PARENTAL ORIGIN AND MECHANISM OF FORMATION OF X CHROMOSOME STRUCTURAL ABNORMALITIES: FOUR CASES DETERMINED WITH RFLPs

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Summary Parental origin and mechanism of formation of X chromosome structural abnormalities were studied in one each case of dup(X)(pter→p11.4::p22.1→qter), del(X)(qter→p11::), i(X)(qter→cen→qter), and inv dup(X) (pter→q22::q22→pter) using various X-linked RFLPs as genetic markers. Segregation and densitometric analyses on polymorphic DNAs revealed that the dup(Xp) and the del(Xp) are both of paternal origin and the i(Xq) and i dic(X) are of maternal origin. The dup(Xp) had arisen by an unequal sister chromatid exchange and the del(Xp) had occurred through an intrachromosomal breakage-reunion mechanism, both in the paternal X chromosome. The i(Xq) had arisen either through centromere fission of a maternal X chromosome, followed by duplication of its long-arm, or through a translocation between two maternal X chromosomes after meiotic crossing-over. The inv dup(X) arose through sister chromatid breakage and reunion in a maternal X chromosome. These results, together with those of previous studies, suggest that the de novo abnormalities due to events involving centromere disruption arise predominantly during oogenesis, while those due to simple breakage-reunion events occur preferentially during spermatogenesis.

INTRODUCTION

Parental origin and mechanism of formation of chromosome abnormalities in man have been studied mainly in the autosomes, especially in the acrocentric chromosomes and a few other chromosomes that bear heteromorphic cytogenetic markers.
useful for segregation analysis (cf. Magenis, 1988, for reference). It has been demonstrated that autosomal trisomies are predominantly maternal in origin (Juberg and Morey, 1983; Ishikiriyama and Niikawa, 1984; Hassold and Jacobs, 1984; Hassold et al., 1984). On the other hand, the origin of autosomal structural abnormalities other than Robertsonian translocations are preferentially paternal (Chamberlin and Magenis, 1980; Olson and Magenis, 1988). In contrast, there is a dearth of information on the origin of structural abnormalities of the X chromosome, mainly due to the lack of its cytogenetic markers. A few studies that employed RFLPs (restriction fragment length polymorphisms) as markers, however, were successful in tracing their origin. They included preferential paternal sex-chromosome loss in 35 cases of monosomy X (Hassold et al., 1988) and chromatid breakage and reunion of sister chromatids at the breakpoint in three cases of dicentric X chromosome (Phelan et al., 1988).

We ascertained the parental origin and the mechanism of formation in four cases of X chromosome structural abnormalities by segregation and gene-dose analyses using X-linked RFLPs.

MATERIALS AND METHODS

Cases. Patient I, a three-year-old Chinese girl, has mental retardation, hypertelorism, low-set ears, a high-arched palate and a 46,X,dup(X)(pter→p11.4::p22.1→qter) karyotype. Patient II is a 22-year-old Chinese woman with a 46,X,del(X)(qter→p11:) karyotype. Patient III is a 13-year-old Chinese girl with a 46,X,i(X)(qter→cen→qter) karyotype. Both patients II and III have the stigmata of Turner syndrome. Patient IV is a 15-year-old Japanese girl with primary amenorrhea and cleft palate, and has a 46,X,inv dup(X)(pter→q22::q22→pter) karyotype.

Southern blot analyses. Genomic DNAs were extracted from peripheral blood leukocytes of the four patients and their parents. DNA samples were digested with various endonucleases of interest, according to the supplier specifications. Electrophoresis, Southern blotting, hybridization, autoradiography, and all other experiments were performed according to the standard techniques. The following 14 probes, mapped at various regions of the X chromosome, were employed in this study: L782 (the identified locus, DXS85; located at Xp22.3-p22.2); p99-6 (DXS41; Xp22.1); cDMD1a (DMD; Xp21.3-p21.1); P20 (DXS269; Xp21.2); pERT87-1 and pERT87-15 (DXS164; Xp21.2); J-Bir (DXS270; Xp21.2); L754 and 754-11 (DXS84; Xp21.1); p22-33 (DXS11; Xq24-q25); pDSK1 (HPRT; Xq26); p482.6 (F8C; Xq28); DX13 (DXS15; Xq28); St14-1 (DXS52; Xq28). The RFLPs already detected with these probes (Mandel et al., 1989) and our newly found cDMD1a/PvuII RFLPs (Deng and Niikawa, 1990) were used as markers for segregation analyses. Gene doses of polymorphic and constant autoradiographic bands were determined by densitometry as described previously (Kondoh et al., 1988).