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# Natural history of alpha-thalassemia X-linked intellectual disability syndrome: A case report of a 45-year-old man

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## Abstract

We have followed the clinical course of a 45-year-old man with a severe form of alpha-thalassemia X-linked intellectual disability syndrome for 40 years. The most challenging health issue is the combination of rumination, drooling, and vomiting. The patient achieved present adaptive and motor skills in his teenage years. He is able to move on the floor in a sitting position. He seems happy and has not shown any behavioral or psychiatric symptoms. New signs not described in the literature before are accelerated growth after puberty and atypical sleeping position with upper body resting on legs.

## KEYWORDS

alpha-thalassemia X-linked intellectual disability, rumination-drooling-vomiting sign, X-chromosomal syndrome

## 1 | INTRODUCTION

The number of males with an intellectual disability (ID) is greater than that of females primarily due to X-chromosomal ID syndromes. The most common of these is fragile X syndrome. Other genetic X-linked syndromes include, for example, Partington and Coffin-Lowry syndromes and alpha-thalassemia X-linked ID syndrome (ATRX-IDS).

The *ATRX* gene (MIM \*300032) on chromosome Xq21.1 encodes a protein which belongs to the switch/sucrose non-fermentable (SWI/SNF) family of chromatin remodeling proteins. It has various functions in the cell including gene expression and DNA replication (Bérubé et al., 2000; Cardoso et al., 1998; Picketts et al., 1996; Xue et al., 2003). The protein is highly expressed in various tissues, including the brain. The X-linked disorder, ATRX-IDS (MIM #301040) is caused by mutations of the *ATRX* gene (Gibbons & Higgs, 2000). There are currently more than 150 putative disease-causing variants in *ATRX*, of which approximately a third are loss of function variants (frameshift, nonsense, splice site, gross deletions), while the majority of the remaining variants are missense variants (Gibbons & Higgs, 2000). Pathogenic variants located in the zinc finger domain of the *ATRX* protein have been reported to produce severe psychomotor

impairment (Badens et al., 2006), whereas pathogenic variants in the helicase domains cause milder phenotypes (Gibbons & Higgs, 2000; Moncini et al., 2013). In general, the phenotype is characterized by distinctive craniofacial features, microcephaly, genital anomalies, skeletal anomalies, hypotonia, and ID that is typically severe to profound (Gibbons, 2006; Smith et al., 1980). Many patients have been reported to have alpha-thalassemia, as indicated by the presence of hemoglobin H inclusions (Gibbons et al., 1995).

We describe the disease history of a 45-year-old man with a severe form of ATRX-IDS. He lives in institutional care where the first author has followed him for 40 years. Clinical information and images are published with the consent of the patient's mother.

## 2 | CASE DESCRIPTION

The patient is the only child of a healthy nonconsanguineous couple. He was born normally after an uncomplicated pregnancy at 37th gestational week. His birth measurements were normal (weight 3110g [−1SD], height 49 cm [−1SD], head circumference 33 cm [−1SD]). He spent the first weeks of life in hospital because of vomiting and

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failure to breastfeed. At the age of 3 months, alternating strabismus, undescended testes, and muscular hypotonia were recorded. By the age of 9 months, he had learned to turn from supine to prone position. At the age of 1, his adaptive age according to the Vineland test was 2 months, indicating severe developmental delay. He was diagnosed as having dystonic tetraplegia of unknown cause.

During childhood, the patient showed advances in his motor skills. By the age of 7 years, he had learned to rise into a sitting position and to sit without support. Facial anomalies at this age are illustrated in Figure 1(a). By the age of 10 years, he could move on the floor in a sitting position. He had no speech. His adaptive age according to the Vineland test was 4–5 months, corresponding to profound ID.

As a teenager the patient (Figure 1(b)) learned to stand with support and to use a spoon and drink from a cup. There appeared to be no pubertal growth spurt, at the age of 17 years his height was

120 cm (–9SD). Otherwise, his condition remained stable. He communicated with eye contact and reacted to simple instructions.

At present, the patient has short stature, although between the ages of 17 and 45 years he grew 27 cm, and his present height is 147 cm (–6SD), weight 47 kg, and head circumference 51 cm (–6SD). His dysmorphic facial features show coarsening with age (Figure 1(c)). His genitals are dysmorphic with a long shaft and an enlarged glans penis and an undescended, small testis on one side and a small testis on the contralateral side (testis saltans). He needs constant help and wears diapers. He assists when being dressed by straightening his arms and legs. When standing supported his legs are rotated outwards at the hips (Figure 2). His feet exhibit *pes cavus calcaneovalgus* deformity (Figure 2). He can walk with a walker. He speaks no words but understands a little and may become excited by music and smells. He sleeps well and often in an atypical sitting position with his upper



**FIGURE 1** (a) The patient at the age of 3 years. (b) The patient at the age of 13 years. (c) The patient at the age of 45 years [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**FIGURE 2** The patient's feet, pes cavus calcaneovalgus [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIGURE 3** The sleeping position [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

body resting on his legs (Figure 3). He seems happy and has not shown any behavioral or psychiatric symptoms.

### 3 | HEALTH

Rumination–drooling–vomiting is the main health concern of our patient. Since the age of 2 years, he has pushed his fingers into his throat to provoke vomiting which has also caused finger skin irritation. His extensive drooling and rumination have resulted in dental erosion and caries. These symptoms have been treated without success with several medications including antihistamine, scopolamine, and anticholinergic drugs. He wears a helmet and thick gloves to hamper mouth touching; however, this does not prevent rumination. At present, his only medication is esomeprazole and while rumination is less frequent than before, he continues to vomit several times per week.

## 4 | DIAGNOSTICS

Etiological studies during childhood revealed no cause for his abnormally slow development. Pneumoencephalography, karyotype, and metabolic screening were normal. Electroencephalogram showed general attenuation. Radiological examinations revealed osteoporosis, slight scoliosis, and Erlenmeyer deformity in femurs (Faden et al., 2009).

In 1994, the patient was the first individual to receive an ATRX diagnosis in Finland. A clinical geneticist suggested hematological studies in which inclusions of abnormal hemoglobin in erythrocytes were observed. The clinical picture and hematological findings matched an ATRX-IDS diagnosis. Furthermore, in 2000 the ATRX-IDS diagnosis was confirmed by Sanger sequencing of the gene and in 2020 Blueprint Genetics X-linked ID Panel identified a hemizygous missense variant ATRX c.717C>G, p.Phe239Leu. This DNA variant has not been reported in the Genome Aggregation Database control population cohorts (gnomAD, in >120,000 exomes and >15,000 genomes). It is also not found in the exAC or 1000 G databases either. Phenylalanine is a highly conserved amino acid and there is a physicochemical difference between phenylalanine and leucine. The observed missense variant is in Exon 8 in a functionally important domain which also is a mutation hotspot (Badens et al., 2006). All in silico tools utilized predict this variant to be damaging to protein structure and function. Another variant of the same codon, ATRX c.717C>A has been identified in a patient with ATRX syndrome (Gibbons & Higgs, 2000). Both variants lead to the same amino acid change p.Phe239Leu.

The mother of our patient has received genetic counseling but has not been tested for carrier status. The patient does not have sisters or close female relatives at risk.

## 5 | DISCUSSION

We describe the history of a middle-aged man with severe ID whose ATRX-IDS is most likely caused by a previously undescribed variant of the ATRX gene.

Sequence analysis of the three most important exons 20 years ago and recently of all the exons of the gene using a gene panel for X-linked ID identified a hemizygous missense variant *ATRX* c.717C>G, p.Phe239Leu in our patient. The amino acid alteration is, however, the same as in one previously reported patient. Unfortunately, his clinical picture was not reported (Gibbons & Higgs, 2000, Patient 14).

Otherwise, the clinical picture of *ATRX*-IDS has been largely described in the literature (Badens et al., 2006; Gibbons & Higgs, 2000); however, we found no description of a natural history up to middle age.

To summarize, our patient achieved his present adaptive and motor skills in his teenage years and since his teenage years no major changes in his condition have been observed. He has short stature due to exceptionally slow growth and lack of pubertal acceleration. However, ongoing growth may have taken place in adulthood, since his present height is almost 30 cm more than at the age of 20 years. Unfortunately, we found no height measurements between ages 20 and 45 years. His facial appearance is typical for the syndrome. Comparing present and childhood photographs, progressive coarsening of facial features can be observed. The most important skeletal finding is the external rotation at both hips. The most challenging health issue is the combination of rumination, drooling, and vomiting. These symptoms have only slightly attenuated since his teenage years. The atypical sleeping position has earlier been published in our paper describing a patient with Coffin–Siris syndrome (Määttänen et al., 2018) but reports of this sleeping position in patients with *ATRX*-IDS is not found in the literature. The observation of our patient's abnormally slow but long-lasting growth may be a new medical finding. This may be related to the role of *ATRX* in the cells as an important transcriptional regulator.

To conclude, in spite of severe and multiple disabilities, the patient is happy and without any behavioral or psychiatric symptoms.

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## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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