Case reports

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Duchenne muscular dystrophy in a female with a translocation involving Xp21

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SUMMARY A female with Duchenne muscular dystrophy, diagnosed at the age of 3 years 8 months, is reported. Chromosome studies revealed an X;autosome reciprocal translocation t(X;5)(p21·2;q31·2). With the BrdU-Hoechst 33258-Giemsa technique, there was non-random preferential inactivation of the normal X. Our patient is the ninth reported case of Duchenne muscular dystrophy associated with an X;autosome translocation. In all cases the breakpoint in the X chromosome is in band p21 at or near the site of the DMD gene.

Duchenne muscular dystrophy (DMD) is a severe X linked recessive disorder. Over the past few years, nine females each with progressive muscular dystrophy and an X;autosome translocation have been reported.[1–13] In each case, the breakpoint on the X chromosome was in band Xp21. This suggested that the gene responsible for Duchenne muscular dystrophy is situated in band Xp21 and that the translocation has disrupted the normal gene function on the X chromosome. This paper describes the clinical history and investigations in a female with Duchenne muscular dystrophy with an X;5 translocation (previously reported in abstract form[12]).

Case report

The patient, a female, born at term after an uneventful pregnancy was the only child of a 20 year old mother and a 23 year old father. Birth weight was 2750 g. There was no family history of neurological or muscle disease. She was first evaluated at the age of 3 years 8 months because of delayed speech and DMD was diagnosed. She sat unaided at 9 months, stood at 11 months, and walked at 16 months. Since the age of 2 years 6 months, she tended to walk on her toes. At 6 years 6 months there was weakness of neck flexors (grade 2), of the deltoids (grade 4), and of the quadriceps (grade 4). The calves were large. Tendon reflexes were barely present except at the ankles. Plantar responses were flexor. There were no contractures at her hips or iliotibial bands, but her ankles could only be moved to 5 to 10° beyond the neutral position. She was only able to get up from the floor by putting her hands on her knees. At the age of 5 years, she had a mental age of 4 years 4 months with the Merrill-Palmer test, and of 3 years 6 months with the Goodenough Draw-a-Man test.

Creatine kinase (CK) was 24 125 and 10 880 IU/l (normal range 30 to 140 IU/l) and electrophoresis showed a strong MM band and a definite MB band. CK in the mother on three occasions was 71, 75, and 38 IU/l. The electromyogram had a characteristic myopathic pattern. The electrocardiogram showed left ventricular dominance. A muscle biopsy (biceps) revealed marked pathological change with marked variation in muscle fibre size and some fibre hypertrophy. There was also distinct basophilia, central nuclei, and splitting of muscle fibres. Fibrosis and fatty infiltration were not pronounced. Specialised histochemistry showed predominance of type I fibres. Electron microscopy revealed degenerate fibres containing residual fibrillary material, disruption of myofibrils, and focal disorganisation of the Z bands. There was an increased amount of interstitial collagen surrounding each of the muscle fibres.

Cytogenetic investigations revealed a balanced reciprocal translocation involving the short arm of the X chromosome and the long arm of chromosome 5 (figure). Prometaphase studies demonstrated the breakpoint on the X chromosome at p21·2. The karyotype was 46,X,t(X;5)(p21·2;q31·2). Replication of the X chromosome was investigated in cultured lymphocytes by bromodeoxyuridine (BrdU) incorporation followed by Hoechst 33258 and Giemsa staining.[14] In all 35 informative cells

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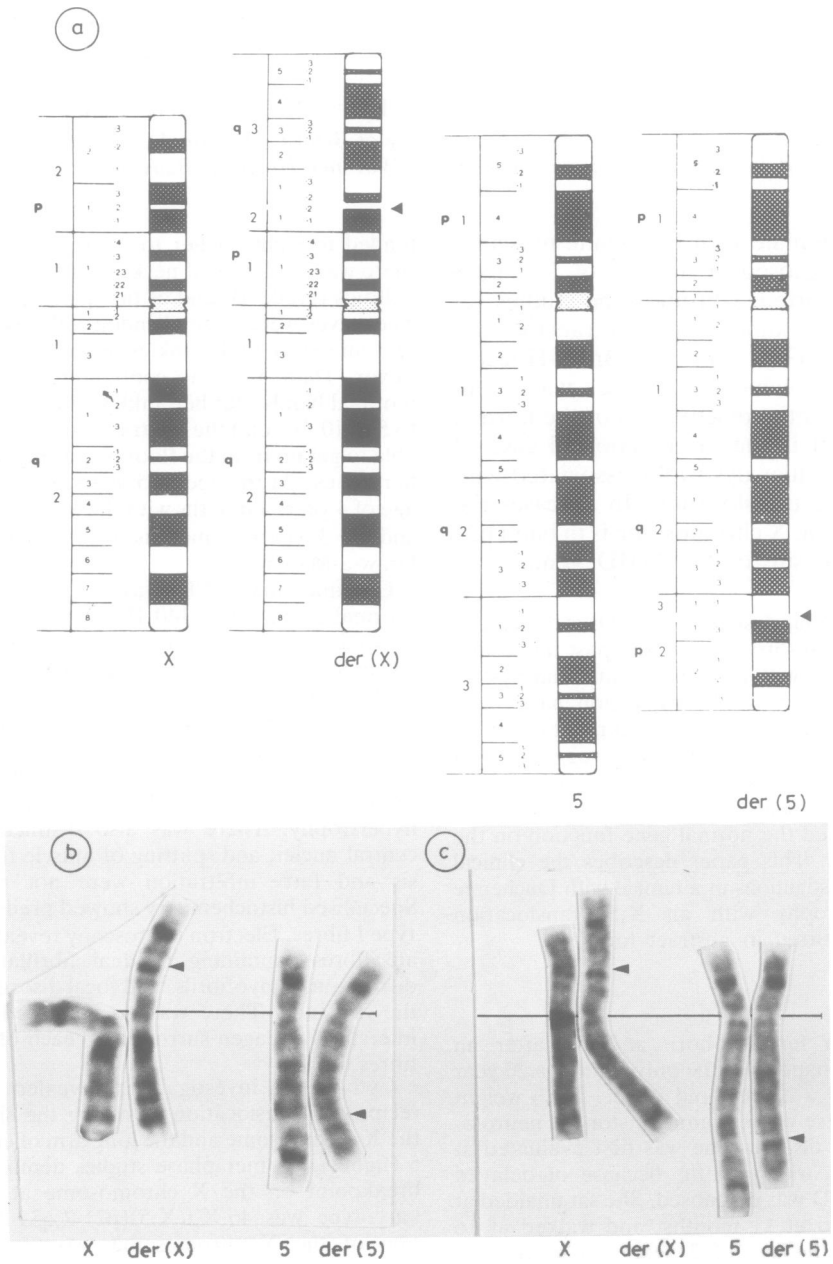

FIGURE *(a) Diagram of the normal and abnormal chromosomes X and 5; (b) and (c) G banded partial karyotype showing normal and derivative chromosomes X and 5. Arrows show the breakpoints.*

TABLE *Females with Duchenne muscular dystrophy and X;autosome translocations.*

Reference	*Year*	*Translocation*	*Late replication [X^l/X^m]*
Verellen *et al*[3 4 5]	1977, 1978, 1984	t(X;21)(p21·2;p12·09)	6/99
Canki *et al*[7]	1979	t(X;3)(p21;q13)	4/54
Lindenbaum *et al*[6]	1979	t(X;1)($^{p21\cdot07*}_{p11\cdot06}$;p34·00)	0/75
Greenstein *et al*[1 2]	1977, 1980	t(X;11)(p21·05;q13)	
Jacobs *et al*[8]	1981	t(X;5)(p21;q35)	10/576
Emanuel *et al*[10 11]	1981, 1983	t(X;9)(p21;p22)	2/84
Zatz *et al*[9]	1981	t(X;6)(p21;q21)	1/55
Bjerglund Nielsen and Nielsen[13]	1984	t(X;9)(p21;p21)	0/100
This report		t(X;5)(p21·2;q31·2)	0/35

*A complicated translocation and inversion with two breakpoints on the X chromosome.

examined, the late replicating X was the normal one, indicating a non-random preferential inactivation. The parents' chromosomes were normal.

Discussion

Our patient is the ninth reported female with Duchenne muscular dystrophy resulting from a structural alteration of the short arm of the X chromosome[1–13] (table). Cytogenetic studies in the nine females showed an X;autosome translocation involving a break in band Xp21 and breaks in seven different autosomes (chromosomes 1, 3, 5 (two cases), 6, 9 (two cases), 11, and 21). In each case the translocation was de novo and the normal X was late replicating. In no instance was the mother a proven carrier for the DMD gene. In our case, there was a negative family history and no compelling data to suggest that the mother was heterozygous for the DMD gene. The findings provide strong evidence that the DMD locus is situated within the Xp21 band and that in each of the nine reported cases the mutation is the direct result of the translocation. The translocation presumably has disrupted the normal activity of the DMD gene which, together with the non-random inactivation of the normal X chromosome, results in the manifestation of Duchenne muscular dystrophy.

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