**INTRODUCTION**

Turner syndrome (TS) is classically a sporadic cause of short stature and gonadal dysgenesis in girls. Here we report familial variant TS affecting twelve individuals of both sexes over three generations. The affected children display short stature with varying degrees of neurodevelopmental disorder and visceral abnormality. The family demonstrates the phenomenon of sexual dimorphism, with boys being more severely affected than girls.

**METHODS**

A white British family in Peterborough was referred to Paediatrics following an antenatal genetic diagnosis. The proband’s 20 week anomaly scan revealed a rounded right ventricle and echogenic kidneys. Subsequent fluorescence in-situ hybridisation (FISH) analysis on amniotic fluid identified a deletion of the short arm of the X chromosome, consistent with a diagnosis of variant TS. Family testing led to twelve members of the family being identified with variant TS.

**RESULTS**

In summary, the key features are:
- **Meso-melic short stature** (fig. 3) in eleven out of twelve affected individuals
- **Neurodevelopmental disorder of varying degrees**
- **Visceral abnormality in one child only**

This family illustrates some unexpected and interesting features of TS. TS classically causes short stature in girls, but here three boys are affected. Typically, TS is due to a sporadic non-disjunction event and TS patients are infertile. This pedigree demonstrates **inheritance in a X-linked dominant pattern**.

Usual visceral features of TS are overshadowed by neurodevelopmental disorders in this family. Sexual dimorphism is seen. Neurodevelopmental seems more severely disrupted in boys; all three boys are affected by developmental delay and two out of three have autism.

All children but one have normal echocardiograms, normal renal ultrasound imaging, normal thyroid function and normal vision and hearing. One boy (III-11) has congenital heart disease and one mother (II-1) has hypothyroidism.

Many typical dysmorphic features of TS, e.g. webbed neck and shield chest, are absent, however, some dysmorphism is seen. The proband (III-3) has pedal and hand lymphoedema and one girl (III-5) has cubitus valgus and high arched palate.

**DISCUSSION**

Variant TS in this family is due to deletion of a segment of the short arm of the X chromosome: Xp22.3. Of the 42 known contiguous genes in Xp22.3, deletion of NLGN4, ARSE and SHOX may explain the phenotypes seen.

- NLGN4 is involved in synapse formation. Its deletion is linked to developmental delay and autism as well as neuropsychiatric disorders such as attention deficit hyperactivity disorder (ADHD) and motor tics.
- ARSE gene deletion is linked with short stature and intellectual disability. It shows X-linked recessive inheritance, hence only affecting boys in this family.
- SHOX haploinsufficiency accounts for most of the height deficit in TS as well as skeletal features such as cubitus valgus and high arched palate.

Xp22.3 deletion has been described once before in a mother and two sons with learning disability, ADHD and skeletal abnormalities. Whilst we report appreciably different phenotypes, there is a similar male preponderance for neurological involvement in both families.

Sexual dimorphism in neurodevelopment may be due to many factors. Firstly, parent-of-origin imprinting of a locus involved in ‘social cognition’ has been shown on the X chromosome in classical TS patients. Secondly, there is increasing evidence for the role of oestrogen in establishing and maintaining sex differences in the brain via the mechanism of epigenetic modification.

**CONCLUSION**

Familial variant TS should be considered as a diagnosis in short boys with concomitant neurodevelopmental disorder and relevant family history.