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Alpha-thalassemia/mental retardation syndrome, X-Linked (ATR-X, MIM #301040, ATR-X/XNP/XH2 gene MIM #300032)

Laurent Villard*,[1] and Michel Fontes[1]

[1]*Inserm U491, Faculté de Médecine La Timone, 27, Bd. Jean Moulin, 13385 Marseille Cedex 5, France*

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Clinical definition

Syndromic X-linked mental retardation syndrome. It is characterised by severe mental retardation, absent speech or speech reduced to a few words, delayed developmental milestones and congenital microcephaly. The patients present a characteristic facial dysmorphism: carp-shaped mouth, anteverted nostrils, midface hypoplasia, telecanthus and epicanthic folds.[1] The facial features usually become more marked with age. Genital anomalies are frequently found, ranging from cryptorchidism and hypospadia to ambiguous external genitalia. Alpha-thalassemia is a very frequent, but not constant characteristic of the syndrome. A number of patients presenting with variant phenotypes, described under the names of Juberg-Marsidi, Carpenter-Waziri, Holmes-Gang or Smith-Fineman-Myers syndromes, do not have haematological signs. Miscellaneous other anomalies were reported in several patients. They are not systematically associated with the syndrome and are rather aspecific. They include but are not limited to: abnormal fingers, scoliosis, abnormal verterbra, cleft palate, cardiac defects, recurrent chest infections. Intrafamilial variation in severity of phenotype has been observed in some families, extending even to mild mental retardation without dysmorphism.[2]

*Correspondence: L Villard, Inserm U491, Faculté de Médecine La Timone 27, Bd. Jean Moulin, 13385 Marseille Cedex 5, France.
Tel: 04 91 78 44 77; Fax: 04 91 80 43 19;
E-mail: laurent.villard@medecine.univ-mrs.fr
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Diagnosis

Presence of alpha-thalassemia (detected by haemoglobin electrophoresis or the presence of haemoglobin H inclusions on brilliant cresyl blue stained peripheral smears) in a male patient presenting severe mental retardation and a typical facial appearance. Evidence of X-linked inheritance for familial cases. Presence of skewed X-inactivation in the mother of the patient further strenghten the diagnosis but may be inadequate for sporadic occurences.

Most important differential diagnosis

Coffin-Lowry syndrome, mainly because of the facial dysmorphism of the patients which can be very similar.

Disease frequency

No figures available. Very rare, probably with an incidence of less than 1/100 000 liveborn males.

Gene

ATR-X, XNP, XH2. The gene was initially identified in the mouse in 1993 and subsequently in humans in 1994. It was shown to be responsible for the disease by a positional candidate gene approach in 1995.[3] The gene is composed of 35 exons and spans more than 300 kilobases of genomic DNA in Xq13.3, centromeric to ATP7A. It contains an unusually large exon 9 of 3 kilobases. The transcript has a size of 10 485 nucleotides and contains an open reading frame of 7476 bp.[4] Exon 6 (114 bp) is alternatively spliced and the frame is maintained in the spliced form. The two transcripts are ubiquitous although

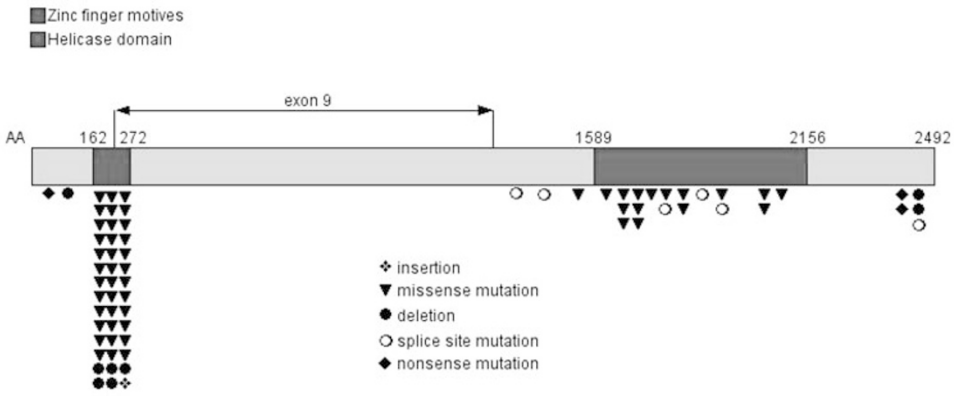

Figure 1 Schematic representation of the ATR-X protein (2492 amino acids). The position and type of mutations is shown together with the position of the zinc finger domain, the helicase domain and the portion of the protein encoded by the large exon 9.

the transcript containing exon 6 is the most abundant in the embryo at 12 weeks of age. The large transcript encodes a protein of 2492 amino acids (38 amino acids missing in the spliced form). The protein contains the seven motives characteristic of the SNF2/SWI2 family of ATP-dependent DNA-helicases. It also contains three zinc fingers of the C2-C2 type in its NH2 terminal region. Homologous genes were identified in the mouse, marsupial and *C. elegans* genomes.

Genetic heterogeneity

None documented. The ATR-16 syndrome (alpha-thalassemia with mental retardation linked to chromosome 16) patients do not exhibit the facial dysmorphism observed in ATR-X syndrome nor the same degree of mental handicap.

Function of the protein

The ATR-X protein is a nuclear protein found principally associated to the short arm of acrocentric chromosomes during mitosis[5] and tightly associated with the nuclear matrix at interphase; the differential localisation of the protein during the cell cycle could be regulated by phosphorylation.[6] Interactions between the murine Atrx protein and the heterochromatin protein HP1 was reported[7] and the human ATRX protein was shown to associate with another chromatin protein (EZH2) in yeast two-hybrid assays and *in vitro*.[8] Since methylation defects were observed in a number of patients,[9] the ATR-X protein is suspected to play a role in chromatin remodelling and/or activation/repression of targeted loci through a methylation-dependent mechanism. Mutations in the zinc finger coding region were shown to disturb the nuclear localisation and/or to reduce the DNA-binding capacity of the mutant protein.[9]

Animal model

Transgenic mice overexpressing the ATR-X protein[10] show growth retardation, neural tube defects and a high incidence of embryonic death, indicating that ATR-X dosage is important for normal development.

Mutations

As of 12-31-01, 74 mutations were reported in the gene in unrelated individuals (Figure 1). Forty-five (61%) are located in the three exons coding for three zinc fingers (exons 7, 8 and 9). Truncating mutations are underrepresented compared to most other X linked dieseases, and missense mutations represent 75% of the total (56 mutations) with the R246C amino acid change representing 36% of all missense mutations. Three nonsense mutations, seven splicing defects and eight deletions were also identified. Of these 17 events, five fall within the last two exons of the gene. No clear-cut genotype-phenotype correlations can be established but the most severe urogenital defects are found in patients with mutations in the two last exons of the gene.

Treatment

None available.

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