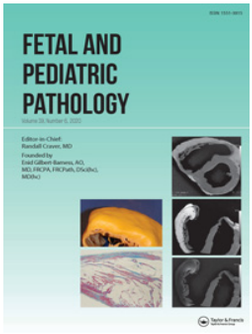

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A Novel ATRX Mutation Presenting with Intellectual Disability and Severe Kyphoscoliosis

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ABSTRACT

Background: ATR-X syndrome is an X-linked clinical condition usually associated with profound intellectual disability, facial dysmorphism and alpha-thalassemia. The syndrome is clinically heterogeneous with a broad phenotypic spectrum. Although, alpha-thalassaemia is commonly present, it may not manifest in some patients.

Case report: A novel missence mutation (NM_000489: ATRX; c.6130C > T; p.Leu2044Phe) was detected in the ATR-X gene in two male siblings with severe intellectual disability, dysmorphic facial appearance and skeletal anomalies. Severe kyphoscoliosis was the main finding. Hematologic findings, one of the well-known clinical entities, were not present.

Conclusion: The missense mutation we have described in our patients has not been previously reported. This finding enriches mutation spectrum of *ATRX* (OMIM #300032) gene. This missense mutation, which is associated with ID and kyphoscoliosis and without alpha-thalassemia, contributes to genotype-phenotype correlation of the ATR-X spectrum. This case report provides further evidence that reverse genetics is a useful approach in diagnostic process of syndromic patients in adulthood.

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KEYWORDS
ATR-X Syndrome; *ATRX*; *XH2*; kyphoscoliosis

Introduction

Alpha-thalassemia X-linked intellectual disability (ATR-X) syndrome is characterized by intellectual disability, short stature, microcephaly, districtive facial features, genital anomalies, hypotonia and in some cases mild microcytic anemia secondary to alpha-thalassemia. Hypogonadism, renal anomalies, skeletal defects are other commonly reported findings of this phenotype [1–5]. The syndrome is inherited in an X-linked manner and carrier females do not manifest typical findings of the sydrome [4]. Gibbons et al. [6] showed that mutations in the *ATRX* gene (# 300032) [7] causes ATR-X syndrome.

We present two male siblings with severe intellectual disability, slender body, microdolichocephaly, open mouth, kyphoscoliosis and micropenis. Widely spaced upper incisors, medical history of hypotonia, cryptorchidism and constipation were noted in one. Both of them carry a novel missense mutation in the *ATRX* gene.

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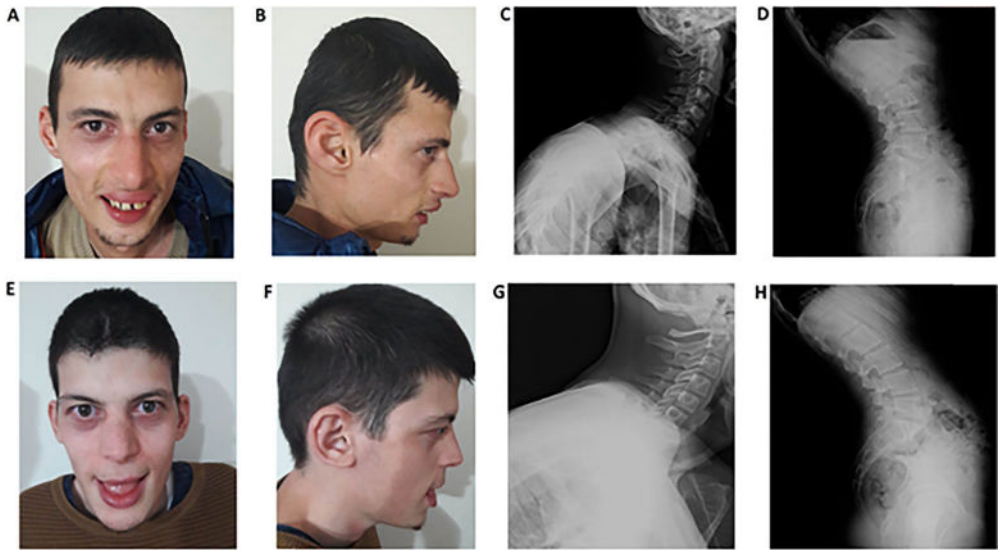

Figure 1. Facial appearance and radiological findings of patients (A–D: older sibling, E–H: younger sibling). Facial dysmorphism of the patients comprised micro-dolichocephaly, midface hypoplasia, hyperfolded ears, open mouth, full lips (A,B,E,F). Also widely spaced upper incisors in older sibling (A). Spine X-ray shows severe kyphoscoliosis (C,D,G,H).

Clinical report

The older siblings, (Fig. 1A,B) was 24-years old and the first child of non-consanguineous parents. He had severe intellectual disability, absent speech and micro-dolichocephaly with slender body (occipital frontal circumference (OCF): 50 cm, height: 165 cm, weight: 38 kg). Clinical examination also showed midface hypoplasia, hyperfolded ears, open mouth, full lips, widely spaced upper incisors, kyphoscoliosis (Fig. 1C,D), slender fingers and micropenis. His medical history was remarkable for cryptorchidism, constipation and hypotonia.

The younger sibling (Fig. 1E,F) was 22-year old. He also had severe intellectual disability, absent speech and micro-dolichocephaly with slender body as his brother (OFC: 51 cm, height: 172 cm, weight: 49 kg). Bitemporal narrowing, midface hypoplasia, open mouth, thick everted vermilion of the lower lip, prognatism, kyphoscoliosis (Fig. 1G,H), slender fingers and micropenis were also noted. He had repetitive movements and aggressive behavior.

Both patients have normal complete blood count parameters and hemoglobin electrophoresis.

Pedigree was remarkable for a maternal uncle, who had micro-dolichocephaly, profound intellectual disability and kyphoscoliosis. He had died at the age of 18. The family originates from Turkey and the patients have no other siblings.

Methods

Informed consents were received from family for genetic investigation and publication. Peripheral blood DNA samples were used for analyses. Whole Genome Sequencing was performed by Illumina sequencing generating 100–125 bp (on HiSeq 2500) or 150 bps

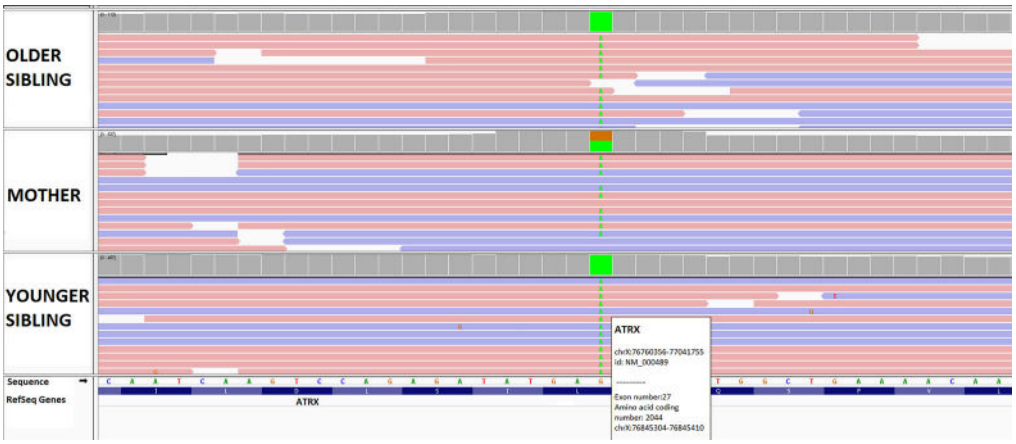

Figure 2. MiSeq of variant (NM_000489: *ATRX*; c.6130C > T; p.Leu2044Phe). Male siblings were both hemizygous and mother was carrier for the same variant.

(on HiSeq X Ten) paired-end reads per lane. Variant filtering steps were processed to identify the disease related mutation. Variant was further confirmed by MiSeq. The *ATRX* gene exon 27 was amplified by PCR using appropriate primers. Post-PCR products were confirmed by agarose gel electrophoresis. The library was prepared using the Nextera XT DNA library preparation kit and were run on the MiSeq instrument. The results were analyzed using Integrative Genomics Viewer.

Results

De novo, autosomal, homozygous, compound heterozygous, X-linked and structural variants were analyzed. A hemizygous, missense c.6130C > T; p.Leu2044Phe variant in *ATRX* gene was considered to be responsible for the phenotype. The variant was not identified in 1000 Genomes (http://browser.1000genomes.org/index.html) [8] and ExAC databases (http://exac.broadinstitute.org/) [9]. The impact of the mutation on ATRX structure and function was described as damaging by *in silico* analysis: Mutation tasterVR software predicted this variant as a disease causing variation (prob: 0.99999999903957) [10], damaging by SIFT (score: 0.001) [11] and probably damaging by PolyPhen-2 (score: 0.999) [12]. Mother was shown to be a carrier for the same mutation (Fig. 2).

Discussion

Mutations of the *ATRX* gene (*ATRX*, helicase 2 X linked – *XH2*, X linked nuclear protein gene – *XNP*), located on chromosome Xq21.1, was shown to cause ATR-X syndrome [7]. ATRX protein is a nuclear protein, belongs to a subgroup of SWI/SNF DNA helicases related to DNA recombination, DNA repair and transcription regulation [6]. Belonging to a DNA helicases subgroup, ATRX protein may exert its function by regulating gene expression over chromatin structure or function [13]. The missense mutation we identified in this report is (NM_000489: *ATRX*; c.6130C > T; p.Leu2044Phe) on the helicase domain of ATRX [14]. This part of the protein interacts with MeCP2 [15]. The mutation probably disrupts MeCP2 and ATRX interaction, with resultant intellectual disability.

Although two missense mutations, at positions 2041 and 2050 were previously reported (p.Ser2041Asn, p.Ile2050Thr) in patients with ATR-X syndrome (http://www.ncbi.nlm.nih.gov/clinvar/) [16], no polymorphisms were reported in this area of the protein. The impact of the missense mutation we identified (NM_000489: *ATRX*; c.6130C > T; p.Leu2044Phe) on the protein structure and function is described as damaging. Based on all the information above, this variant was interpreted as likely pathogenic.

Hematologic manifestations vary in ATR-X syndrome. Alpha-thalassemia is seen in %90 of patients with ATR-X syndrome while hematologic findings are normal in some patients [17]. The most sensitive test for HbH is the observation of HbH inclusions in erythrocytes by light microscopy after incubation with 1% brilliant cresyl blue [18]. Although a search for HbH inclusions was not conducted, complete blood count parameters and hemoglobin electrophoresis were normal.

Most phenotypic findings are more characteristic in early childhood compared to later in life in ATR-X syndrome [4]. Alpha-thalassemia is the important finding in distinguishing this syndrome from other overlapping ones. The siblings were adults at initial evaluation and alpha-thalassemia was not detected. Molecular genetic testing was a comprehensive tool for final diagnosis.

In this family, the mother was carrier for the mutation. She was phenotypically normal, probably due to skewed X-inactivation of the chromosome carrying *ATRX* mutation [19].

Intrafamilial variation was shown in our patients. McDowell et al. [13] showed that ATRX protein associated to the short arm of acrocentric chromosomes at metaphase. This unexpected association of a putative transcriptional regulator with highly repetitive DNA was suggested for phenotypic variations among patients with the same mutations in the *ATRX* gene.

In summary, we identified a novel missense mutation in *ATRX* gene in two male siblings who had kyphoscoliosis, intellectual disability and dysmorphic facial appearance without hematologic abnormalities. This report both enriches mutation spectrum of *ATRX* gene and phenotypic features related to *ATRX* gene mutations.

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Statement of ethics

The authors have no ethical conflicts to disclose.

Disclosure statement

No potential conflict of interest was reported by the authors.

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