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High-resolution banding study of an X/4 translocation in a female with Duchenne muscular dystrophy

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Summary. A rare female case of Duchenne muscular dystrophy with an X/4 translocation was found. Detailed cytogenetic analyses by R-banding and high-resolution G-banding techniques revealed that the exchange point involved in the translcoation was at the p21.1 band on the X chromosome.

Introduction

Duchenne muscular dystrophy (DMD) is a characteristic X-linked disorder affecting mostly males. Recently, ten female cases of DMD have been reported, all of which had X/autosomal translocations (Lindenbaum et al. 1979; Canki et al. 1979; Greenstein et al. 1980; Jacobs et al. 1981; Zatz et al. 1981; Nielsen et al. 1983, 1984; MacLeod et al. 1983; Emanuel et al. 1983; Verellen-Dumoulin et al. 1984). Although different autosomes were involved in these translocations, the chromosomal exchange in each case occurred in the p21 band on the X chromosome. This finding suggests that the DMD gene responsible for Duchenne muscular dystrophy is within the band Xp21. In the present study, more detailed chromosome analyses using R-banding and high-resolution G-banding techniques were performed on a female patient with an X/4 translcoation.

Case report

The propositus was a 3-year-old girl with presumed Duchenne muscular dystrophy. She was born apparently normal and started to walk when she was 14 months old. At the age of two years, she showed signs of atrial septal defect with extra murmur, stiffness of calf muscle, and some physical disabilities. For the detailed examinations she was brought to the Yokohama City University Hospital. Diagnostic studies showed the elevated activity of creatinine kinase (CK; 26,960 mU/ml) and aldolase (196 mU/ml) and the histology of muscle biopsy consistent with MDM. The CK activity of her parents and brother was measured and found to be within the normal range.

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Material and methods

Chromosomes of the patient and her parents were examined on the phytohemagglinin (PHA)-stimulated lymphocytes by means of conventional Trypsin-Giemsa banding and high-resolution G-banding (Ikeuchi and Sasaki 1979) techniques. In addition, late replicating patterns of the X chromosomes were studied using bromodeoxyuridine (BrdU) incorporation followed by Hoechst 33258 and G-staining.

Results and discussion

The result of Trypsin-Giemsa banding revealed that the patient was a carrier of balanced X/4 translocation (Fig. 1a) and her parents were normal. The exchange point located at p21 on the X chromosome was very similar to those of the previously reported seven cases with X/autosomal translocations. The detailed analyses by R-banding and high-resolution G-banding techniques revealed that the exchange point on the X chromosome was at sub-band p21.1 (Figs. 1b, c; 2). Thus the translocation was described as t(X;4)(p21.1;q26).

The late replicating chromosome was found to be the normal X in all of the 104 informative cells using the BrdU-Hoechst 33258/Giemsa staining technique. This suggested that there was a complete non-random preferential inactivation of the normal X chromosome in the patient. The inactivation of the normal X chromosome was the common finding among the previously reported cases with balanced X/autosomal translocations as mentioned by Hagemeijer et al. (1977).

Since this patient has a negative family background of DMD and her mother had a normal level of CK activity, there was no compelling evidence to suggest that the mother was heterozygous for the DMD gene. The phenotypic expression of the DMD disease is said to be brought about by translocation which produces the abnormal DMD gene, followed by the nonrandom inactivation of the structurally normal X chromosome. The present result agrees with this hypothesis.

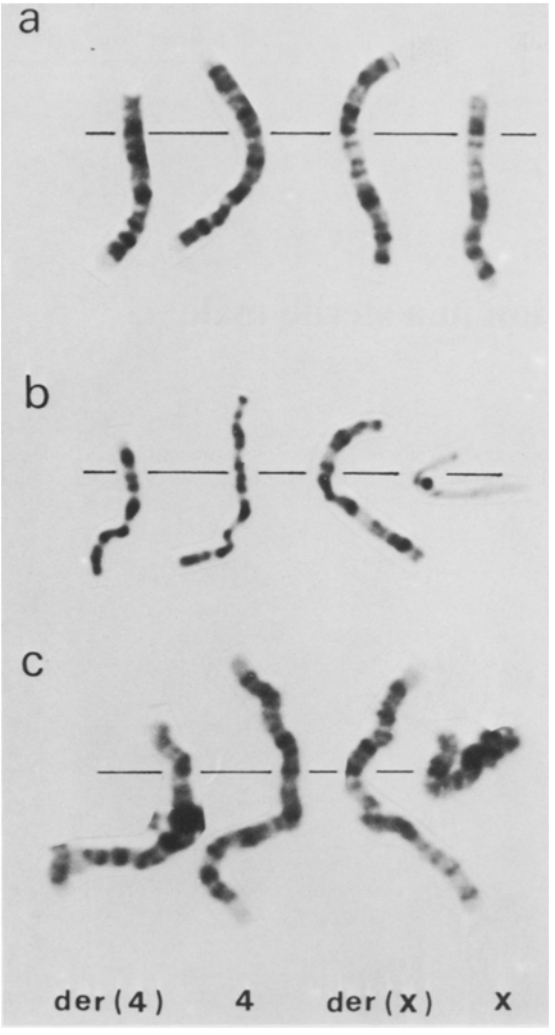

Fig. 1a–c. Partial karyotypes of the X/4 translocation stained with G-banding (**a**), R-banding (**b**), and high-resolution G-banding (**c**) methods. The *line* indicates the exchange point in the translocation

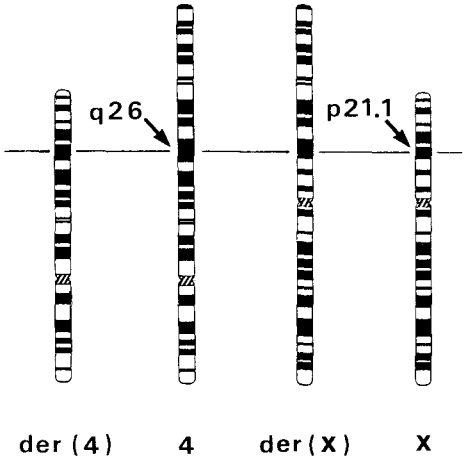

Fig. 2. Schematic representation of the X/4 translocation

Recent molecular findings showed that a DNA fragment mapped to the region Xp21.1–Xp21.3 had a genetic distance of 3 centimorgan to the DMD locus (Hofker et al. 1985). This result was compatible with the cytogenetic finding of the DMD gene localization on Xp21. The present study suggests that the DMD locus could be restricted at or near band Xp21.1. The lymphoblastoid cells of the patient transformed by Epstein-Barr virus are presently maintained in the laboratory for further studies.

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