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Original article

A new X-linked mental retardation (XLMR) syndrome with late-onset primary testicular failure, short stature and microcephaly maps to Xq25–q26

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Abstract

X-linked mental retardation (XLMR) is a heterogeneous disorder with both syndromic and non-syndromic forms. Here we describe the clinical and molecular characterisation of a family with a syndromic form of XLMR with hypogonadism and short stature. We investigated a family in which four male members in two generations presented with hypergonadotrophic hypogonadism associated with development of small and abnormal testes. In two of the males, late-onset testicular ascent was noted. In addition, all affected males had short stature (<0.4th centile) and mild learning difficulties and three out of the four had microcephaly. Karyotypes were normal and endocrine investigations confirmed primary testicular failure.

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The phenotype segregated as an X-linked trait. Haplotype and genetic two-point linkage analysis with 22 microsatellites excluded the whole X chromosome except for a region on Xq25–Xq27 encompassing 13.7 Mb with a maximum LOD score of 1.1 for marker DXS8038 at $\theta = 0.05$.

One family previously described as having XLMR with hypogonadism and short stature maps to the same X chromosome region implicated in our family. However, the more severe mental retardation, muscle wasting and tremor described in this other family would suggest that our family is affected by a novel XLMR syndrome.

Keywords: X-linked mental retardation (XLMR); Hypogonadic hypogonadism; Short stature; Late onset testicular failure

1. Introduction

X-linked mental retardation (XLMR) is a heterogeneous disorder with both syndromic and non-syndromic forms. Numerous studies have classified the syndromic forms dependent upon clinical and biochemical features. In addition, many XLMR syndromes have been characterised at the molecular level with either linkage studies defining either the X chromosome loci containing the causative genes or identification of the causative gene itself. A combination of these approaches has led to a more stringent classification of XLMR (http://www.ggc.org/xlmr.htm).

At present, at least 14 XLMR syndromes include hypogonadism and short stature as a feature. Several of these conditions are allelic [1–21] and so probably represent a smaller true number of XLMR conditions with these features.

Here, we report on the clinical and genetic characterisation of a novel form of XLMR associated with hypergonadotrophic hypogonadism and short stature.

2. Clinical report

Individual II-1 (Fig. 1) presented to the genetics clinic at the age of 28 years for investigation of his incomplete puberty and mild learning difficulties. His birth weight was normal and his testes were of normal size and normally descended at birth. In infancy, he was investigated for poor weight gain and failure to grow, but no cause was identified. He had difficulties at school, and required extra help, and left with a basic qualification in English. He had failed to progress through puberty and subsequent investigation revealed that he had primary testicular failure with small, atrophic testes. On examination, he had short stature with a height of 153 cm (−3.9SD). His head circumference was also small at 51.8 cm (−3.6SD). He had small hands with bilateral fifth finger clinodactyly, and mildly dysmorphic facial features with deep-set eyes, prominent supra-orbital ridges (Fig. 2), a high nasal bridge and large ears. He lived semi-independently and needed help to prepare food, shop and manage his financial situation. He was not in employment. He had a shy, introverted personality, and had been under the care of a psychiatrist for paranoid and obsessional behaviour. He commenced testosterone treatment, which he has used intermittently. The endocrine and karyotype results of all the affected family members are presented in Table 1.

Individual II-2 (Fig. 2) was a full brother of II-1. He had been born at 36 weeks gestation with a birthweight of 2.52 kg (0SD). The testes had been normal and descended at birth. He

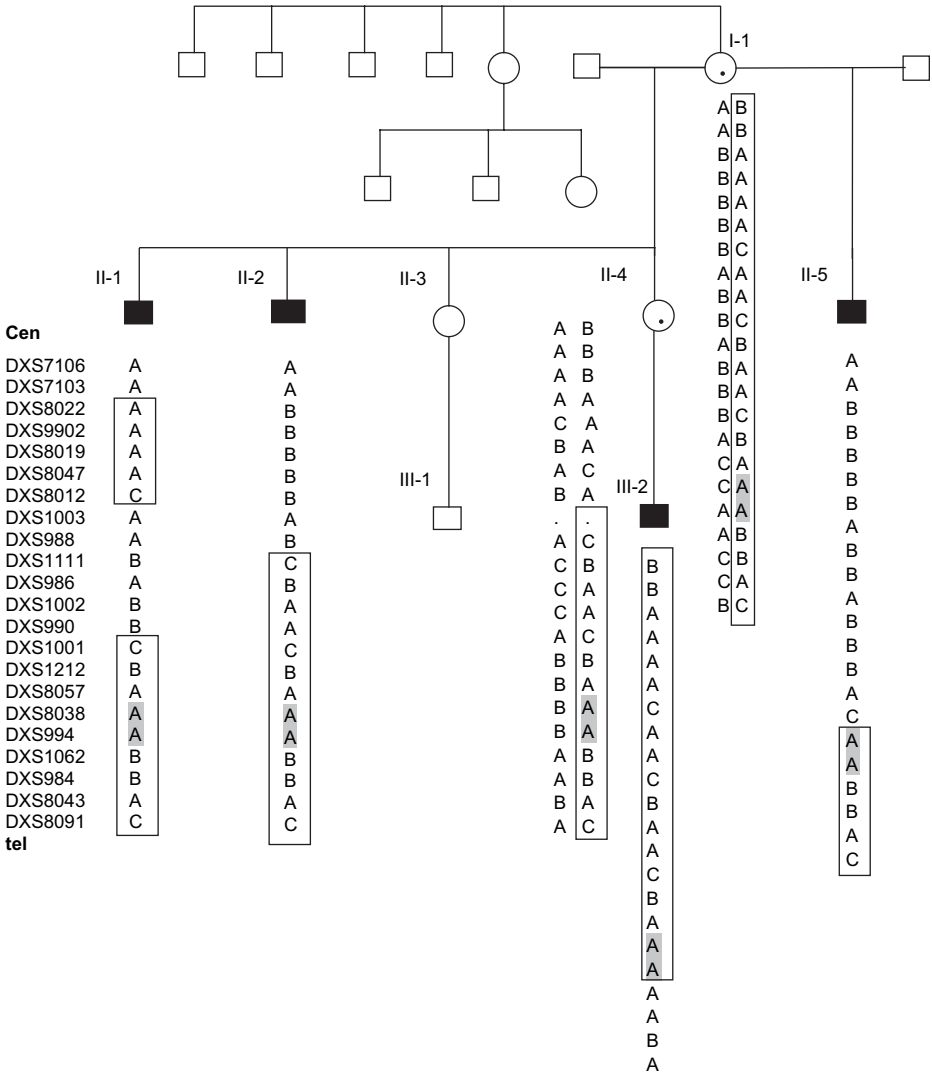

Fig. 1. Three-generation pedigree and haplotype analysis with 22 microsatellite markers in the family with syndromic XLMR. Recombination in III-2 defines the telomeric boundary of linkage and recombination in II-5 defines the centromeric border of linkage.

remained a small child, but was in good health apart from migraine headaches. He required extra help at school and was considered to have dyslexia. He left school without qualifications and subsequently worked in a shop. He had delayed puberty and was referred for investigation at the age of 17, when he was found to have testosterone deficiency due to primary gonadal failure, and was started on testosterone treatment. At the age of 23 years his height was 150.6 cm (−4.3SD), weight was 80 kg (+2.1SD) and OFC 55.8 cm (−0.9SD). He had similar facial features to his brother and was noted to have small fifth fingernails. His testes were small and had a soft, abnormal consistency.

Fig. 2. Facial features of affected family members. II-1: face and profile. Note deep-set eyes, prominent supraorbital ridges and high nasal bridge. Face of II-2, II-4 and II-5: note similar facial features of II-5 to II-1. Beard growth improved after testosterone treatment: III-2 at age 13 years.

II-5 (Fig. 2) was a half-sibling of cases II-1 and II-2, related through their mother. He had been born prematurely with a low birth weight. No abnormalities of the testes were noted at birth. He was in good health as a child, but was always small. He had mild learning difficulties and required extra help at school. He felt that he had progressed through puberty normally, but was evaluated at the age of 28 because of undescended testes. At this stage primary testicular failure was diagnosed and he underwent bilateral orchidectomies. He was commenced on testosterone replacement therapy. On examination at the age of 34 years, he was 149 cm tall (−4.6SD) and had an OFC of 53.1 cm (−2.7SD). He had the same dysmorphic facial features as his brothers and also had small hands.

Individual III-2 was the nephew of cases II-1, II-2 and II-5. He was born at term by Caesarean section for fetal distress and birth weight was 2.98 kg (−1.5SD). He was noted to have hypospadias and had this surgically repaired. He had poor growth in infancy and early childhood. On starting school it was noted that his general development was delayed, and that he had special educational needs. When seen in the genetic clinic at the age of 13 years, he was in early puberty with genital development at Tanner stage 4, pubic hair at stage 5 and axillary hair at stage 2. He had very small, soft testes, both measuring 1–2 ml in volume. Whilst the left testis was in the scrotum, the right testis was high in the inguinal canal. Endocrine investigations suggested that he also had late onset primary testicular failure. Over the subsequent two years his pubertal progress and his growth slowed. His height at 13 years was 139.2 cm (−2.1SD) and OFC 51.2 cm (−3SD).

Table 1
Summary of clinical features in affected family members

	II-1	II-2	II-5	III-2
Normal testes at birth	+	+	+	+
Late-onset testicular failure	+	+	+	+
Late testicular ascent	−	−	+	+
Small atrophic testes	+	+	+	+
Hypospadias	−	−	−	+
Mild learning difficulties	+	+	−	+
Microcephaly (<2nd centile)	+	−	+	+
Short stature (<0.4th centile)	+	+	+	+
Small hands	+	+	+	+
5th finger clinodactyly, small nails	+	+	+	+
Dysmorphic features	+	+	+	+
FSH (1.5–12.4 IU/L^{-1})	48*	19*	12*	87.4
LH (1.7–8.6 IU/L^{-1})	20*	11*	6*	20.6
Testosterone (11–35 nmol/L^{-1})	5.6	ND	3.8	8.4
Free T4 (pmol/L^{-1})	N	13.7(N)	15 (N)	18.6 (N)
Peak growth hormone (mU/L)	ND	ND	ND	24 (N)
Karyotype	46,XY	46,XY	ND	46,XY
FRAX	Neg	ND	ND	ND

* denotes on replacement testosterone treatment. ND denotes not done.+ feature present, − feature absent.

I-1, the mother of II-1, II-2 and II-5 (and the grandmother of II-3) had no fertility problems or hormone problems. She had four brothers, two of whom did not have any children. Her sister has two boys and a girl with no health problems.

II-4, the sister of II-1 and II-2 (and half sister of II-5) and mother of III-2, was 31 years old when referred to clinical genetics. She was born at term, had a normal development, and her performance at school was average. She entered puberty normally and her menarche was at 12 years old with regular menses following this. After giving birth to III-1 at 17 years old, she was given the diagnosis of idiopathic secondary infertility. Subsequently, she has developed polycystic ovaries, but without sufficient hormonal changes to cause infertility. On examination she was 150 cm tall (−2.5SD) and her OFC was 55.1 cm (−0.25SD). She has normal female secondary sexual characteristics.

Her sister, II-3, was well. She entered puberty at approximately 11 years old and has normal breast development. She is 153.2 cm tall (−1.9SD) and her OFC is 54.3 cm (−0.83SD). Her son, III-1, aged 11 years old has a high right testicle, 1 cm in volume and soft. His height is approximately −1SD. He is currently being observed for signs of puberty.

3. Linkage analysis

A standard set of 22 polymorphic microsatellites spanning the X chromosome (Fig. 1 and Table 2) were analysed on genomic DNA extracted from peripheral leukocytes on available family members (Fig. 1). Standard PCR amplification was performed for 32 cycles. One volume of PCR product was extracted with one volume of phenol/choloform and was loaded onto an 8% non-denaturing polyacrylamide gel. Products were subjected to electrophoretic separation at 400 volts at room temperature until the desired separation was achieved. Gels were then silver stained using standard protocols and allelotyped.

Table 2
LOD scores

Locus	Recombination (θ)			
	0.05	0.1	0.2	0.4
DXS7103	−0.18	0.023	0.13	0.04
DXS8047	−0.48	−0.26	−0.1	0
DXS1003	0.27	0.26	0.2	0.08
DXS1111	0	0	0	0
DXS986	−1.16	−0.63	−0.18	0.04
DXS1002	−0.18	0.026	0.14	0.08
DXS990	−1.16	−0.63	−0.18	0.04
DXS1001	−0.18	0.026	0.14	0.08
DXS1212	−0.46	−0.22	−0.06	0
DXS8057	−0.18	0.026	0.14	0.08
DXS8038	**1.1**	**0.97**	**0.72**	**0.06**
DXS994	**0.27**	**0.25**	**0.20**	**0.08**
DXS1062	−0.18	0.026	0.14	0.08
DXS984	−0.18	0.02	0.11	0
DXS8043	−0.18	0.02	0.11	0
DXS8091	−0.18	0.02	0.11	0

Two-point linkage analysis was performed using MLINK. Only obligate carrier females and affected males were analysed. Full penetrance of the X-linked gene was assumed and the frequency of the disease allele set at 0.0001. Map locations and genetic distances were obtained from the MLINK database. Analysis has excluded the majority of the X chromosome: the only region shared by all four affected individuals is a region of 14 cM (from 123.2 Mb–137.0 Mb) that is flanked by the markers DXS8057 (recombinant in II-5) and DXS1062 (recombinant in III-2) (Fig. 1 and Table 2). This family is not large enough to provide a significant LOD score although importantly negative LOD scores were obtained for the majority of the markers tested (Table 2).

4. Discussion

This family represents a newly described syndromal form of mild XLMR. All affected males have evidence of mild mental retardation, short stature, hypogonadism, microcephaly and characteristic dysmorphic features (Table 2). The phenotype described shares many characteristics with previously reported syndromic forms of XLMR. Renpenning syndrome (MIM 309500) is characterised by microcephaly, a long narrow face, short stature with lean body build, and small testes, however mental retardation is usually of severe degree. Mutations in the polyglutamine tract binding protein 1 (PQBP1) have been identified in Renpenning syndrome and a number of other allelic conditions with XLMR [19]. MRXS9 is characterised by severe XLMR in association with microcephaly and variable short stature but without hypogonadism and maps to Xq13.1–Xq21.31 [22]. Most recently a Belgian family with XLMR, short stature, microcephaly and hypogonadism has been mapped to Xp22.1–p21.3 [18]. However all these syndromic forms of XLMR map to loci outside the Xq25–q26 locus implicated in our family.

Compared to the other regions of the X chromosome, relatively few previously described XLMR conditions have been linked to Xq25–26. One XLMR syndrome with hypogonadism which maps to Xq24–Xq25 region, was described in a family, who presented with muscle

wasting of the lower legs, tremor and severe intellectual handicap with an IQ in the range of 29–54 [5]. Affected males also had decreased fine motor co-ordination, joint hyperextensibility, kyphosis, aggressive and hyperactive behavioural problems and a normal head circumference. The phenotype is strikingly dissimilar from that in our family, but this does not exclude the possibility that they are caused by mutations in the same gene. Likewise, Börjeson-Forssman-Lehman (BFL) syndrome is characterised by severe learning difficulties with hypogonadism, moderate short stature and small external genitalia. The severe intellectual handicap and other clinical features of BFL including hypotonia during infancy, macrocephaly, gynecomastia, truncal obesity and specific facial features make this diagnosis unlikely in our family, although recent evidence has suggested that the BFL phenotype is broader than originally suspected and also includes more moderately affected individuals [15,20]. In addition to the syndromic forms of XLMR that map to Xq25–26, eight non-syndromic XLMR families overlap the region, including MRX27 [23], MRX35 [24], MRX42 [25], MRX57, MRX70, MRX71, MRX75, MRX82 [26]. The region between the microsatellite markers flanking the linked markers in our family spans 14 cM and is predicted to contain over 70 genes [27]. Of these, a number have been associated with XLMR, including PHF6 (BFL syndrome), OCRL1 (Lowe syndrome), HPRT (Lesch-Nyhan syndrome) and GPC3 (Simpson-Golabi-Behmel syndrome). Additional attractive candidates include SLC25A14 (brain mitochondrial carrier protein-1) and RBMX2 (an RNA binding motif protein).

Examination of future offspring in this family and continued follow up of individual III-1 may help to refine the linkage region. A candidate gene approach could then be employed to determine the causative gene, which may have a pivotal role in normal intellectual development and in gonadal function.

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