SHORT STATURE WITH NEURODEVELOPMENTAL DELAY IN FAMILIAL VARIANT TURNER SYNDROME

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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 demonstrate 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 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.

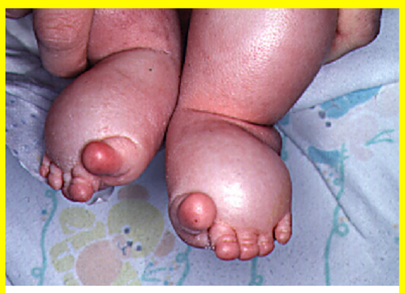

Fig. 1[1]: Pedal lymphoedema.

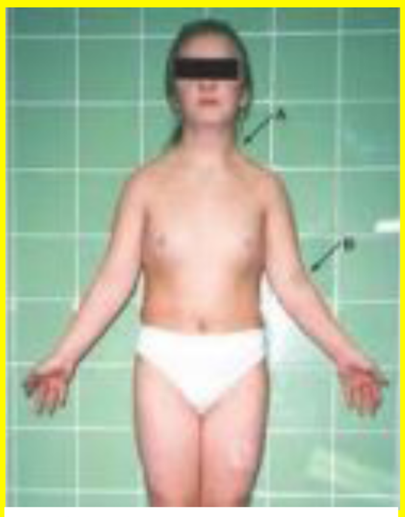

Fig. 2[1]: Cubitus valgus.

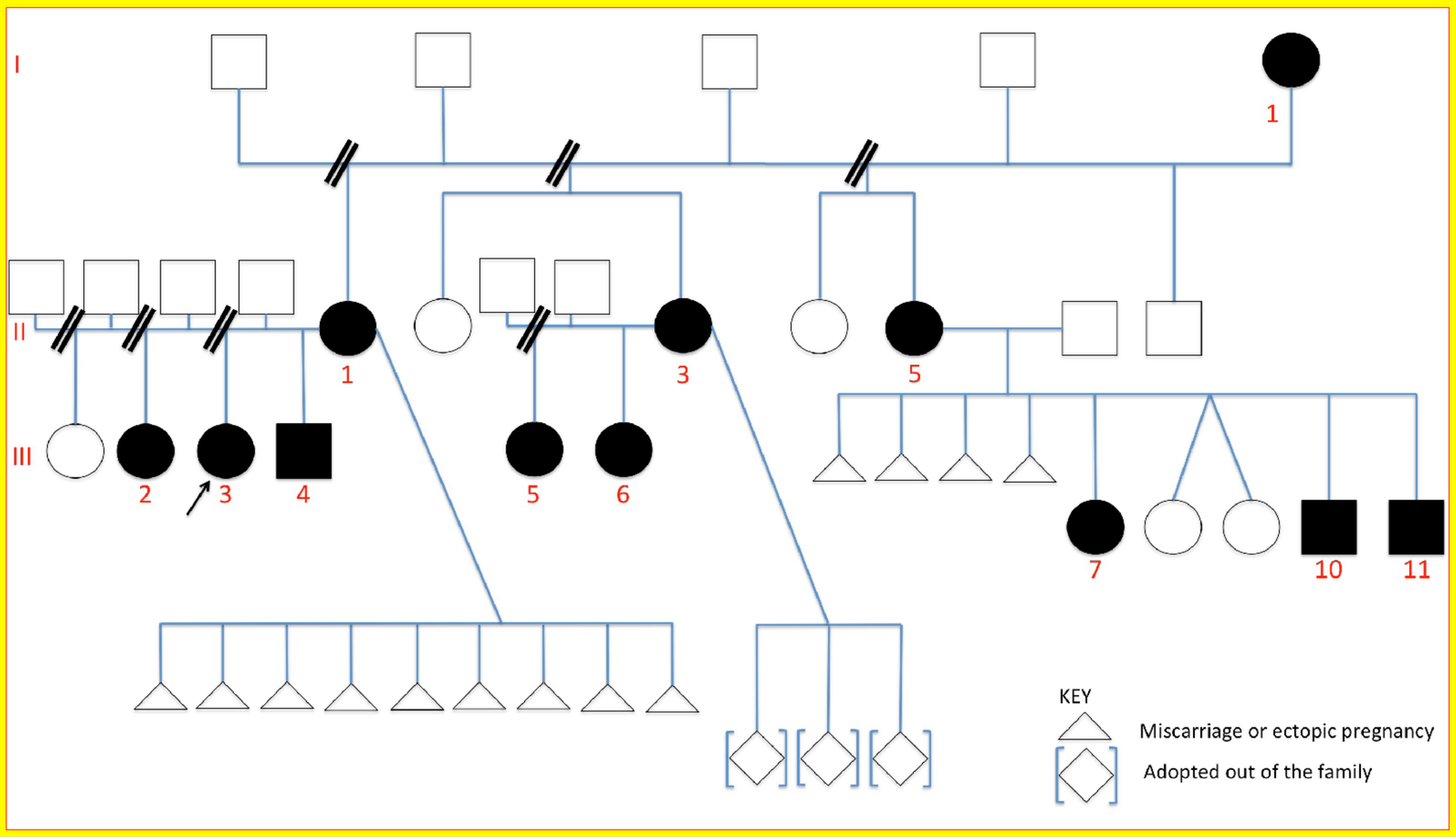

Fig. 3[1]: Mesomelic dwarfism; note extreme shortening of the limbs.

MOTHERS II-1, II-3, II-5, AND GRANDMOTHER I-1

Short stature
Learning disability
Hypothyroidism (II-1)
Multiple miscarriage (II-1, II-5)

CHILD III-2	CHILD III-3	CHILD III-4
5 years 1 month ♀	3 years 6 months ♀	12 weeks ♂
Height <0.4th centile Weight 25th centile	Height 25th centile Weight 75th centile	Length <0.4th centile Weight 50th centile
Speech & language delay Delayed toilet training	Speech & language delay concerns	Motor developmental delay
	Pedal & hand lymph-oedema at birth (*fig. 1*)	

CHILD III-5	CHILD III-6
6 years 1 month ♀	2 years 7 months ♀
Height <0.4th centile Weight 25th centile	Height <2nd centile Weight 50th centile
Mild cubitus valgus (*fig. 2*) High arched palate	

CHILD III-7	CHILD III-10	CHILD III-11
7 years 10 months ♀	4 years 10 months ♂	1 year 8 months ♂
Height <2nd centile Weight 50th centile	Height <2nd centile Weight 25th centile	Height <0.4th centile Weight 2nd centile
	Global developmental delay Autism	Global developmental delay Autism concerns
		Bicuspid aortic valve and dilated aortic root
	Mild hypertelorism Flattening of nasal bridge	Mild hypertelorism Flattening of nasal bridge

RESULTS

In summary, the key features are:

- Mesomelic 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. Neurodevelopment 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[2].

- NLGN4 is involved in synapse formation. Its deletion is linked to developmental delay and autism[3] 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[4]. It shows X-linked recessive inheritance, hence only affecting boys in this family.
- SHOX haploinsufficiency accounts for most of the height deficit in TS[5] as well as skeletal features such as cubitus valgus and high arched palate[6].

Xp22.3 deletion has been described once before[7] 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[8]. 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[9].

CONCLUSION

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

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Turner Syndrome

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