FAMILIAL MOSAIC TURNER SYNDROME WITH SHORT STATURE AND PRESERVED FERTILITY DUE TO A RING X CHROMOSOME WITH DISTAL XP22.3 AND XQ26 DELETION

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INTRODUCTION

Monosomy X is characterised by loss of oocytes at the pachytene stage of meiotic prophase during female development, resulting in streak gonads at birth. Fertility in women with Turner syndrome is usually a result of tissue mosaicism, with one cell line containing two normal X chromosomes. Fertility has occasionally been reported in women with a structural X chromosome rearrangement.

We describe a family where the mother had a clinical diagnosis of Turner syndrome, with mosaicism for 45,X and a ring X chromosome, who achieved 3 pregnancies, two of which resulted in the live births of healthy females. One daughter was also mosaic for the ring chromosome, and the other daughter had monosomy X in all cells analysed.

CASE HISTORY

Patient 1

- 12 years old and recently moved from Poland
- Referred for investigations of short stature (Ht SDS -2.1)
- Maternal height 142.9 cm (-3.5 SD) , paternal height 176.1cm (-0.31 SD)
- Birth weight 2.63kg at 37 weeks (20th centile), length 54cm (99.5th centile)
- Growth in Poland tracking only 25th centile till aged 10
- Proportionate short stature
- Non-dysmorphic
- Tanner stage B3
- Bone age: 11 years at a chronological age of 12.25 years.
- X ray radius/ulna: some bowing of the radius
- Normal renal USS and echocardiogram
- Pelvic USS: normal appearance of ovaries

Karyotype: 45,X[20]/46,X,r(X)(p22.3q26)[10]
Mosaic Tuner syndrome with ring chromosome

- Spontaneous menarche aged 12.8 years, regular peroids
- GH treatment aged 13-15 years. Height 146 cm aged 15.0 (-2.60SD)

Mother of patient 1

- Subsequently revealed that she also had mosaic Turner syndrome
- Spontaneous puberty and menarche
- Needed assistance to conceive

Karyotype, 45,X[48]/46,X,r(X)(p22.3q26)[2]

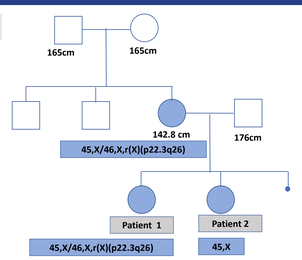
Patient 2 (younger sister of patient 1)

- Spontaneous puberty and menarche aged 12.
- Regular periods
- Height: 145 cm at 12.0 yr (-0.67 SD), 148.5 cm at 13.5 yr (-1.50 SD)
- Non-dysmorphic
- Karyotype undertaken

Karyotype: 45,X (in extended count of 50 cells)

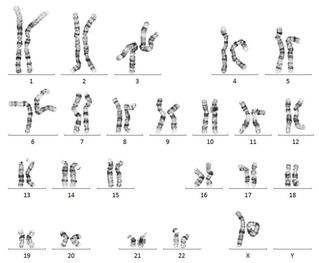
- Normal renal USS and echocardiogram
- Pelvic USS: normal appearance of ovaries
- X ray radius/ulna: Madelung deformity

Pedigree of family



RESULTS

Karyotype in Patient 1:
45,X[20]/46,X,r(X)(p22.3q26[10]

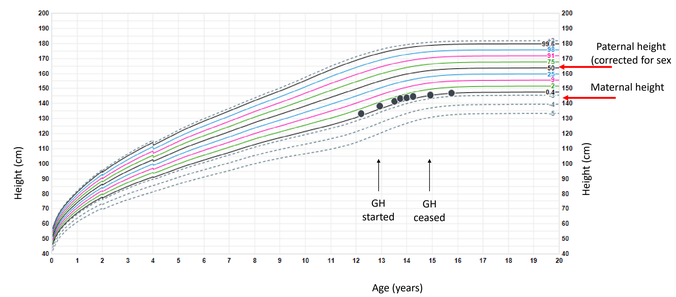


46,X,r(X)(p22.3q26) in 10/30 metaphases
45,X in 20/30 metaphases

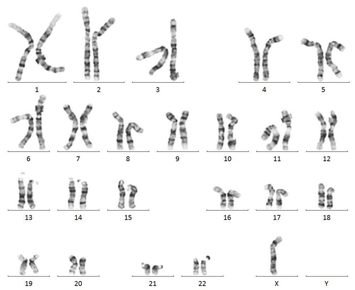
Patient 1	12.8 yrs, B4 M1
LH (U/L)	54.6
FSH(U/L)	34.0
AMH (pmol/L)	<1

Patient 2	11.2 yrs B3 M0	12.2 yr B3 M0	13.5 yrs B4 M1	13.7 yrs B5 M0
LH (U/L)	1.0	10.6	3.4	14.0 (0.4-4.6)
FSH (U/L)	12.9	46.9	6.5	12.8 (2.1-9.3)
Oestradiol (pmol/L)	183 (55.1-58.7)	98 (98-571)	245 (134-720)	399 (134-720)
AMH (pmol/L)		<3		<3

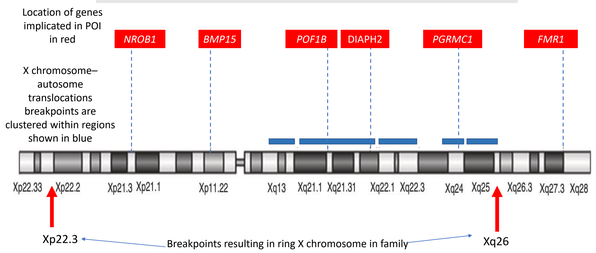
Patient 1: Growth Chart showing height versus age
Source: WHO Child Growth Standards: British 1990 reference data, reanalysed 2009



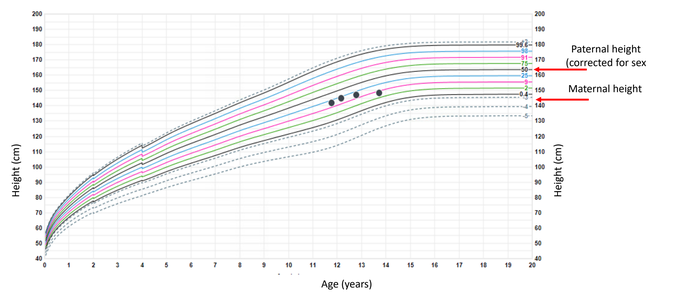
Karyotype in Patient 2: 45,X
(50 metaphases)



X chromosome ideogram showing map of observed gains and losses in fertile and primary ovarian insufficiency (POI) females
Adapted from Yatsenko et al, 2018



Patient 2: Growth Chart showing height versus age
Source: WHO Child Growth Standards: British 1990 reference data, reanalysed 2009



CONCLUSION

We present an unusual family with familial Turner Syndrome. The presence of the unstable ring X chromosome is likely to account for the familial Turner syndrome. Structural rearrangements of the X chromosome can be associated with fertility, which is thought to be related to the positions of the breakpoint. Spontaneous puberty and menarche occurred in the mother and her two daughters may be related to tissue mosaicism and intact X chromosome regions proximal to Xp22 and Xq26 which play a role in ovarian development and maintenance. However, raised gonadotrophins and undetectable AMH in the daughters and are in line with fluctuating ovarian function and developing ovarian failure. Only time will tell whether the daughters may be fertile like their mother.
Short stature and Madelung deformity in the mother and 2 daughters is in line with predicted SHOX deletion at Xp22.33 in the pseudoautosomal region.

REFERENCES

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