

# Distal long arm deletions of the X chromosome and ovarian failure

A Bates, P J Howard

## Abstract

**A mother and daughter are described with premature menopause and deletion of the X chromosome at q28.**

Structural anomalies of the X chromosome and ovarian failure are well known.<sup>1</sup> Secondary amenorrhoea, recognised as premature menopause and involving an X chromosomal deletion, has only been described on two occasions, the breakpoints being at q25<sup>2</sup> and q26.<sup>3</sup> We describe familial inheritance of an X chromosome with a deletion at q28 in mother and daughter, both of whom are reported to have premature menopause.

## Case report

The proband (the second and last child) presented at the gynaecological clinic with secondary amenorrhoea at the age of 28 years. Her periods had started at the age of 14 years. They were described as 'painful' and, for this reason, she started taking the combined oral contraceptive pill at the age of 17 years. She continued taking various preparations of the combined oral contraceptive pill for the next 11 years, finally stopping eight months before presentation. She had not menstruated since stopping the pill. Episodes of flushing and sweating were reported.

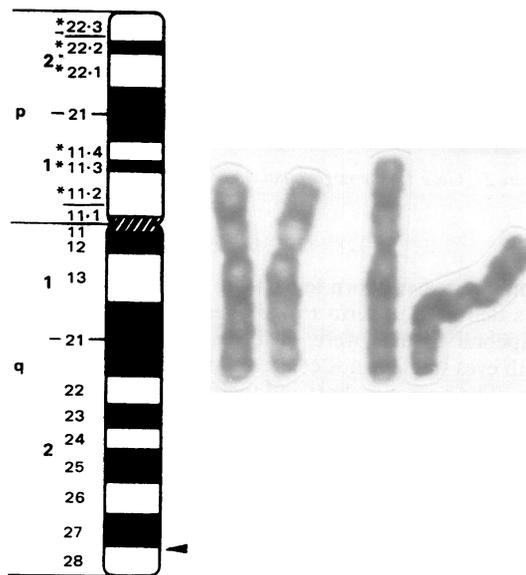
Physical examination proved normal. She was of normal height with full development of secondary sex characteristics and no stigmata of Turner's syndrome. Pelvic examination was normal; normal anatomy had been previously found on ultrasound scanning.

Endocrinological investigations showed the follow-

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*Diagram and partial karyotype of GTG banded X chromosome showing deletion (deleted chromosome on right) at q28. Arrowhead indicates breakpoint site.*

ing: serum FSH, mean 45.2 U/l (normal 1 to 5 U/l); serum LH, mean 61.7 U/l (normal 2 to 13 U/l); serum prolactin, 231 mU/l (normal <500 mU/l); serum progesterone, 1.1 nmol/l (normal, luteal phase >16 nmol/l); 24 hour urinary oestrogen, 27 nmol (follicular phase, 20 to 150 nmol/24 hours; postmenopausal, 10 to 55 nmol/24 hours).

A diagnosis of premature menopause was made and blood was referred for cytogenetic investigation. GTG banding indicated a deletion on one X chromosome at q28 (figure).

The mother had premature menopause at the age of 29 years. Cytogenetic investigation of her blood showed a similar deletion at Xq28 (figure). No information was available concerning the older sister.

## Discussion

One of the outstanding features of partial deletion of the X chromosome is the lack of correlation between karyotype and phenotype. Nevertheless, the associa-

tion between ovarian failure, both primary and secondary, and structural abnormality of the X chromosome is well established. Wyss *et al*<sup>4</sup> postulated that there may be genes located both on the proximal short arm and distal long arm of the X chromosome which determine gonadal dysgenesis. The mother and daughter reported here support earlier evidence that the occurrence of premature menopause may be linked to a deletion of the long arm of the X chromosome. Additionally, our cases refine the breakpoints, indicating that the gene(s) postulated by Wyss *et al*<sup>4</sup> as determining gonadal dysgenesis are located in the telomeric part of the X chromosome in band q28.

What then are the features controlling ovarian function? It is known that germ cells are present in 45,X human embryos, but that their rate of attrition is greatly increased.<sup>5</sup> It was therefore proposed that there are a number of genes, located on multiple sites on the X chromosome, which influence the rate of germ cell attrition. The more of these genes present, the slower the rate of attrition.<sup>6</sup> However, it cannot just be a matter of the number of genes, and it therefore seems likely that the final phenotypic expression is dependent upon the interplay between autosomal genes and those located on the X chromosome. This hypothesis is reinforced by the variable phenotype seen in two sisters described by Fitch *et al*,<sup>3</sup> both of whom had a deletion of the X chromosome at q25.

One suffered premature ovarian failure at 21 years of age, whereas the other had one child and was still menstruating, albeit irregularly, at the age of 37 years.

Undoubtedly, investigation of infertility and premature ovarian failure will identify more cases of partial deletion of the X chromosome, enabling refinement of the phenotypic map. Females with such deletions will require counselling as to possible foreshortened reproductive life and increased risk of miscarriage.

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