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J Med Genet 2000;37:972-974

Abnormal sex differentiation and multiple congenital abnormalities in a subject harbouring an apparently balanced (6;8) translocation

EDITOR—In XY subjects, the testes are influenced by the activity of the sex determining region Y (SRY) gene and its abnormal function usually results in various degrees of sex reversal.¹ However, as suggested by several authors,²⁻⁵ abnormal sexual development may also be caused by errors in genes located on either the X chromosome (the dosage sensitive sex reversal locus (DSS) at Xp21.3) or autosomes. A few reports also describe abnormal sex development in male patients presenting with 6q chromosome rearrangements,^{6,7} but a more precise localisation at this level of a gene involved in sex determination has not been done.

The present report describes a 46,XY subject of Algerian origin, presenting with complete gonadal failure, abnormal external genitalia, and multiple congenital abnormalities. At birth, bilateral undescended testes, glandular hypospadias, and hypoplastic penis were noted. However, owing to sociocultural conditions, no investigations were performed until the age of 34 years, when he was assessed for infertility and learning disability. His phenotype included several dysmorphic features: squint, full lips, broad nasal root, large and low set ears, mildly short neck, gynaecomastia, widely spaced nipples, dorsal and lumbar scoliosis, and gynaecoid morphology. The external genitalia were hypoplastic and no gonads were found in the scrotum. However, the patient presented with post-androgen therapy virilisation, including sparse pubic and facial hair. X ray examination of the skeleton showed L5-S1 vertebral fusion and bilateral lysis of the vertebral isthmus, increased lumbar vertebral canal, and bilateral 4-5 brachymetacarpus. Ophthalmological examination showed considerable

reduction in visual acuity (6/10 on the right side and 3/10 on the left side), amblyopia, divergent strabismus, and visual field loss with right central scotoma. Abdominal ultrasound examination failed to identify any structure that might be interpreted as a gonad. Endocrinological investigation showed complete absence of testicular function: plasma testosterone was 0.57 ng/ml (normal 3.4-9 ng/ml) with no response to HCG stimulation, plasma FSH was 67.5 mIU/ml (normal 1-5 mIU/ml) and plasma LH was 19 mIU/ml (normal 0.8-4 mIU/ml). After administration of

Figure 1 Histological section through the left inguinal structure showing anarctic epididymal tissue surrounded by a small amount of fibrous cells. Microscopic magnification $\times 4$ (A) and $\times 40$ (B).

Figure 2 Balanced translocation 6;8 (A) RHG banding, (B) GTG banding, and (C) high resolution banding. (D) FISH using the probe specific for the chromosomal band 6q27 (arrows 1) showed that the breakpoint on the chromosome 6 is proximal to the TATA binding factor (*hTBR*, *TFIID*) gene. Arrows 2=alpha satellite chromosome 6 (*ONCOR*).

LHRH (0.1 mg/m²) FSH rose to 194 mIU/ml and LH to 63.1 mIU/ml. The other plasma hormonal levels, including oestradiol, prolactin, cortisol, ACTH, TSH, DHT, 17-OH-progesterone, and D-4-androstenedione, were within the normal range. Calcium binding protein and alkaline phosphatase were also normal.

Laparoscopy was performed and a gonad-like structure was identified and removed from the left inguinal canal. However, no such structure was found on the right side. The patient had a post-appendectomy scar in the right lower abdominal quadrant, suggesting that the gonad might have been removed during the surgical procedure. Histology of the left inguinal structure (fig 1) showed hypoplastic deferent and spermatic cords together with a thin albuginea and a structurally anarchic epididymis-like

tube surrounded by a small amount of fibrous cells. The structure did not contain any specific differentiated or undifferentiated testicular tissue.

Cytogenetic analysis using RHG, GTG, GTBG, and RTBG banding showed a homogeneous 46,XY,t(6;8)(q27;q13.2) chromosomal complement (fig 2A, B, and C). No microdeletion or microduplication could be identified at either breakpoint level. A count of 20 QFQ banded metaphases showed a normally fluorescent Y chromosome. The parents, of Algerian origin, were not available for investigation. Fluorescence in situ hybridisation (FISH) performed using chromosome 6 and 8 paints (*ONCOR*) confirmed the balanced translocation (data not shown). To position the distal breakpoint at 6q27 more closely, a FISH technique was performed, using a TATA binding factor gene specific probe (*ONCOR*) that gave a signal close to the breakpoint on the derivative chromosome 8 (fig 2D).

Southern blot and SSCP analysis of the *SRY* gene in the subject were found to be identical to that of a normal male and hybridisation with the *DXS319* probe, which maps to the distal portion of the *DSS* locus at Xp21.3, indicated that he carried a single copy of this region (data not shown). Therefore, abnormalities of either of these loci could be excluded as a cause of the patient's phenotype.

To date, a few reports have described abnormal sex development in 46,XY males with partial deletion of terminal 6q. In 1975, Milosevic and Kalicanin⁸ reported a 46,XY subject presenting with growth and mental retardation, microcephaly, dysmorphism including hypertelorism, a broad nasal root, malformed ears, micrognathia, multicystic kidney, bone abnormalities, and bilateral cryptorchidism. The patient had a *de novo* chromosomal rearrangement resulting in 6q25-6qter deletion. The same cytogenetic abnormality with a similar phenotype was reported by Baroshesky *et al.*⁹ Ito *et al.*¹⁰ described a male child presenting with an 6q21-q27 deletion, mental retardation, and several congenital abnormalities including bilateral cryptorchidism and thymus atrophy. Two other reports described similar patients.^{11,12} Most of these cases also presented with abnormalities of the kidney and Turner-like phenotype (short stature, cervical cystic hygroma, short neck, and widely spaced nipples). Interestingly, deletions of the long arm of chromosome 6 proximal to band 6q25 do not seem to result in either kidney, genital, or Turner-like anomalies. In our patient, gonadal failure was diagnosed by ultrasound and endocrinological studies, which also excluded pituitary gonadotrophin deficiency, anomalies of the androgen receptor, or a block in testosterone synthesis. In 1987, Fonatsch *et al.*¹³ assigned the *TCP1* locus to band 6q25-q27. This gene is the human homologue of the mouse *Tcp-1* locus, which is part of the mouse *t* complex and codes for a protein abundantly expressed in testicular germ cells. Another testis expressed gene, *TCP10*, which is genetically linked to the oestrogen receptor locus, has been assigned to the same region.¹⁴ Experimental *knock-out* mice for the *Tcp-1* and *Tcp-10* loci show abnormal testis development and are sterile. In our patient, the 6q breakpoint was shown to be located at 6q27, proximal to the TATA binding factor gene. The human homologue (*T*) of the mouse *T* (*Brachyury*) gene has also been located in this region.¹⁵ In vertebrates, the protein product of the *T* gene is a transcription factor crucial for the formation of the normal mesoderm. *T* mutant *Brachyury* mice die in mid gestation with severe defects in posterior mesoderm tissues. Heterozygous mice are viable but have posterior axial malformations. *T* protein has been shown to be associated with the mouse *t* haplotype, a variant form of the *t* complex characterised by transmission ratio distortion, male sterility, and recombination suppression. In humans, the *T* protein is involved in susceptibility to spina bifida, a multifactorial

neural tube defect. Morrison *et al*¹⁶ showed that the human *T* gene maps to 6q27 and lies between the two other genes of the T complex, *TCP1* and *TCP10*.

The present report suggests that male sex determination and differentiation is a complex process, involving several autosomal loci, and at least one of them is possibly located at 6q27.

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J Med Genet 2000;37:974-976

Distal trisomy 2p and arachnodactyly

EDITOR—We report two sibs with an unbalanced translocation of chromosomes 2 and 10 resulting in distal 2p trisomy. We feel that this sib pair could help to delineate the common features that may result from duplication of this specific region, in particular to show that arachnodactyly is a key feature. We suggest that the combination of arachnodactyly with developmental delay should prompt investigation of this region within the differential diagnosis.

This sib pair was first seen in 1995 aged 8 years (male) and 11 years (female). They were referred with a combination of speech and language delay, poor coordination, and concordant dysmorphic features.

The male sib (fig 1) was born at 38 weeks' gestation weighing 3200 g (25th centile). He was noted to have gross motor delay with hypotonia and walked at 22 months. Speech development was severely delayed necessitating Makaton from the age of 2 years. He attended a school for moderate learning difficulties and required intensive speech therapy. His motor development is still delayed and at the age of 11, he cannot ride a bicycle, catch a ball, or fasten shoe laces. He continues to require considerable supplemental educational input and speech therapy.

His height has followed the 90th centile with weight between the 25th and 50th centile and head circumference on the 50th. There is no limb or body segment disproportion. Joint flexibility is normal. He has arachnodactyly (palm length 10.5 cm (75th centile), middle finger length 8.0 cm (97th centile), middle finger to total hand ratio 43%) with fifth finger clinodactyly and prominent finger pads. His feet (fig 2) are narrow with metatarsus varus, medial deviation of the second toe, and a wide sandal gap.

His face is long and triangular with semilunar palpebral fissures (length 2.8 cm). There is a bulbous tip to the nose with a high bridge. The palate is high and arched.

Figure 1 Male sib aged 8 years showing facial dysmorphism and arachnodactyly.