A duplication/deficient X chromosome in a girl with mental retardation and dysmorphic features

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SUMMARY A structurally abnormal X chromosome was found in a nine year old girl with mild mental retardation and dysmorphic features. Subsequent clinical examination at 18 years of age showed tall stature and gonadal dysgenesis. Re-examination of her karyotype using a variety of banding techniques on prometaphase chromosomes allowed the identification of the abnormal chromosome as a duplication/deficient X chromosome, 46,Xder X(pter→q28::p11.2→pter). The clinical features are discussed in terms of karyotype/phenotype correlation.

Duplication/deficient X chromosomes, consisting of a nearly entire X chromosome with a terminal deletion of the short arms replaced by an extra pair of long arms, are cytogenetically a well defined group.¹ Clinically, they show symptoms of Turner's syndrome, including short stature, gonadal dysgenesis, and Turner's stigmata. The alternate

duplicated short arms attached to deleted long arm rearrangement, however, appears to be a rare event. To our knowledge, only one such case has been reported in a tall girl with gonadal dysgenesis. This arose as a recombinant product from a maternal pericentric inversion. The present report documents a similar case in which a de novo rearrangement has resulted in a duplication of most of the short arm (p11.2→pter) and deletion of the terminal portion of the long arm (q28→qter).

Case report

The patient, born on 14.3.65, is the second child of healthy, non-consanguineous parents. At birth at 36 weeks' gestation, after an uneventful pregnancy, she weighed 2900 g and made satisfactory neonatal progress. Hypertelorism and epicanthal folds were noted. At two years, speech development was delayed, at three years she had only a few single words, and at five years she attended special school.

She was first seen for cytogenetic screening at nine years of age. Assessment noted a short

FIG 1 The proband aged 18 years.

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TABLE Chart of clinical progress and treatment.

Date	Treatment	Height (m)	Weight (kg)	Breast development	Pubic hair	Bone age
3.4.84	Ethinyl oestradiol 0.02 mg daily for 3 weeks out of 4	1.79	68.2	2	2	11
26.6.84		1.79	70.6	3	2	—
16.10.84		1.79	72.2	4	3	—
22.1.85		1.79	75.3	4	3	13.5
August 85						
13.5.86		1.82	76.6	4	3	
21.10.86		1.82	78.5	5	3	

attention span, verbal comprehension at 3.3 years, and an EPVT score of 66. She had mild dysmorphic features. No other abnormalities were noted.

The patient was reassessed at 18 years of age. She had a tall, eunuchoid habitus (height=175 cm, weight=64.5 kg; mother's height=1.58 m, father's height=1.74 m). Her appearance was child-like with some dysmorphic features (fig 1). The head was large (OFC=58 cm) and the face long with a prominent upper part. The eyes exhibited epicanthal folds and the nose was round tipped with a wide and prominent nasal bridge. The ears were low set with poor lobule formation. She was prepubertal with no history of periodic abdominal pain or hormone treatment. She had slight breast (grade II+) but no nipple development, sparse pubic and axillary hair, undeveloped labia, small clitoris, and a patent vagina. There was a small uterus seen on ultrasound scan, but neither ovary could be identified. Her bone age was 11 years.

Gonadotrophin and oestrogen plasma levels taken on two occasions three months apart were as follows: LH 7.8 and 9.0 IU/l; FSH 27 and 25 IU/l; oestradiol 59 and <37 IU/l. Testosterone was within the female range (1.1 nmol/l), prolactin and thyroid hormones were normal, and alkaline phosphatase was raised for her age (207 IU).

The clinical picture of eunuchism, retarded bone age, and hormone findings were considered sufficient to diagnose ovarian failure without submitting her to ovarian biopsy. Oestrogen replacement therapy was commenced with ethinyl oestradiol 0.02 mg daily for three weeks out of four. Over the next nine months (table), there was puberty development, advancement of bone age, and arrest of height. Part of her weight gain was accounted for by the feminisation. There was no menstrual loss.

After 15 months she stopped attending for hormone therapy, mainly because height restriction seemed to have been achieved. After nine months without hormones her height had increased another 3 cm, but weight and puberty development were stable. When seen six months later there was no further growth in height, breast development was complete, and pubic hair was stage 3.

CYTOGENETIC STUDIES

Standard analysis of G banded chromosomes (1974) showed extra material attached to the long arm of one of the X chromosomes. Studies using tritiated thymidine autoradiography showed that the abnormal X chromosome was consistently late labelling along the entire length.

Cytogenetic reassessment (1983) using GTG

FIG 2 Partial karyotype of proband with diagrammatic representation of the abnormal X chromosome.

FIG 3 RBG banded cell showing the late replicating abnormal X chromosome

banding on prometaphase chromosomes (fig 2) showed that the band q28→qter was deleted while the extra material consisted of X short arm (p11.2→pter). C banding showed only one heterochromatin block indicating that it was not dicentric, while replication banding using the BUdR incorporation technique (fig 3) confirmed the previous labelling results that the abnormal chromosome was consistently late replicating. The karyotypes of both parents were normal.

Discussion

The proband has an abnormal X chromosome consisting of duplication of the short arm p11.2→pter and deletion of the long arm q28→qter. Her main clinical features are tall stature, gonadal dysgenesis, mental retardation, and dysmorphic features. A similar reported case² with duplication p22→pter and deletion q24→qter also had tall stature and gonadal dysgenesis. In this case it was postulated that duplication of the distal portion of the short arm, a region known to carry statural determinants, was responsible for the tall stature, while deletion of the region q24→qter was responsible for the gonadal dysgenesis. This could also apply to the present case where trisomy Xp is again associated with tall stature; however, the deletion of

the long arm is quite small (q28→qter) and is more likely to give rise to impaired ovarian function rather than complete ovarian failure.³ Pairing problems at meiosis rather than straightforward deletion of genetic material are probably responsible for the dysgenetic ovaries.

The mental retardation and dysmorphic features are more difficult to explain in terms of phenotype-karyotype correlation. Mental retardation is present in a proportion of XXX females and has been reported in three out of seven cases with Xp duplication/Xp deficient chromosomes,¹ suggesting an association with extra X material. However, mental retardation has also been reported in several cases with apparently balanced X chromosome inversions.⁴⁻⁶ A particularly interesting case is that of dizygotic twins with an inversion Xp11q22, in which one twin had mild mental retardation, coarse facies, and irregular menses, while the other twin was phenotypically normal.⁴ The inverted X in the affected twin was selectively inactivated while in the normal twin the inactivation was random. This case illustrates the importance of considering the inactivation pattern in structural abnormalities of the X chromosome. When an abnormal X is non-randomly inactivated, any mutation in the active X is not compensated for and is, therefore, expressed. It has been suggested that the differences in pheno-

typic expression in families with identical X chromosome abnormalities and non-random inactivation are the result of the differences in the genetic content of the normal, active X.⁷ The mental retardation or dysmorphic features or both in the proband could, therefore, be the result of the expression of genes on the normal X which is active in all the cells.

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Martsolf's syndrome in a non-Jewish boy

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SUMMARY Martsolf's syndrome has been described in Jewish people. We describe a patient of non-Jewish ancestry who has minor differences from other patients. The possible pattern of inheritance is discussed.

In 1978, Martsolf *et al*¹ described two brothers, born to consanguineous Jewish parents, with severe mental retardation, cataracts, short stature, and primary hypogonadism. Another Jewish family with the same syndrome has recently been described.² We describe here a non-Jewish boy, to clarify the clinical picture of this syndrome further and to determine its mode of inheritance which is still uncertain.

Case report

The proband was a 13 month old male, born to a G1 P1 A0 20 year old woman after an uncomplicated term pregnancy. There was no exposure to any known teratogenic agents during pregnancy. Delivery was uncomplicated and spontaneous. His birth weight was 2100 g. The parents, of non-Jewish origin, were healthy and non-consanguineous.

There was no family history of other congenital malformations. At three months of age, the patient was admitted to hospital because of bronchopneumonia and retardation of growth. On this

occasion bilateral cataracts were noted and at the age of seven months he underwent a surgical operation for these. At 13 months of age, he was admitted to our hospital because of growth and psychomotor retardation. On admission, physical

FIG 1 The proband at 13 months of age.

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