

# Alpha thalassemia-mental retardation, X linked

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[Abstract](#)

[Keywords](#)

[Disease name and synonyms](#)

[Diagnosis criteria](#)

[Differential diagnosis](#)

[Frequency](#)

[Clinical description](#)

[Hematology](#)

[Life expectancy](#)

[Etiology](#)

[Genotype/phenotype correlations](#)

[Diagnostic methods](#)

[Genetic Counseling](#)

[Unresolved Questions](#)

[References](#)

## Abstract

*X-linked alpha thalassemia mental retardation (ATR-X) syndrome is associated with profound developmental delay, facial dysmorphism, genital abnormalities and alpha thalassemia. The learning difficulties are not progressive with time. It is X-linked recessive and results from mutations in ATRX gene. ATRX protein is a member of the SNF2 family of ATPases and putative helicases, which are thought to have chromatin remodelling activity. Since alpha globin expression is down regulated in patients with ATRX mutations it may play a role in gene expression. It is a widely expressed protein, which is associated with heterochromatin. Mutations cause diverse changes in the pattern of DNA methylation at heterochromatic loci but it is not yet known whether this is responsible for the clinical phenotype.*

## Keywords

intellectual impairment, facial dysmorphism, genital abnormalities, ATRX gene

## Disease name and synonyms

X-linked alpha thalassemia mental retardation (ATR-X) syndrome

X-linked mental retardation-hypotonic face syndrome

**Allelic conditions:** Juberg-Marsidi (Villard *et al.*, 1996a), X-linked mental retardation with spastic paraplegia (Lossi *et al.*, 1999), Carpenter-Waziri (Abidi *et al.*, 1999), Holmes-Gang (Stevenson *et al.*, 2000), and Smith-Fineman-Myers (Villard *et al.*, 2000) syndromes.

## Diagnosis criteria

Since the identification of the disease gene, ATRX, and the ability to confirm the diagnosis by molecular means, it is clear that there are few *sine qua none* diagnostic features. Generally however, affected individuals have moderate to profound learning difficulties associated with a severe expressive language disorder (95% severe to profound mental retardation (MR)). Most cases (>90%) as infants will have a characteristic and recognisable facial gestalt. Some degree of genital abnormality is common (80%). Many affected individuals (90%) will have hematological signs of alpha thalassemia.

Other features: skeletal abnormalities (90%), microcephaly (75%), short stature (65%), seizures (30%), cardiac defects (20%), renal/urinary abnormalities (15%).

### Differential diagnosis

[Coffin-Lowry syndrome](#) may be confused with ATR-X syndrome, particularly in early childhood. Distinguishing features are the down-slanting palpebral fissures, broad nose, pudgy tapering digits, absence of genital abnormalities and the frequent presence of carrier manifestations in Coffin-Lowry syndrome. There is phenotypic overlap with Angelman syndrome (profound MR with absent speech and walking, seizures, happy disposition, emotional lability) and Smith-Lemli-Opitz (facial dysmorphism, skeletal and genital abnormalities). Diagnostic testing or mutational analysis should allow these conditions to be excluded in most cases.

### Frequency

Unknown.

### Clinical description

#### **Psychomotor Retardation and Central Nervous System**

Most cases of ATR-X syndrome have global developmental delay. However, even in less severely affected cases where general performance may be classified in the moderate level, expressive language is usually very limited.

In early childhood, all milestones are delayed. More severely affected cases do not walk until later in childhood and some never ambulate. Most have no speech, although an increasing number of individuals are being identified who have a few words or signs. The most severe cases may only have situational understanding, and most are dependent for almost all activities of daily living. More recent reports, however, point to a wider spectrum of intellectual handicap than previously thought. A mutation in the *ATRX* gene has recently been identified in family originally described by Carpenter and colleagues (Carpenter *et al.*, 1999). All affected males have moderate MR and exhibit expressive language delay though no psychometric evaluation is available. Guerrini and colleagues have reported a mutation in an Italian family with four affected male cousins, one has profound MR, whereas the others have intellectual quotient IQs of 41, 56 and 58 (Guerrini *et al.*, 2000). The basis for this marked variation is unknown.

Generally, affected individuals continue to acquire new skills though a brief period of neurological deterioration has been reported in three cases. In one report,

electroencephalogram EEG changes were consistent with encephalitis (Donnai *et al.*, 1991). The family originally reported by Holmes and Gang (Holmes and Gang, 1984) was subsequently shown to have a *ATRX* mutation (Stevenson *et al.*, 2000). All three affected males from this family died in childhood and the death of one was attributed to encephalitis.

As affected individuals age there is often a tendency toward spasticity. A recent report described a family with an *ATRX* mutation where affected members had spastic paraplegia from birth (Lossi *et al.*, 1999).

Seizures occur in approximately one third of cases and most frequently are clonic/tonic or myoclonic in nature. A number of parents have reported jerking movements which are not associated with epileptiform activity on EEG.

Assessment of vision and hearing is difficult. Vision usually appears normal although two cases have been reported as blind. Optic atrophy or pale discs are commonly noted as are refractive errors (especially myopia). Sensorineural deafness has previously been considered a feature that distinguishes ATR-X syndrome from the allelic condition Juberg-Marsidi syndrome (Saugier-Veber *et al.*, 1995). However, of the 13 cases with a documented sensorineural hearing deficit 7 have a thalassemia.

Although the head circumference is usually normal at birth, post-natal microcephaly usually develops. Macrocephaly has not been reported. Computed tomography CT or medical resonance MR brain imaging are generally unremarkable, although mild cerebral atrophy may be seen. In two cases, partial or complete agenesis of the corpus callosum has been reported. There have been autopsy reports in only three cases. The brain was small in each; in two the morphology was normal, in one the temporal gyri on the right were indistinct and there was hypoplasia of the cerebral white matter.

### **Behavioral phenotype**

No systematic study of behaviour has been carried out in ATR-X syndrome. Consequently most reports of behavioral characteristics are anecdotal and ascertainment has been limited. Nevertheless a thumbnail sketch of the mannerisms of this condition is slowly emerging (Kurosawa *et al.*, 1996) (Wada *et al.*, 1998) and this may be diagnostic.

The subjects are usually described by their parents as content and of a happy disposition. Affected individuals exhibit a wide range of emotions that are usually appropriate to their circumstances. There have been reports, however, of unprovoked emotional outbursts

with sustained laughing or crying. There may be emotional fluctuation with sudden switches between almost manic-like excitement or agitation to withdrawal and depression. In several instances the episodes of crying have been thought to be associated with pain, possibly of a gastrointestinal origin (see below).

Whereas many of the individuals are affectionate to their caregivers and appreciate physical contact, some cases exhibit autistic-like behavior: patients appear to be in a world of their own, show little interest or even recognition of those around them, and avoid eye contact. The latter behavior may be associated with an unusual and persistent posture.

Affected persons may be restless, exhibiting choreoathetoid-like movements. Frequently, they put their hands into their mouths and may induce vomiting. Sometimes, they engage in self-injurious behavior, biting or hitting themselves. They may hit, push or squeeze their necks with their hands to the point of cyanosis, a state they may also achieve through breath-holding. They may exhibit obsessional behaviour such spinning on one spot while gazing into a light. Repetitive stereotypic movements may be manifest and these may vary from pill-rolling or hand flapping. These characteristic behaviors are reminiscent of Angelman syndrome and may lead to diagnostic confusion.

#### **Facial Anomalies**

Distinctive facial traits are most readily recognized in early childhood and the gestalt is probably secondary to facial hypotonia. The frontal hair is often upswept, there is telecanthus, epicanthic folds, flat nasal bridge and mid-face hypoplasia, a small triangular upturned nose with the alae nasi extending below the columella and septum. The upper lip is tented, the lower lip full and everted giving the mouth a "carp-like" appearance. The frontal incisors are frequently widely spaced, the tongue protrudes and there is prodigious dribbling. The ears may be simple, slightly low set and posteriorly rotated.

#### **Genital Abnormalities**

Genital abnormalities are seen in 80% children. These may be very mild, e.g., undescended testes or deficient prepuce, but the spectrum of abnormality extends through hypospadias, micropenis to ambiguous or female external genitalia. The most severely affected children, who are clinically defined as male pseudohermaphrodites, are usually raised as females. In such cases, there are no Mullerian structures present and dysgenetic testes or streak gonads have been found intra-

abdominally (Wilkie *et al.*, 1990) (Ion *et al.*, 1996). Of particular interest is the finding that these abnormalities breed true within families (McPherson *et al.*, 1995). Puberty is frequently delayed and in a few cases appears to be arrested. Curiously, premature adrenarche has been noted in two children.

#### **Skeletal Abnormalities**

A wide range of relatively mild skeletal abnormalities have been noted some of which are probably secondary to hypotonia and immobility (Gibbons *et al.*, 1995). Fixed flexion deformities, particularly of the fingers, are common. Other abnormalities of the fingers and toes that have been observed are: clinodactyly, brachydactyly, tapering of the fingers, drum stick phalanges, cutaneous syndactyly, overlapping of the digits, and a single case with a bifid thumb. Foot deformities occur in 29% and include pes planus, talipes equinovarus and talipes calcaneovalgus. Almost a third of the cases have kyphosis and/or scoliosis and chest wall deformity has been seen in 10 cases. Sacral dimples were present in 3 cases, radiological spina bifida in 2 and other abnormalities of the vertebrae in 5 cases. Only a few of the cases have had thorough radiological investigation. In those who have, the most common findings were delayed bone age and coxa valga. Short stature was seen in two thirds of cases. Longitudinal data are available in only a few cases. As has been noted previously, in some patients growth retardation is apparent throughout life whereas in others it has become manifest at a later stage, e.g. at the time of the pubertal growth spurt.

#### **Miscellaneous Abnormalities**

Recurrent vomiting, regurgitation or gastroesophageal reflux, particularly in early childhood, is a common finding and seems likely to be a manifestation of a more generalised dysmotility of the gut. In severe cases, surgical treatment by fundoplication has been undertaken as have feeding gastrostomies. An apparent reluctance to swallow has been reported by several parents and probably reflects the dyscoordinated swallowing that has been observed radiologically in two well studied cases. The tendency to aspiration is commonly implicated as a cause of death in early childhood. Excessive drooling is very common as is frequent eructation. Constipation occurs often and in some individuals is a major management problem. Hospital admissions for recurrent ileus have been reported in 2 cases and reduced intestinal mobility has been observed radiologically in 4 cases. Two patients required partial resection of the ileum after developing ischaemia of the small

bowel which in one case was attributed to a volvulus. Volvulus has been reported in an additional case. One child required a right hemicolectomy following an episode of necrotising enterocolitis at 13 days of age.

There is evidence to suggest that the affected individuals are susceptible to peptic ulceration. Esophagitis, esophageal stricture and peptic ulcer have been observed endoscopically in single cases. In five cases there has been evidence of an upper gastro-intestinal bleed, one of which required transfusion (hemoglobin 5g/dl). Pain resulting from peptic ulceration is one possible explanation for the episodes of persistent crying and food refusal reported by a number of parents.

A wide range of cardiac abnormalities have been noted: septal defects (10 cases); patent ductus arteriosus (6); pulmonary stenosis (3); aortic stenosis (2); Tetralogy of Fallot (2) and single cases of transposition of the great arteries, dextracardia with situs solitus and aortic regurgitation.

Renal abnormalities (hydronephrosis, renal hypoplasia or agenesis, polycystic kidney, vesico-ureteric reflux) may present with recurrent urinary tract infections.

### Hematology

Although initially the presence of a thalassemia was one of the defining elements of the syndrome, it is clear that there is considerable variation in the hematological manifestations associated with *ATRX* mutations. A number of families have been identified in which some or all of the affected members have no signs of a thalassemia (Villard *et al.*, 1996b,c). Nevertheless, the test for a thalassemia is simple and, when positive, quickly establishes the diagnosis. The most sensitive test uses light microscopy to detect red cells containing HbH inclusions after incubation, at room temperature, of venous blood with 1% brilliant cresyl blue for 4-24 hours. HbH is unstable and cells with inclusions may be more difficult to find in older blood samples. When the family history and phenotype are strongly suspect, a careful search for inclusions should be made in all the affected individuals and repeated if necessary as they may be very infrequent. It is important to note that, in most cases of ATR-X, there is insufficient HbH to be detected by electrophoresis. The hematology is often surprisingly normal considering the presence of a thalassemia. Neither the hemoglobin concentration nor mean cell hemoglobin are as severely affected as in the classical forms of a thalassemia that are associated with cis-acting mutations in the a

globin complex and this probably reflects the different pathophysiology of the conditions.

### Life expectancy

In the 168 patients described there have been 25 deaths. The cause was established in just over half of which there were six cases of pneumonia and four due to aspiration of vomitus. They appear to be particularly vulnerable in early childhood with 19 of the deaths occurring under the age of five years and this may be associated with the fact that gastro-esophageal reflux and vomiting are often more severe in the early years. There are no long term longitudinal data in this relatively newly described syndrome but a number of affected individuals are fit and well in their 30s and 40s.

### Etiology

The disease gene, *ATRX*, lies at Xq13.3 (Gibbons *et al.* 1995). It spans about 300 kb of genomic DNA and contains 36 exons (Picketts *et al.*, 1996). It encodes at least two alternatively spliced ~10.5 kb mRNA transcripts which differ at their 5' ends and are predicted to give rise to slightly different proteins of 265 and 280 kD respectively. The protein belongs to the SNF2 family of helicase/ATPases, members of which are involved in a wide variety of cellular functions including the regulation of transcription (SNF2, MOT1 and brahma), control of the cell cycle (NPS1), DNA repair (RAD16, RAD54 and ERCC6) and mitotic chromosome segregation (Iodestar). It is believed that their function is to facilitate these processes by remodelling chromatin. Another important feature of the *ATRX* protein is the presence, at the N terminal, of a zinc finger domain (called the ADD domain) which is related to sequences seen in the DNMT3 (DNA methyltransferase 3A) family of *de novo* DNA methyltransferases (Xie *et al.* 1999). It is not known if this domain is involved in protein or DNA interactions. The majority of naturally occurring mutations in the *ATRX* gene occur in the ADD and helicase domains (Gibbons and Higgs, 2000). It is thought likely that all the mutations are associated with loss of function.

The function of the *ATRX* protein is unknown but the fact that alpha globin expression is perturbed in the patients suggests that it may play a role in gene expression. Protein studies have shown that *ATRX* is a nuclear protein with a punctate staining pattern (McDowell *et al.*, 1999). In mouse cells and to a lesser extent in human cells, the majority of the protein is associated with DAPI bright regions of the nucleus, which are known to represent pericentromeric heterochromatin. Evidence is also accumulating

for an interaction between ATRX and another heterochromatic protein, HP1 (Le Douarin *et al.*, 1996) (Berube *et al.*, 2000). One additional striking finding in human metaphase preparations is that ATRX antibodies consistently localize to the short arms of acrocentric chromosomes and co-localizes with a transcription factor (upstream binding factor) that is known to bind the rDNA arrays in nucleolar organizer regions (McDowell *et al.*, 1999).

The effects of ATRX mutations on the chromatin structure of the rDNA arrays located in these regions have been studied. Although no gross changes in DNAase1, micrococcal nuclease or endonuclease accessibility was detected, striking differences were noted in the pattern of rDNA methylation between normal controls and patients with ATR-X syndrome (Gibbons *et al.*, 2000). In normal individuals, approximately 20% of the transcribed units were methylated; whereas, in ATR-X patients, rDNA genes were substantially unmethylated. An extensive survey of the genome has identified two additional sequences that are abnormally methylated in ATR-X patients. Y-specific repeats (DYZ2) are almost all methylated in ATR-X patients, while ~6% are unmethylated in peripheral blood of normal individuals. Subtle changes in the pattern of methylation have also been observed in the TelBam3.4 family of repeats that are mainly found in the subtelomeric regions.

It is not clear whether the perturbation of methylation that is observed in affected individuals plays a role in the etiology of the condition. To date, no change in the pattern of methylation has been detected in the  $\alpha$  globin gene cluster that might explain the reduced expression of the  $\alpha$  globin genes compared with expression of the  $\beta$  globin genes.

### Genotype/phenotype correlations

Since the discovery of the ATRX gene, most new cases have been defined on the basis of severe MR with the typical facial appearance associated with a mutation in the ATRX gene. This allows a less biased evaluation of the effect of ATRX mutations on the commonly associated clinical manifestations. The severity of three aspects of the phenotype, mental retardation, genital abnormality and alpha thalassemia, are quantifiable to some degree.

The greatest variation in intellectual handicap is associated with a truncating mutation at the N-terminal of the protein (Guerrini *et al.*, 2000). Analysis of the RNA derived from patient cell lines showed no alternate splicing that might be associated with skipping of the mutation and degrees of phenotypic rescue. As discussed

above, protein analysis by Western blotting has shown small amounts of full-length protein for each patient. This may be associated with inefficient recognition of the premature stop codon or possibly the use of an alternative, downstream translational initiation codon. Nevertheless, there is no obvious correlation between the degree of retardation and the amount of full-length protein.

There are now eight different mutations associated with the most severe urogenital abnormalities. In five, the protein is truncated resulting in the loss of the C-terminal domain including a conserved element and polyglutamine tract. From the available data it appears that in the absence of the C-terminal domain, severe urogenital abnormalities are likely (though not inevitable as one mutation in this region was associated with cryptorchidism) suggesting that this region may play a specific role in urogenital development. At other sites, however, there is no obvious link between phenotype and genotype and there is considerable variation in the degree of abnormality seen in individuals with identical mutations.

The relationship between ATRX mutations and a thalassemia is unclear. Since the presence of excess  $\beta$  chains (HbH inclusions) was originally used to define the ATR-X syndrome, current observations are inevitably biased. Nevertheless, there is considerable variability in the degree to which a globin synthesis is affected by these mutations as judged by the frequency of cells with HbH inclusions. Some patients do not have HbH inclusions (Villard *et al.*, 1996a,b,c), although this does not rule out down regulation of a globin expression since inclusions may not appear until there is 30-40% reduction in a chain synthesis (Higgs *et al.*, 1989). It is interesting that patients with identical mutations may have very different, albeit stable, degrees of a thalassemia suggesting that the effect of ATRX protein on a globin expression may be modified by other genetic factors. Furthermore, comparison of the 32 cases from 26 pedigrees with the common 736C>T mutation shows a variation in the frequency of HbH inclusions from 0 to 14%.

### Diagnostic methods

#### Detection of alpha thalassemia

The most sensitive test uses light microscopy to detect red cells containing HbH inclusions after incubation, at room temperature, of venous blood with 1% brilliant cresyl blue (in normal saline) for 4-24 hours.

**Mutation detection**

The majority of disease causing mutations are single base changes, most of which are missense mutations. The gene is large and comprehensive mutation analysis, even of the coding region, is a time consuming and expensive enterprise. However, the missense mutations are clustered, 50-60% of mutations are identified in the ADD domain, and the next most commonly affected region is the helicase domain. A sensible and economical approach is to start by analysing these regions.

**Protein studies**

Levels of ATRX protein were found to be substantially reduced in a number of patients with missense mutations involving the ADD domain (McDowell, *et al.*, 1999) (Cardoso *et al.*, 2000). Analysis of the ATRX protein may also show a truncation in affected individuals which allows more directed sequencing.

**X inactivation studies**

X-chromosome inactivation studies may be used to determine the carrier status of at-risk women. Because the number of carriers with random X-chromosome inactivation has not been thoroughly studied, the possibility of false positives and false negatives in this test is of concern. Most females who are unaffected carriers for alpha-thalassemia X-linked mental retardation syndrome have skewed X-chromosome inactivation (Gibbons *et al.* 1992). In normal women, one X-chromosome in each cell is randomly inactivated; only 10% of normal females show skewed X-chromosome inactivation. In some X-linked conditions, including alpha-thalassemia X-linked mental retardation syndrome, the X chromosome with the mutated ATRX gene is preferentially inactivated (Plenge *et al.* 2002). This phenomenon is referred to as "non-random" or "skewed" X-chromosome inactivation and can be identified by established laboratory techniques. Since non-random X-chromosome inactivation is not unique to ATR-X syndrome, the test is a supportive test only, to be used in the context of a suggestive clinical and/or family history.

**Genetic Counseling**

ATR-X syndrome is an recessive X-linked condition. Female carriers are phenotypically and intellectually normal and therefore additional tests are required to determine a female's genotype. In the past, skewed X-inactivation has been utilized as a marker for carriers of the ATRX mutation. However, for the reasons given above, this method should be used with caution; 25% obligate female carriers exhibit rare cells with HbH inclusions but obviously a negative

result does not exclude carriage of a mutation. Since the identification of the ATRX gene, mutation detection has become the mainstay of carrier identification. In families in which the causative mutation has not been identified, linked markers may be used to identify whether descendants of an obligate carrier have inherited the disease-associated haplotype.

For the female who has been identified as a carrier, there is a 50% risk of passing on the disease allele but, since only males are clinically affected, the risk of having an affected child is 25% for each pregnancy. Prenatal diagnosis for such at risk females is feasible.

The principal issue when counseling is determining the risk of recurrence for families with a sporadic case of ATR-X. One small study showed that 17/20 mothers of sporadic cases were carriers (Bachoo and Gibbons, 1999). Therefore, in families where the mutation has not been identified, 85% of the mothers of sporadic cases would be expected to be carriers.

Another important consideration concerns the possibility of germline mosaicism. This has been recently reported in ATR-X syndrome and means that, despite a negative mutation test, a mother of an ATR-X case may still be at risk of further affected offspring (Bachoo and Gibbons, 1999). It is advisable to offer all mothers of affected children prenatal diagnosis even if they are negative for the ATRX mutation.

**Unresolved Questions**

1. The function of ATRX protein is not known. It is not clear how loss of function mutations in a protein associated with repressive heterochromatin might lead to reduced expression of a target gene (eg alpha globin). Its role in DNA methylation is also unknown.
2. What are the 'target' genes whose expression is directly influenced by ATRX? How are these related to the observable phenotype?
3. Why is there variability in the features of the phenotype, for example the presence and severity of alpha thalassemia is variable even for a given mutation and it seems likely that modifying genes are involved. Obvious candidates are genes encoding for other protein components of heterochromatin.
4. What is the frequency of ATR-X syndrome?

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