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A Novel Mutation in the Putative DNA Helicase *XH2* Is Responsible for Male-to-Female Sex Reversal Associated with an Atypical Form of the ATR-X Syndrome

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Summary

We describe a pedigree presenting X-linked severe mental retardation associated with multiple congenital abnormalities and 46,XY gonadal dysgenesis, leading in one family member to female gender assignment. Female carriers are unaffected. The dysmorphic features are similar to those described in the α-thalassemia and mental retardation (ATR-X) syndrome, although there is no clinical evidence of α-thalassemia in this family. In addition, the family had other clinical features not previously observed in the ATR-X syndrome, including partial optic-nerve atrophy and partial ocular albinism. Mutations in a putative DNA helicase, termed *XH2*, have been reported to give rise to the ATR-X syndrome. We screened the *XH2* gene for mutations in affected members of the family and identified a 4-bp deletion at an intron/exon boundary that removes an invariant 3′ splice-acceptor site. The mutation cosegregates with the syndrome. The genomic deletion causes missplicing of the pre-mRNA, which results in the loss of 8 bp of coding sequence, thereby generating a frameshift and a downstream premature stop codon. Our finding increases the range of clinical features associated with mutations in the *XH2* gene.

Introduction

The α-thalassemia and mental retardation (ATR-X) syndrome is a hereditary X-linked disease that associates severe mental retardation, typical dysmorphic features, multiple congenital anomalies, and a nondeletion-type α-thalassemia (Gibbons et al. 1995*a*). Affected XY individuals may present with small external genitalia and hypogonadism and in some cases may be raised as females (Gibbons et al. 1995*a*; McPherson et al. 1995). Mapping studies indicates that the disorder is linked to Xq12-21.3 (Gibbons et al. 1992). Mutations in a gene termed *XH2* (Gecz et al. 1994; Stayton et al. 1994) recently have been identified in some ATR-X–affected males (Gibbons et al. 1995*c*). The *XH2* gene is located at Xq13.3, and sequence analysis predicts that the gene encodes a member of the helicase II superfamily, within the *SNF2* subgroup (Kolsto et al. 1993; Gecz et al. 1994; Stayton et al. 1994). These genes have significant homology to each other in both putative DNA helicase domains and flanking regions. Helicase activity might result in disruption of the chromatin structure and alteration of DNA topology, thereby permitting access for DNA-regulatory molecules. The function of the XH2 protein is unknown, although the most closely related helicase (*Saccharomyces cerevisiae* protein, RAD54) plays a role in DNA repair and mitotic recombinations (Cole et al. 1987, 1989). Other members of the helicase superfamily, including the yeast and human *SNF2* genes, *MOT1* and *brahma*, appear to function as regulators of DNA transcription (Carlson and Laurent 1994).

Here we describe the analysis of the *XH2* gene in a large, previously unreported pedigree presenting with male-to-female sex reversal and gonadal dysgenesis associated with some of the characteristic dysmorphic facial features of the ATR-X syndrome. There were no clinical signs of α-thalassemia. Detailed analysis of the genomic DNA revealed a 4-bp deletion at an intron/exon boundary, which included the invariant acceptor splice site. This resulted in missplicing by the use of a cryptic 3′ splice site adjacent to the exon boundary and the loss of 8 bp of the *XH2* transcript. The missplicing generated a frameshift and a downstream premature stop codon. This finding expands the clinical spectrum of phenotypes associated with mutations of this gene.

Subjects and Methods

Subjects

We identified a large pedigree (fig. 1) of French origin with an apparently X-linked syndrome consisting of severe psychomotor retardation, 46,XY gonadal dysgenesis with ambiguous genitalia, dysmorphic features, partial optic-

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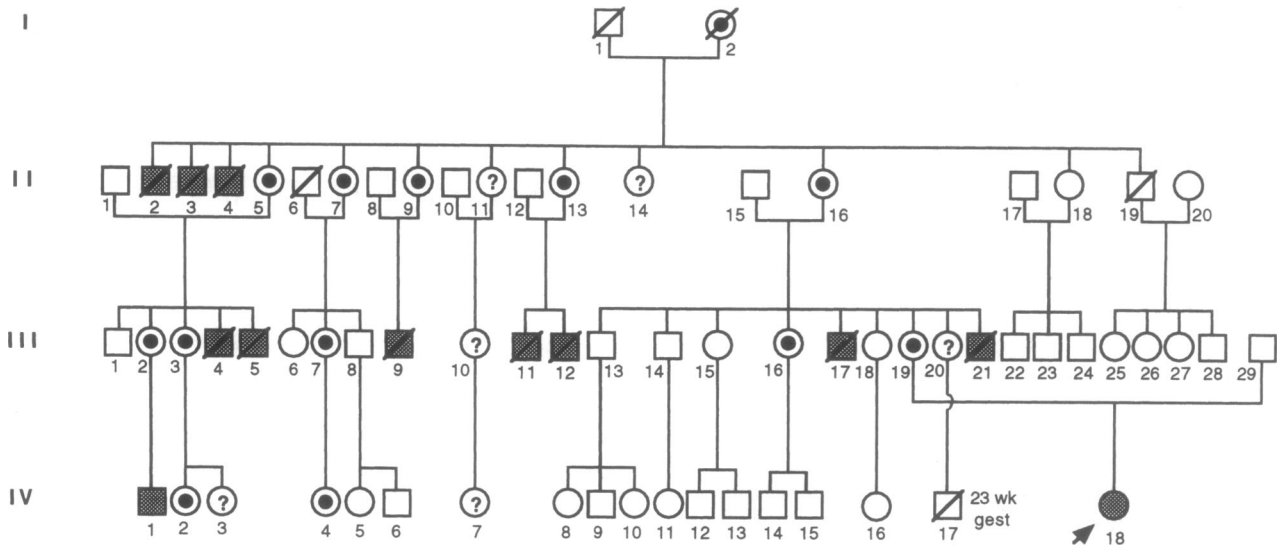

Figure 1 Family with X-linked recessive ATR-X syndrome and 46,XY gonadal dysgenesis. The proband (*arrow*) has a 46,XY karyotype and was raised as a female. Affected XY individuals are shown by solid symbols.

nerve atrophy with partial ocular albinism, pyramidal syndrome, and skeletal abnormalities. Table 1 compares the features present in our family to those recognized in the ATR-X syndrome. The proband (IV-18) has a facial dysmorphy characteristic of the ATR-X syndrome, including microcephaly, hypertelorism, epicanthic folds, anteverted nares and "carp"-shaped mouth (fig. 2*a* and table 1). Her external genitalia were ambiguous, and the subject was raised as a female (fig. 2*b*). Her karyotype was found to be 46,XY. Gonadal dysgenesis was determined by histological examination of the streak gonads (fig. 2*c* and *d*). Table 2 details the endocrinological investigations. These excluded pituitary gonadotropin deficiency, anomalies in the androgen receptor, and a block in testosterone synthesis. The second cousin of the proband (IV-1) presented with ambiguous genitalia at birth. At age 5 years, the child underwent appendectomy. The surgeon noted that the right gonad was present at the level of the peritoneum, forming together with its annexe, a streak of fibrous tissue. The gonads were not removed. There were several other affected males in this family (subjects II-2, II-3, II-4, III-4, III-5, III-9, III-11, III-12, III-17, and III-21, in fig. 1). They all presented severe psychomotor retardation and multiple congenital abnormalities and died at between 6 mo and 5 years of age (table 1). Details of their external or internal genitalia were not described. There were no signs of the syndrome in any of the 46,XX obligate carriers.

Cytogenetic Analysis

Karyotype was performed on lymphocyte cultures from total peripheral blood. Chromosome analysis was done by using "R" (reverse) bands by heat denaturation and Giemsa staining, or RHG, and "R" bands by tymidin and BrdU incorporation and Giemsa staining, or RTBG, banding and FISH with total painting of chromosomes X and Y as described elsewhere (Telvi et al. 1995). The karyotype was found to be normal in each family member examined.

Hematologic Analysis

Peripheral red blood cells (RBCs) were screened for hemoglobin (Hb) H inclusion bodies, following incubation with 1% brilliant cresyl blue preparations. Globin-chain synthesis was studied according to classical methods (Clegg 1983). A high-performance liquid chromatography (HPLC) program (β-thalassemia short program BOIRAD) was used to quantify Hb A2 and F. Another cation-exchange HPLC procedure, which can detect as low as 0.1% Hb H or Hb Bart's, was applied. Isoelectric focusing was also performed to visually detect abnormal Hb fractions.

DNA Analysis

Southern blot analysis was performed on DNA prepared from peripheral blood lymphocytes as described elsewhere (McElreavey et al. 1992). Southern blotting and hybridization were performed by standard procedures using the ^{32}P-labeled probe pY53.3, which contains the *SRY* gene, and the probe QST59 (DXS319), which maps to the distal portion of the *DSS* locus at Xp21.3. Southern analysis was performed using the reverse transcriptase (RT)–PCR products generated by the primer pairs XHSQ9-XH9 and XHSQ2-XH6 described below. In addition, *SRY* coding sequences were checked for mutations by denaturant gradient-gel electrophoresis (DGGE) using conditions described elsewhere (McElreavey et al. 1992).

Isolation of RNA and cDNA Synthesis

Total RNA was prepared from Epstein-Barr virus (EBV)–transformed lymphocytes as described else-

Table 1

Clinical Findings in Proband and Subjects, Compared with the Frequency of Pathological Traits in Classic ATR-X Syndrome

Trait	Patient					Frequency of Trait (%)
	IV-18	IV-1	III-11	III-12	III-21	
Mental retardation	+	+	+	+	+	100
Microcephalia	+	+	+	+	+	68
Facial anomalies:						
Relative to OFC telecanthus	+	+	+	+	+	92
Epicanthic folds	+	+	+	+	+	84
Flat nasal bridge	+	−	U	+	+	72
Midface hypoplasia	+	−	U	U	+	88
Small triangular nose	+	−	U	U	−	87
Anteverted nares	+	−	U	U	−	89
Triangular mouth	+	+	U	U	+	98
Abnormal ears	+	+	U	U	+	78
Genital abnormalities:						
Ambiguous external genitalia	+	+	−	−	−	11
Cryptorchidism	+	+	U	U	+	69
Hypospadias	−	+	U	U	−	18
Small penis	10 mm	15 mm	U	U	+	22
Small testes	+	+	U	U	+	18
Hypoplastic scrotum	+	+	U	U	+	20
Skeletal abnormalities:						
Clinodactily	−	−	−	−	−	27
Tapering fingers	−	−	−	−	−	16
Overlapping fingers/toes	−	−	−	−	−	33
Fixed flection deformity	+	+	+	+	+	33
Foot deformity	+	+	+	+	U	40
Kyphosis/scoliosis	+	+	+	+	U	47
Spina bifida	+	−	−	−	U	2
Abnormal vertebra	+	−	−	−	U	35
Delayed bone age	+	+	U	U	U	59
Coxavalga	−	−	−	−	U	35
Ocular abnormalities:						
Partial optic-nerve atrophy	+	+	U	U	U	0
Partial ocular albinism	+	+	U	U	U	0
Blepharitis/conjuncitivitis	−	−	−	−	U	25
Other frequent abnormalities:						
Abnormal teeth	+	+	+	U	+	49
Vomiting/regurgitation/reflux	+	+	+	+	+	55
Severe constipation	−	−	−	−	−	30
Excessive salivation	−	−	−	−	−	87
Cold/blue extremities	−	−	−	−	−	47
Apnoeic/cyanotic spells	−	−	−	−	−	61
Recurrent chest infections	−	−	−	−	−	46
Self biting/hitting	−	+	+	−	−	50
Extreme emotion	−	−	−	−	−	85

NOTE.—Traits in classic ATR-X syndrome from study by Gibbons et al. (1995). U = unrecorded data.

where. RNA (2 μg) was reverse transcribed in 20-μl reactions with random hexamer primers (100 ng) and Superscript II enzyme (Gibco/BRL) according to manufacturer's instructions. Following the reaction (2 h at 42°C), the cDNA was preciptated with 500 μl ethanol, 25 μl NaCl (2.5 M), and 10 μl Tris.Cl pH 8.0. Following 30-min incubation in dry ice, cDNA was collected by centrifugation and the pellet was washed in 70% ethanol, dried, and resuspended in 100 μl H_2O. PCR reactions were performed in a total volume of 100 μl by using a 10-μl aliquot of cDNA.

RT–PCR

Various combinations of primers were tested for RT-PCR amplifications. Primer sequences were selected from a published XH2 cDNA sequence (Stayton et al. 1994). Only the successful combinations are listed here.

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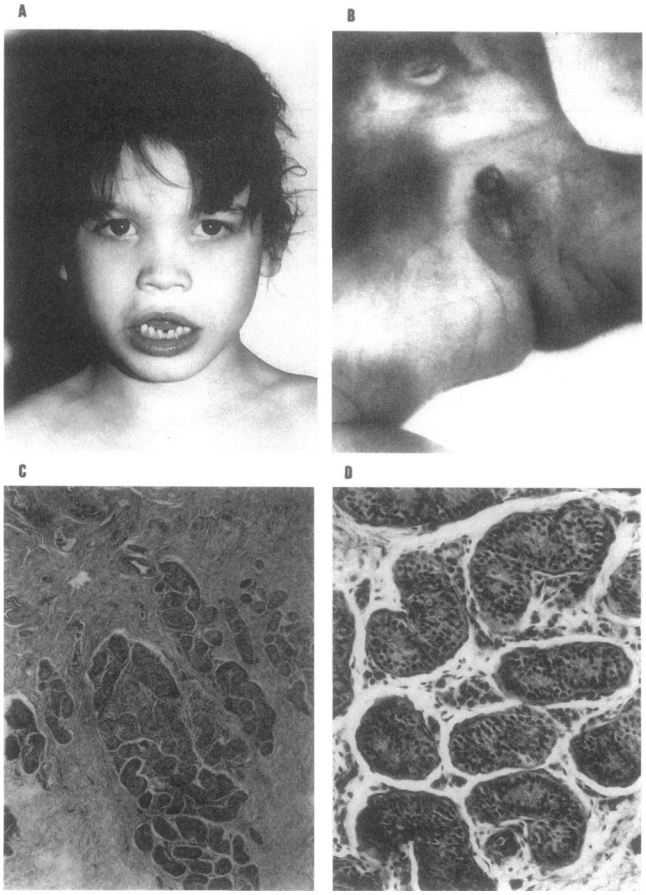

Figure 2 Phenotypic features of the proband (IV-18), showing face, external genitalia, and histology of the dysgenetic testicle. *a*, Facial dysmorphy characteristic of the ATR-X syndrome with microcephaly, hypertelorism, epicanthic folds, anteverted nares, and "carp"-shaped mouth. *b*, External genitalia, noted as ambiguous at 10 mo of age. Histology of the dysgenetic testis revealed (*c*) islands of testicular material surrounded by abundant wavy fibrous tissue (×25). At higher magnification (×40), seminiferous tubules (*d*) were observed bordered by Sertoli cells. Leydig-like cells were present between the tubule structures. Germ cells were not observed.

The primer sequences were the following: XHF1: TACAAAAGATTTTGACTCTTCT; XHR1: AACAATCTTGTCTCTTCCTTGAACTC; XHSQ5: GAGTAAGAATGGAGCATATGGTAGAGA; XH2-2: CACTGGATGAATCTTTCTTCTTGAACC; XHF2: TTCTGAATCAGATTCAGATTCTGAAGAA; XHR4: GTTATTGGACACTTGGTGGGTG; XHSQ8: GAAGATGCTTCACCCACCAAGTGTCCA; XH8: CACCACCATCTTCTTGCCACC; XHSQ9:GCTTGAGGTTTCTGAATTAGCAACTG; XH9: CCACATTTCCTTCACCACCT; XH5: AAGGTCTGGAATTCAAGATCT; XHR6: TCTGAAGGAGCTCTGCAAGTATGG; XHSQ2: GATCAGCAGCAGGTGGAGCGTCA; and XH2-6: TGGTGGCTGCATACCACCAG.

Primer pairs amplify the following products: XHF1 and XHR1, 796 bp; XHSQ5 and XH2, 1,075 bp; XHF2 and XHR4, 639 bp; XHSQ8 and XH8, 466 bp; XHSQ9 and XH9, 962 bp; XH5 and XHR6, 858 bp; and XHSQ2 and XH6, 840 bp. Thirty-five cycles of amplification were performed. PCR amplification using primer pairs XHF1 and XHR1, XHSQ5 and XH2, XHSQ8 and XH8, and XHSQ2 and XH6 was performed with a denaturation step of 95°C for 1 min, annealing at 56°C for 1 min, and polymerization at 72°C for 1 min. Amplification using primer pairs XHSQ9 and XH9 was performed with a denaturation step of 95°C for 1 min, annealing at 55°C for 30 s, and polymerization at 72°C for 1.5 min.

PCR from Genomic DNA

Amplification of genomic DNA at an intron/exon boundary was performed using the primer pairs XH2-6 (above) and KL-LM3 (GGATCCTTGATCATGTTTCC), which amplify a 795-bp product. PCR amplification conditions were identical to those described above for primer pairs XHSQ2 and XH6 by use of 100 ng (10 μl) of genomic DNA in a total volume of 100 μl. PCR-amplified products were gel purified using the Geneclean II kit and directly sequenced by the dideoxynucleotide chain-termination method using the Sequenase kit (USB). A complete list of sequencing primers is available from A.I. on request.

Results

In contrast to previously reported familial cases of the ATR-X syndrome, there was no family history of

Table 2

Endocrinological Findings in Proband and Affected Subject

	Patient IV-18	Patient IV-1
Age at investigation	9 wk	17 years
FSH (basal level)	19 UI/L (N = 2–5 UI/liter)	23.6 UI/L (N = 0.6–4.8 UI/liter)
FSH after LHRH (0.1 mg/m2)	104 UI/L	U
LH (basal level)	1.2 UI/L (N = 0.5–2.5 UI/liter)	4.7 UI/L (N = 0.9–2 UI/liter)
LH after LHRH (0.1 mg/m2)	46 UI/L	U
Testosterone (basal level)	0.2 ng/ml (N = 0.5–1.5 ng/ml)	0.2 ng/ml (N = >10 ng/ml)
Testosterone rise after HCG test	Absent	U
Oestradiol	15 pg/ml (N = <5–15 pg/ml)	U
DHT	0.1 ng/ml (N = 0.05–1.5 ng/ml)	U
Δ-4-Androstendion	0.6 ng/ml (N = 0.3–1.4 ng/ml)	U

NOTE.—U = unrecorded data; FSH = follicle stimulating hormone; LH = lutenizing hormone; LHRH = lutenizing hormone–releasing hormone; HCG = chorionic gonadotrophin hormone; DMT = dihydrotestosterone; and N = normal value.

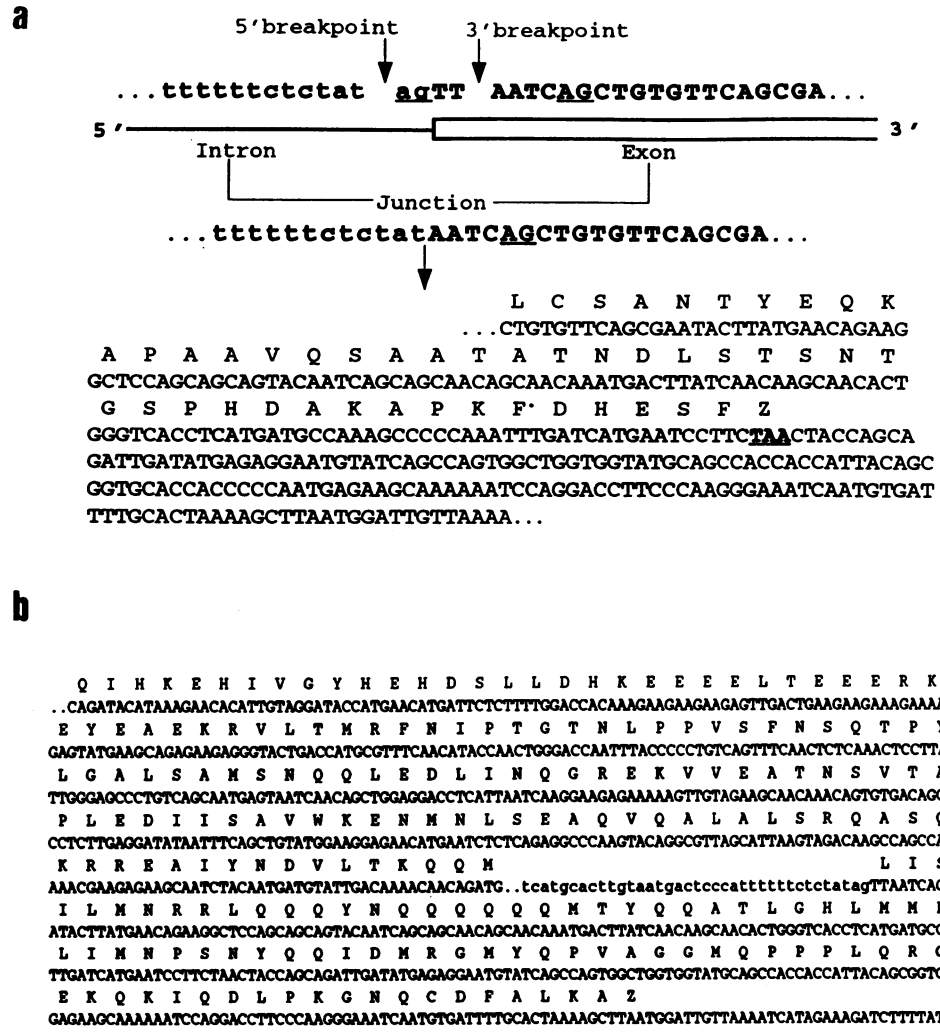

Figure 3 Proposed mechanism of XH2 pre-mRNA missplicing. *a*, Loss of the acceptor splice site, which results in an altered splicing pattern by the use of an adjacent cryptic splice site, which eliminates 8-bp from the coding sequence. In *b*, this results in a frame-shift and a termination codon at amino acid position 1592.

microcytic anemia. A screen of 5,000 peripheral RBCs for the presence of Hb H (β4) inclusions failed to identify any inclusions in RBCs from either the proband (IV-18) or an obligate carrier (III-19). In addition, a cation-exchange HPLC procedure, which can detect as few as 0.1% Hb H (Clegg 1983,) failed to detect Hb H in IV-18, III-16, or III-19. The apparent absence of inclusion bodies in peripheral RBCs may be caused by sequestering by the spleen of cells that are deficient in the alpha chain. Measurement of globin chain synthesis in IV-18 indicated a reduction in the ratio of α/β-synthesis of ~15% in comparison with carrier and unaffected family members (IV-18, 0.80; III-19, 0.92; and III-14, 0.95).

On the basis of the facial dysmorphy, severe mental retardation, and X-linked transmission of the phenotype, we decided to screen members of the family for mutations in the *XH2* gene. Southern blot analysis using *XH2* partial cDNA probes failed to detect abnormal bands in genomic DNA from affected subjects (data not shown). We searched for mutations in *XH2* coding sequences by using RT-PCR of *XH2* mRNA isolated from EBV-transformed lymphocytes followed by direct sequencing. cDNA was synthesized from the proband IV-18, her affected second-degree cousin (IV-1), an unaffected male family member (III-14), and three unrelated normal males.

A series of PCR primer pairs were designed that amplified seven overlapping fragments spanning the majority of *XH2* coding sequences (see Methods). Direct sequencing of these PCR products revealed several significant differences from previously published *XH2* sequences (Gecz et al. 1994; Stayton et al. 1994) in the region encoding the C-terminal portion of the protein (shown in fig. 3*b*), but it was found to identical to a sequence deposited in Genbank (accession no. X83753). The sequence was found in the affected and unaffected males of the family

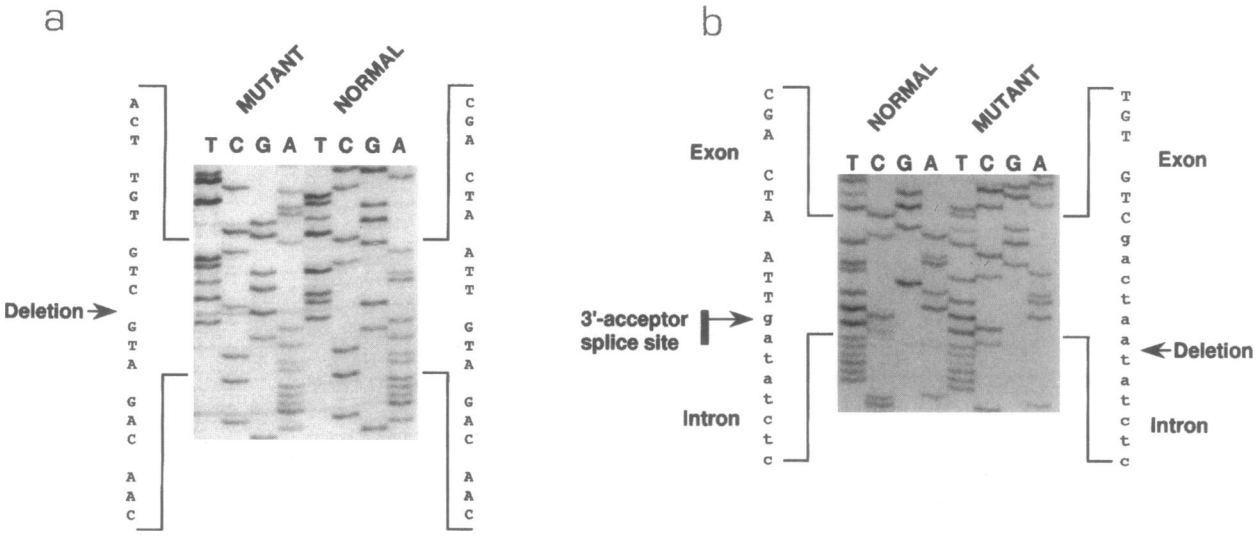

Figure 4 Nucleotide sequencing of the mutated cDNA and genomic DNA In *a*, by comparison with the normal cDNA sequence an 8-bp segment corresponding to nt 4680–4687 is missing. In *b*, sequencing of the genomic DNA in the proband demonstrated a 4-bp deletion at an intron/exon boundary, which abolishes a 3′ acceptor splice site

and in cDNA sequences from three unrelated males, without evidence of polymorphism. However, in contrast, an 8-bp deletion was detected in cDNA sequences of affected individuals IV-1 and IV-18 corresponding to nt 4680–4687 (fig. 4*a*). This change was not found in cDNA from unaffected males of the family (III-13 and III-14) nor in three unrelated normal males. The deletion results in a frameshift leading to a stop codon at amino acid residue 1592. The premature stop codon predicts the synthesis of a truncated polypeptide.

To determine the underlying abnormality at the genomic DNA level, we PCR-amplified a genomic DNA fragment at this region. At present, the genomic organization of the *XH2* gene is unknown; however, an intron/exon boundary is present at nt 4679 (R. Gibbons, personal communication, and Genbank accession no. X83753). This lead us to speculate that perhaps the deletion may be caused by an RNA splicing error. To test this hypothesis, a 795-bp genomic DNA fragment that straddled this intron/exon boundary was amplified. Direct DNA sequence analysis revealed a 4-bp deletion that included the AG invariant 3′ splice-acceptor site in the proband and affected XY individual IV-1 (fig. 4*b*). The deletion consists of either AGTT or GTTA. It is impossible to distinguish between these two alternatives, since the site of the deletion is flanked by two A residues. In either of these alternatives the mutation abolishes the splice-acceptor site. A comparison of the DNA and cDNA sequences indicates that this deletion has caused incorrect splicing of the XH2 pre-mRNA. The nearest AG dinucleotides, at position 4686–4687 in the downstream exon, have been utilized as a cryptic splice-acceptor site (fig. 3*a*). This causes the loss of TTAATCAG from the mature messenger RNA. Sequence analysis of other members of the family indicated that the deletion cosegregates with the syndrome (see fig. 1). All unaffected male family members had a wild-type XH2 sequence. Direct sequencing of PCR-amplified genomic DNA indicated that family members II-5, II-7, II-9, II-13, II-16, III-3, III-7, III-16, III-19, IV-2, and IV-4 were carriers of the mutation.

Discussion

We have demonstrated that 46,XY male-to-female sex reversal with an apparent absence of α-thalassemia is associated with a novel missplicing mutation in the putative DNA helicase *XH2*. 46,XY gonadal dysgenesis causing male-to-female sex reversal is caused, in ~10%–15% of cases, by mutations in the Y-linked testis-determining gene, *SRY* (Hawkins et al. 1992; McElreavey et al. 1992). Somatic abnormalities are usually absent in these subjects.

The relationship between SRY and XH2 is unknown; however, the absence of Müllerian structures in our family, together with ambiguous genitalia, indicates partial Sertoli and Leydig cell function in utero. This suggests that testicular development was impaired at a moment of fetal development following testis determination.

As suggested by Gibbons and colleagues (Gibbons et al. 1995*b*), the lack of clinical evidence for ultraviolet sensitivity, or premature development of malignancy together with the absence of any chromosomal breakages, suggests that XH2, unlike RAD54, is not involved in DNA repair but rather DNA transcription. This hypothesis is supported by the specific downregulation of α-globin gene expression observed in ATR-X subjects har-

boring mutations in the *XH2* gene. In all male individuals known to have mutations in the *XH2* gene, α-thalassemia was determined clinically by microcytic anemia and biologically by the presence of Hb H inclusion bodies in peripheral RBCs. In our family, α-thalassemia was not detected, although a reduction of ~15% in alpha-chain synthesis was observed. The apparent absence of α-thalassemia has several explanations. Variable expressivity may be due to the genetic background or caused by stochastic or environmental factors. Alternatively, the truncated XH2 protein may have residual activity that is sufficient for α-globin gene regulation. This family also has other phenotypic abnormalities that have not been described in association with the ATR-X phenotype, including partial optic-nerve atrophy with partial ocular albinism. This expands the range of clinical features associated with mutations in the *XH2* gene.

A total of 10 mutations have been described in the *XH2* gene (Gibbons et al. 1995*c*). They are a small deletion that considerably reduced expression of the XH2 gene, two premature in-phase stop codons, and seven missense mutations. Together with our results, this suggests that the C-terminus of the protein may not be required for expression of the α-globin chain but may be necessary for urogenital development. It is interesting to note that two of the three mutations associated with severe urogenital abnormalities leading to male-to-female gender assignment were nonsense mutations (R1528* and E1530*) in the region encoding the C-terminal domain of the protein.

Our findings indicate that splice-junction mutations may represent a novel molecular mechanism for an ATR-X variant. Other syndromes that map to this region of the X chromosome, have a similar clinical presentation to the ATR-X phenotype, and yet lack α-thalassemia, such as Juberg-Marsidi syndrome (Juberg and Marsidi 1980; Saugier-Veber et al. 1993), may be also caused by mutations in the XH2 gene.

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