ATR-X

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SummaryClinical 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 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.

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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 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.

DiagnosisAlpha-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 birthGenital anomalies (in an individual with a 46,XY karyotype) that can range from hypospadias and undescended testes to ambiguous genitalia to normal external female genitaliaDevelopmental delay / intellectual disability, typically in the severe-to-profound rangeHematologic 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

DiagnosisThe 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 TestingMolecular 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 SyndromeView in own windowGene 1MethodProportion of Probands with a Pathogenic Variant 2 Detectable by Method

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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.

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

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

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Clinical CharacteristicsClinical DescriptionA 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 SyndromeView in own windowFeature% of Persons with FeatureCommentsDevelopmental delay100%A minority never speak or have meaningful speech.Intellectual disability100%Variable severity, from mild to profoundCharacteristic facies HypertelorismTelecanthusSmall noseTented upper lipOpen mouthProminent lips90%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.Microcephaly75%-85%Usually present at birth; head size of those w/out microcephaly usually in lower centilesShort stature60%-70%Usually present at birthGastrointestinal dysfunction70%-80%A major morbidity; incl: early feeding difficulty, vomiting, reflux, abdominal distention, obstruction, pain, & constipationGenital anomalies70%-80%Wide range, from minimal hypospadias or undescended testes to normal-appearing female external genitaliaNeurologicHypotonia80%-90%Contributes to facial phenotypeSeizures30%-40%Developmental Impairment / Intellectual DisabilitySevere 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 ImpairmentGrowth 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 ManifestationsGastrointestinal 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 AnomaliesGenital 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.HypotoniaHypotonia, a hallmark of ATR-X syndrome, contributes to the facial manifestations, drooling, developmental delay, and possibly to the gastrointestinal manifestations.SeizuresSeizures 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].OtherThe 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 yearsOne child, diagnosed with osteosarcoma of the femur with pulmonary nodules at age four years, who succumbed 18 months laterHeterozygous FemalesHeterozygous 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 CorrelationsPathogenic 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].PrevalenceThe 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.

Clinical DescriptionA 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 SyndromeView in own windowFeature% of Persons with FeatureCommentsDevelopmental delay100%A minority never speak or have meaningful speech.Intellectual disability100%Variable severity, from mild to profoundCharacteristic facies HypertelorismTelecanthusSmall noseTented upper lipOpen mouthProminent lips90%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.Microcephaly75%-85%Usually present at birth; head size of those w/out microcephaly usually in lower centilesShort stature60%-70%Usually present at birthGastrointestinal dysfunction70%-80%A major morbidity; incl: early feeding difficulty, vomiting, reflux, abdominal distention, obstruction, pain, & constipationGenital anomalies70%-80%Wide range, from minimal hypospadias or undescended testes to normal-appearing female external genitaliaNeurologicHypotonia80%-90%Contributes to facial phenotypeSeizures30%-40%Developmental Impairment / Intellectual DisabilitySevere 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 ImpairmentGrowth 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 ManifestationsGastrointestinal 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 AnomaliesGenital 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.HypotoniaHypotonia, a hallmark of ATR-X syndrome, contributes to the facial manifestations, drooling, developmental delay, and possibly to the gastrointestinal manifestations.SeizuresSeizures 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].OtherThe 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 yearsOne child, diagnosed with osteosarcoma of the femur with pulmonary nodules at age four years, who succumbed 18 months laterHeterozygous FemalesHeterozygous 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.

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Hypertelorism/telecanthus

Small nose

Tented upper lip

Open mouth

Prominent lips

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PrevalenceThe 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) DisordersNo 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 DiagnosisTable 3. Genes of Interest in the Differential Diagnosis of Alpha-Thalassemia X-Linked Intellectual Disability SyndromeView in own windowGene(s)DiffDx DisorderMOIClinical Features of DiffDx DisorderOverlapping w/ATR-X syndromeNot observed in ATR-X syndrome
HBA1

HBA2
Hemoglobin H (HbH) disease (See Alpha-Thalassemia.)AR 1Microcytic 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 infectionsAutistic behaviors & GI dysfunction observed in several affected boys50% 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 malesLarge open mouth & prominent lipsShort stature, microcephaly, & dental anomalies commonChildhood-onset kyphoscoliosis (often progressive)Life span ↓ in some persons

Short, soft, fleshy hands, often w/hyperextensible & tapering fingersChildhood-onset SIDAs in ~20% of persons 2Carrier 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-linked1. Alpha-thalassemia is usually inherited in an autosomal recessive manner.2. Childhood-onset SIDAs (stimulus-induced drop attacks) 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.

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ManagementEvaluations Following Initial DiagnosisTo 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 SyndromeView in own windowSystem/ConcernEvaluationComment

Growth

Assess height, weight, head circumferenceIn infants & children

Development

Developmental assessment

To incl motor, adaptive, cognitive, & speech-language evalEval 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 evalFor:

Nutritional statusSwallowing difficulties & aspiration riskGERD &/or recurrent vomitingGastric pseudo-obstructionConstipation

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 individualsConsultation w/pediatric urologist if surgical intervention required

Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OT evalTo incl assessment of:

Gross motor & fine motor skillsContractures, clubfoot, & kyphoscoliosisMobility & need for adaptive devicesNeed for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

Congenital

heart defects

Pediatric cardiologistSeptal defects require eval re possible intervention.

Ophthalmologic

involvement

Ophthalmologic examAssess for strabismus, ↓ visual acuity, structural eye defects (e.g., coloboma).

Genetic

counseling

By genetics professionals 1To 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 therapy1. Medical geneticist, certified genetic counselor, certified advanced

genetic nurseTreatment of ManifestationsTable 5. Treatment of Manifestations in Individuals with ATR-X SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

Seizures

Standardized treatment w/ASM by experienced neurologist

Many ASMs may be effective; none demonstrated effective specifically for this disorderEducation of parents/caregivers 1

Gastrointestinal/

Feeding

Feeding therapy; calorie-dense formula; gastrostomy tube placement as needed for persistent feeding issues

Usual treatment for GERD, constipationTreatment for gastric pseudo-obstruction per treating gastroenterologist/pediatric surgeon

Drooling

Anticholinergics, botulinum toxin type A injection of salivary glands &/or surgical redirecting of submandibular ductsOptions when drooling is a serious problem

Genital

abnormalities

Per treating urologist

Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OTUse 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 ophthalmologistASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapyDevelopmental Delay / Intellectual Disability Management IssuesThe 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

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SyndromeView in own windowSystem/ConcernEvaluationFrequency

Growth

Height, weight, head circumferenceAt each visit in infancy & childhood

Development

Monitor developmental progress & educational needs.

Gastrointestinal/

Feeding

Measurement of growth parametersEval of nutritional status & safety of oral intakeMonitor 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 cardiologistPer treating cardiologist

Ophthalmologic

involvement

Per treating ophthalmologistPer treating ophthalmologistEvaluation of Relatives at RiskSee Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.Therapies Under InvestigationSearch 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.

Evaluations Following Initial DiagnosisTo 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 SyndromeView in own windowSystem/ConcernEvaluationComment

Growth

Assess height, weight, head circumferenceIn infants & children

Development

Developmental assessment

To incl motor, adaptive, cognitive, & speech-language evalEval 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 evalFor:

Nutritional statusSwallowing difficulties & aspiration riskGERD &/or recurrent vomitingGastric pseudo-obstructionConstipation

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 individualsConsultation w/pediatric urologist if surgical intervention required

Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OT evalTo incl assessment of:

Gross motor & fine motor skillsContractures, clubfoot, & kyphoscoliosisMobility & need for adaptive devicesNeed for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)

Congenital

heart defects

Pediatric cardiologistSeptal defects require eval re possible intervention.

Ophthalmologic

involvement

Ophthalmologic examAssess for strabismus, ↓ visual acuity, structural eye defects (e.g., coloboma).

Genetic

counseling

By genetics professionals 1To 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 therapy1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

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Treatment of ManifestationsTable 5. Treatment of Manifestations in Individuals with ATR-X SyndromeView in own windowManifestation/ConcernTreatmentConsiderations/Other

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

Seizures

Standardized treatment w/ASM by experienced neurologist

Many ASMs may be effective; none demonstrated effective specifically for this disorderEducation of parents/caregivers 1

Gastrointestinal/

Feeding

Feeding therapy; calorie-dense formula; gastrostomy tube placement as needed for persistent feeding issues

Usual treatment for GERD, constipationTreatment for gastric pseudo-obstruction per treating gastroenterologist/pediatric surgeon

Drooling

Anticholinergics, botulinum toxin type A injection of salivary glands &/or surgical redirecting of submandibular ductsOptions when drooling is a serious problem

Genital

abnormalities

Per treating urologist

Musculoskeletal

Orthopedics / physical medicine & rehab / PT & OTUse of durable medical equipment & positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers)

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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 ConcernsConsultation 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.

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SurveillanceTable 6. Recommended Surveillance for Individuals with ATR-X SyndromeView in own windowSystem/ConcernEvaluationFrequency

Growth

Height, weight, head circumferenceAt each visit in infancy & childhood

Development

Monitor developmental progress & educational needs.

Gastrointestinal/

Feeding

Measurement of growth parametersEval of nutritional status & safety of oral intakeMonitor for excessive vomiting, GERD, abdominal distention & pain, constipation.

Genital

abnormalities

Follow up w/treating urologist as needed.At initial visit in infancy

Neurologic

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At each visit

Congenital

heart defects

Per treating cardiologistPer treating cardiologist

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involvement

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Therapies Under InvestigationSearch 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 InheritanceAlpha-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 DetectionMolecular 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 TestingOnce 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.

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

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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.

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].

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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].

Carrier DetectionMolecular 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].

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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.

Prenatal Testing and Preimplantation Genetic TestingOnce 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: 202-387-1968Fax: 202-387-2193

www.aaidd.org

MedlinePlus

Intellectual Disability

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Molecular GeneticsInformation 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 DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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) View in own window

300032ATRX CHROMATIN REMODELER; ATRX

301040ALPHA-THALASSEMIA/IMPAIRED INTELLECTUAL DEVELOPMENT SYNDROME, X-LINKED; ATRX

309580INTELLECTUAL DISABILITY-HYPOTONIC FACIES SYNDROME, X-LINKED, 1; MRXHF1Molecular PathogenesisATRX 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 VariantsView in own windowReference SequencesDNA NucleotideChangePredictedProtein ChangeComment [Reference]

NM_000489.4

NP_000480.3

c.109C>Tp.Arg37TerA 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 TumorsSomatic 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].

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Chapter NotesAuthor NotesWeb: Greenwood Genetic CenterDr Stevenson's work focuses on the clinical and laboratory delineation of intellectual disability and birth defects.Revision History28 May 2020 (bp) Comprehensive update posted live6 November 2014 (me) Comprehensive update posted live3 June 2010 (me) Comprehensive update posted live13 August 2009 (cd) Revision: deletion/duplication analysis no longer available clinically15 October 2007 (me) Comprehensive update posted live27 October 2006 (cd) Revision: mutation scanning clinically available24 March 2006 (cd) Revision: sequence analysis of all 35 exons and associated splice junctions of ATRX clinically available14 June 2005 (me) Comprehensive update posted live15 April 2003 (me) Comprehensive update posted live19 June 2000 (me) Review posted live29 November 1999 (rs) Original submission

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29 November 1999 (rs) Original submission

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