense) in malignant gliomas [Cancer Genome Atlas Research Network 2015] and frameshift or nonsense variants and intragenic deletions in osteosarcomas [Chen et al 2014].

Chapter Notes

Author Notes

Web: Greenwood Genetic Center

Dr Stevenson's work focuses on the clinical and laboratory delineation of intellectual disability and birth defects.

Revision History

- 28 May 2020 (bp) Comprehensive update posted live
- 6 November 2014 (me) Comprehensive update posted live
- 3 June 2010 (me) Comprehensive update posted live
- 13 August 2009 (cd) Revision: deletion/duplication analysis no longer available clinically
- 15 October 2007 (me) Comprehensive update posted live
- 27 October 2006 (cd) Revision: mutation scanning clinically available
- 24 March 2006 (cd) Revision: sequence analysis of all 35 exons and associated splice junctions of *ATRX* clinically available
- 14 June 2005 (me) Comprehensive update posted live
- 15 April 2003 (me) Comprehensive update posted live
- 19 June 2000 (me) Review posted live
- 29 November 1999 (rs) Original submission

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