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A Case of 45,X/46,X,dic(X) (qter→p22::p22→qter) with Tuner's Phenotype in a Japanese Girl

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ABSTRACT

A 13-year-old Japanese girl with a karyotype of 45,X/46,X,dic(X) (qter→p22::p22→qter) and clinical features of short stature, webbed neck, pectus excavatum and gonadal dysgenesis is described. The dic(X) chromosome was late replicating and assumed to be formed during the first mitotic division. Review of 17 previously published cases with a dic(X) (qter→p22::p22→qter) and the present case revealed no relationship between the phenotype and the percentage of 45,X cells. Therefore, the difference in volume and the part of the chromatin lost by forming a dic(X) chromosome may be mainly responsible for the expression of the phenotype.

Key words: *Turner's syndrome, X chromosome, Dicentric chromosome*

Among various chromosomal aberrations, karyotypes containing a fused pair of X chromosomes are rather uncommon and hitherto 17 cases with a dic(X) chromosome fused at p22 and p22 have been reported[1,3,4,7-18,20,21]. We report an additional case of 45,X/46,X,dic(X) (qter→p22::p22→qter) observed for the first time in a Japanese girl.

CASE REPORT

Clinical Findings

A 13-year-old Japanese girl was referred to us for evaluation of her short stature. She was the product of a normal pregnancy and delivery at term. She was the first child of unrelated parents. Her father and mother were 21 and 22 years old, respectively, at the time of her birth. Birth weight was 2850 g and length was 51 cm. Her record at junior high school was normal. Menarche had not yet occurred. As far as could be determined, none of her relatives was similarly affected.

At physical examination her height was 110.9 cm (-8.0 S.D.) and her weight was 50.0 kg. She showed several Turner's phenotypes such as webbed neck, pectus excavatum and hypoplastic labia, but cubitus valgus was not recognized. She also had epicanthic folds and blephaloptosis. A chest X-ray photograph, electrocardiogram and echocardiogram revealed no abnormality. Lower abdominal ultrasonogram detected a uterus of normal size and shape, but ovaries could not be detected.

Endocrinological examination revealed elevated gonadotropins (LH:91 mIU/ml, FSH:200 mIU/ml) and low sex steroids (estradiol: 22.3 pg/ml, progesterone:0.3 ng/ml). Other hormones such as prolactin, T3, T4, TSH, GH and cortisol were all within normal values for her age.

Cytogenetic Investigation

One-hundred cells obtained from her oral mucosa were counted to determine the proportion with X chromatin by aceto-orcein staining, and 76 of them were found to have a quite large X chromatin (Fig. 1).

Chromosomal preparations made from peripheral blood lymphocytes cultured in RPMI 1640 medium supplemented with 20% fetal calf serum and phytohemagglutinine (PHA) were analyzed with G-, Q-, R- and C-banding techniques. Of 100 metaphases karyotyped, 20 were of 45,X and the remaining 80 showed a karyotype with 46 chromosomes including one unusually large chromosome instead of one normal X chromosome (Fig. 2). The size of the abnormal chromosome was about twice that of a normal X chromosome and it had a symmetrical banding pattern indicating fusion of two X chromosomes at the region of p22. The C-banding pattern of the abnormal X chromosome included two densely staining areas, one in the centromere and the other in the middle of the long arm (Fig. 3). Therefore, the karyotype was designated as 45,X/46,X,dic(X) (qter→p22::p22→qter).

The replication pattern of deoxyribonucleic acid (DNA) of the dic(X) chromosome as analyzed by the BrdU-FPG method[5] was found to be late replicat-

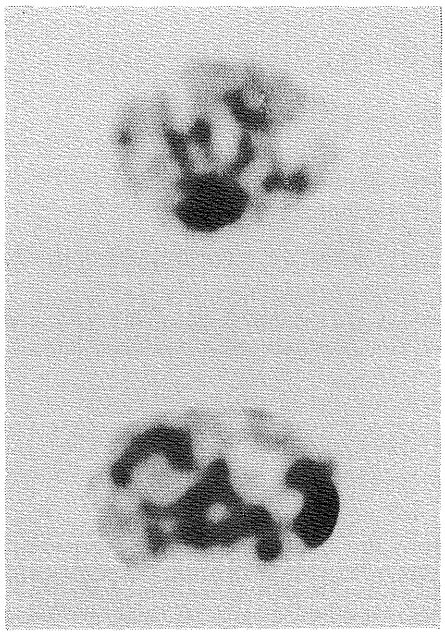


Fig. 1. Large X chromatin obtained from oral mucosa

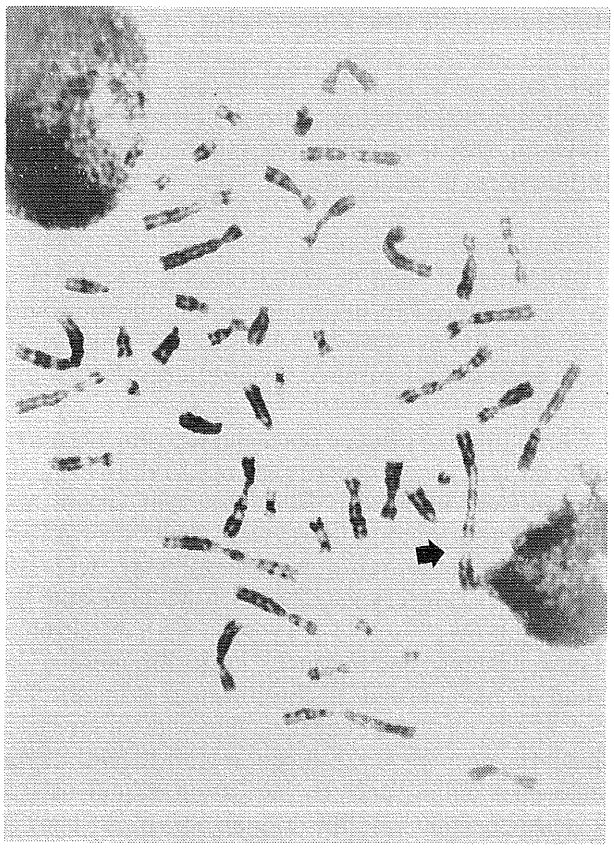


Fig. 2. G-banded preparation of 46,X,dic(X) (qter→p22::p22→qter) cell. The dic(X) chromosome is indicated by an arrow.

ing and synchronous (Fig. 4).

Karyotypes of her parents and physically and mentally normal younger brother were normal.

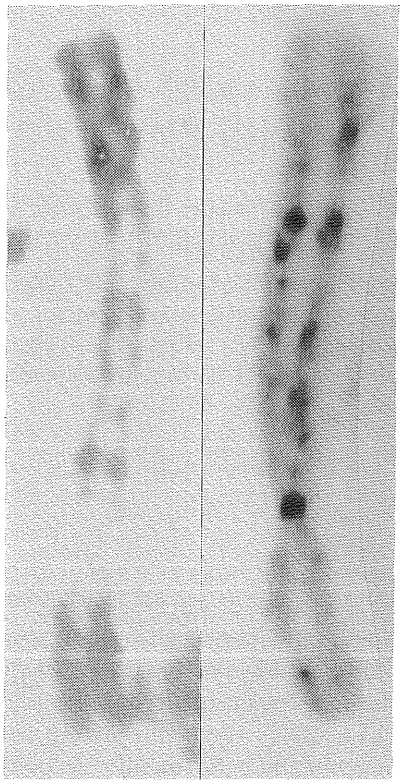


Fig. 3. G-(left) and C-(right) banded dic(X) chromosome

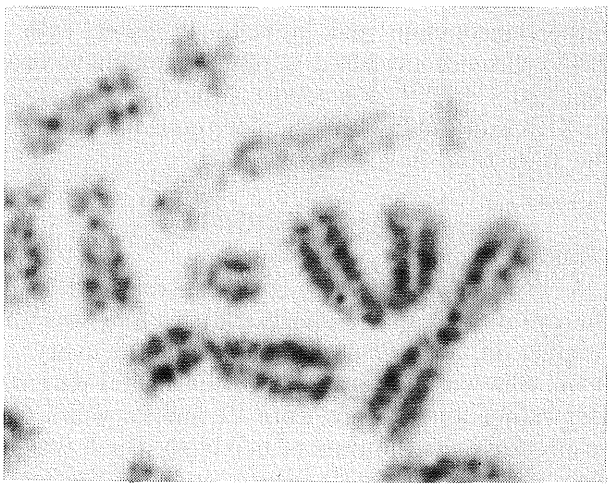


Fig. 4. The dic(X) chromosome showing pale, i.e., late replicating pattern.

DISCUSSION

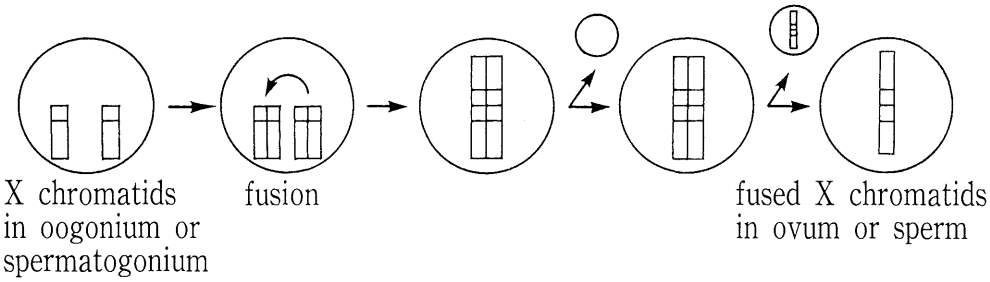
Phenotypic characteristics of the patients with an abnormal X chromosome vary from typical Turner stigmata in cases of 45,X and 46,X,i(Xq) to a normal phenotype in the case 47,XXX. The phenotypic effect of a specific X chromosome aberration is assumed to be simultaneously exerted through different mechanisms[19].

In mosaic cases of Turner's syndrome such as 45,X/46,XX and 45,X/47,XXX, while the exact mechanism is not fully understood, the phenotype

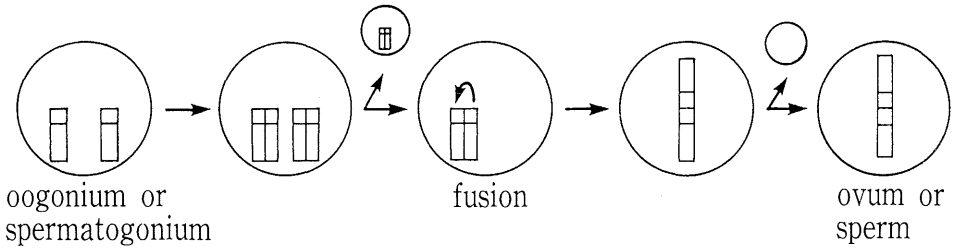
Table 1. Incidence of Turner's phenotypes and the percentage of 45,X cells in the cases of 46,X,dic(X) (qter→p22::p22→qter) or 45,X/46,X,dic(X) (qter→p22::p22→qter)

% of 45,X cells	short stature	PA* or GD**	webbed neck	cubitus valgus	references
0	6/8	5/5	2/5	2/5	4,7,8,12,13,16,18,21
1%—30%	3/3	1/1	1/2	0/2	1,14 present case
31%—60%	5/5	3/3	0/2	1/3	3,9,11,17,20
over 61%	2/2	1/1	0/1	1/2	10,15
Total	16/18	10/10	3/10	4/12	

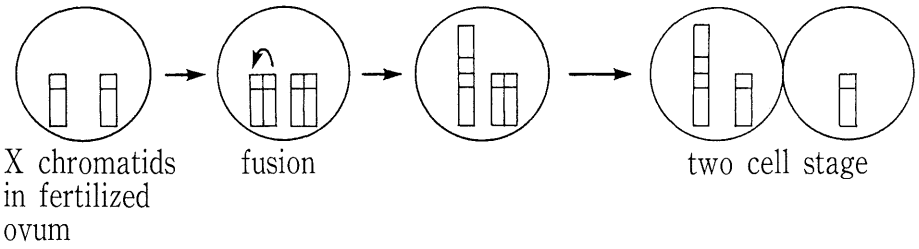
*PA: primary amenorrhea
**GD: gonadal dysfunction



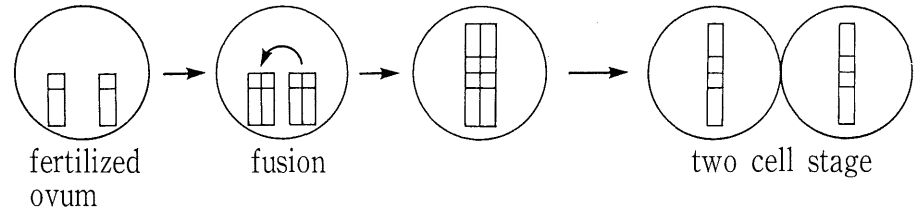
A : Terminal interchomosomal fusion before meiotic division I



B : Terminal interchromatid fusion before meiotic division II



C : Interchromatid fusion during the first mitotic division



D : Interchromosomal fusion at the first mitotic division

Fig. 5. Possible mechanisms of dic(X) chromosome formation

largely depends upon the proportion of 45,X cells[6]. Similarly, Rivera et al[14] reported that the phenotype associated with an X;X terminal rearrangement could vary from typical Turner's syndrome to clinical features of 47,XXX (i.e., normal or almost normal) depending upon both chromatin loss during the fusion and the percentage of 45,X cells.

Since the first report of Disteche et al[4], 17 cases with a karyotype of 46,X,dic(X) (qter→p22::p22→qter) have been reported and nine of them were mosaic cases with 45,X cells. Observed (or described) Turner stigmata and the percentage of 45,X cells in 18 cases including the present case are summarized in Table 1. Short stature defined as less than 25th percentile[2] was recorded in all cases except two[12,16]. Primary amenorrhea in patients older than 16 years of age or gonadal dysfunction detected by elevated gonadotropin levels was recognized in all 10 cases examined. In contrast, webbed neck and cubitus valgus were reported in only about one third of the cases, and the presence or absence of these stigmata seemed to be independent of the percentage of 45,X cells. Therefore, in cases of dic(X), chromatin lost during the fusion of the two X chromosomes is assumed to be mainly responsible for the expression of the phenotype. As the p22 region is the most distal portion of the X chromosome detected by a light microscope, the lost minute chromatin would be different in size among the 18 cases. This potential heterogeneity in chromosome constitution may contribute to the heterogeneity of the phenotype.

In all eight cases including the present case in which DNA replication was examined, the dic(X) chromosome was late replicating[7,9,11,14,16,17,21]. If a normal X chromosome was inactive in a cell, the cell would be non-viable because it would be nullisomic for the lost portion of the dic(X) chromosome.

Theoretically, a dic(X) chromosome is formed either during meiotic or mitotic division, and there are four possible pathways for its formation (Fig. 5). Of these, both pathways A and B would result in the 46,X,dic(X) without 45,X cells. Pathway C would result in 45,X/46,X,dic(X) when the fusion occurs in the first mitotic division. Pathway D also results in mosaicism, 45,dic(X)/46,XX, when the fusion occurs after the first mitotic division. When chromosomal deletion occurs in the terminal region of the X chromosome by the fusion of chromatids or chromosomes, it results in acentric elements, the loss of which leads to the expression of mild Turner characteristics. In the present case, the existence of two cell lines and the expression of Turner's stigmata indicate that pathway C with some chromatin loss occurred.

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