Arch fingerprints, hypotonia, and areflexia associated with X linked mental retardation

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Abstract

A syndrome with distinctive facies, poor muscle tone, absent deep tendon reflexes, tapered fingers, excessive fingerprint arches, genu valgum and mild-moderate mental retardation has occurred in four males in two generations of a white family of European ancestry. The facies are characterised by square configuration, tented upper lip, and thickening of the helices, upper eyelids, and alae nasi. At birth and at maturity, growth (head circumference, height, weight) of affected males is comparable to or greater than unaffected male sibs. Moderate impairment of cognitive function was documented (IQ scores between 40-51). Carriers show no heterozygote manifestations. This X linked condition appears to be different from other syndromes with mental retardation, although there are certain similarities with the α thalassaemia-mental retardation syndrome (ATR-X). Linkage analysis found tight linkage to DXS1166 and DXS995 in Xq13 and Xq21 respectively.

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Keywords: X linked mental retardation; hypotonia; arch fingerprints; linkage

Mutations in 41% of the 277 genes with established loci on the X chromosome cause mental retardation.^{1,2} In some cases, mental retardation occurs without other apparent manifestations and has been termed non-syndromic or non-specific X linked mental retardation (XLMR).³⁻⁵ However, the majority of X linked genes that cause mental retardation produce additional manifestations which comprise more or less distinctive syndromes. In a recent review, Lubs *et al*⁶ listed 105 XLMR syndromes with somatic, neuromuscular, behavioural, or metabolic manifestations. Of these, 34 have been regionally mapped. In 18, the gene responsible has been identified and mutations found.

This report describes an X linked condition characterised by moderate mental retardation, characteristic facies (square configuration, tented upper lip, and thickened helices, upper eyelids, and alae nasi), depressed muscle tone and deep tendon reflexes, genu valgum, tapering of the fingers, and an excess of arch fingerprint patterns. This phenotype differs from that in previously described XLMR syndromes. The condition maps to Xq12-q21.

Patients and methods

Fig 1 shows a partial pedigree of kindred 8035 with four males affected in two generations. The three surviving affected males were available for examination as were two obligate female carriers and five unaffected male sibs. Selected findings are recorded in table 1 and brief clinical summaries of the four affected males are given below. Laboratory studies included normal chromosomes (III.3, III.4), FMR1 analysis (III.3, III.4, III.6), FRAXE analysis (III.3, III.4, III.6), serum creatine kinase (III.6), and haemoglobin electrophoresis (III.6). Brilliant cresyl blue stain for haemoglobin H inclusions was negative (III.6). Obligate carrier females had normal intellect and showed no somatic features. The possibility that carrier females have excessive growth could not be evaluated since there were no non-carrier female sibs for comparison. One obligate carrier died aged 48 years of colon cancer. No other family members have had neoplasms.

CASE II.3

II.3 died at 47 years of age in a car accident. Medical records indicate a birth weight of 4200 g, poor feeding during infancy, poor muscle tone, global delays in motor and language milestones (walked at 2 years, spoke a few words at 5 years), and prolonged drooling. Growth (height and weight) were greater than his four unaffected brothers. Other features include arching of the upper lip, fullness of the upper eyelids, a large, square shaped face, and genu valgum. Pubertal changes occurred normally. His IQ was 46.

CASE III.3

III.3 weighed 3000 g at birth following an estimated 43 week gestation. Developmental milestones were globally delayed (walked at 20 months, spoke a few words at 4½ years), drooling persisted into the school years, and special education was required. He is athletically inclined and likes to swim and play ice hockey, is active socially, and maintains a low skill public job. At the age of 32 years, he was tall (189 cm, 98th centile) and heavy (118 kg, >98th centile) with a normal head circumference (56.0 cm, 30th centile). His face appeared large and squarish in configuration with normal interpupillary measurement (6.3 cm, 55th centile), large ears (7.5 cm, >98th centile), thickening of the helices, thickening of the alae nasi and columella, and small central incisors (fig 2). The hand length was 19.6 cm (60th centile), the fingers tapered, and the fin-

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Figure 1 Partial pedigree of kindred 8035 showing four affected males in two generations and haplotype for selected markers. Bars over pedigree symbols indicate subjects examined. Haplotype contained in the box segregates with the XLMR condition in kindred 8035. Haplotype for II.2 was established from haplotypes of her parents and offspring.

gerprint pattern included five arches, two low ulnar loops, and three ulnar loops. The legs appeared thickened above the ankles, tone was decreased, genu valgum was present, and deep tendon reflexes at the knees and ankles were absent.

CASE III.4
III.4 weighed 4300 g at birth. Movement during pregnancy was decreased. He was delayed in achieving motor milestones and speech, and

growth has been excessive. The Weschler IQ measurement at the age of 21 years was 51. Examination at 28 years showed a height of 185.4 cm (90th centile), weight of 122 kg (>98th centile), and normal head circumference (57.6 cm, 70th centile). His face appeared squarish and large for the cranium, the ears measured 6.2 cm (25th centile) with thickening of the helices and there was mild epicanthus, thickening of the eyebrows laterally, narrowing of the upper alveolar ridge, small teeth, and thickened columella and alae nasi with narrow slits for nostrils (fig 3). The hands were large (hand length 20.4 cm, 85th centile), the fingers tapered, and the fingerprint patterns included one arch, three low ulnar loops, two low radial loops, three ulnar loops, and one whorl (fig 4). The lower legs were thickened, deep tendon reflexes were absent, and genu valgum was present. Genitalia were normal adult with normal testicular volume.

CASE III.6
III.6 had a birth weight of 3800 g and a length of 55.9 cm. He experienced delayed developmental milestones, walking at 17 months and saying his first clear words at about 3 years. He has required special education and had an IQ of 40 (WISC-R) at 11 years. Early childhood growth appeared excessive, but slowed just before puberty. He is outgoing and sociable with a competitive demeanour in sports. At the age of 16 years 4 months he has the following measurements: height 171.5 cm (40th centile), head circumference 54.7 cm (50th centile), and weight 86.4 kg (95th centile). He has downward slanting palpebral fissures with thickening of the alae nasi and helices, slit-like nostrils, cupping of the ears, and arching of the upper lip. The hands and feet are large (hand length 20.6 cm, >98th centile; shoe size 12 EEE), the fingers taper, and dermatoglyphics

Table 1 Selected manifestations and measurements on three affected males and five unaffected brothers

	Affected			Not affected				
	III.3	III.4	III.6	II.4	II.5	II.6	II.7	III.2
Age at examination (y)	32	28	16	53	48	42	39	34
Birth weight (g)	3000	4300	3800	3700	3800	3700	3800	—
Head circumference, cm	56 (30)	57.6 (70)	56.3 (55)	56.5 (45)	56.7 (50)	57 (55)	57 (55)	56.5 (45)
Interpupillary measurement, cm	6.3 (35)	6.2 (25)	5.7 (40)	6.1 (15)	6.7 (75)	6.6 (65)	6.5 (55)	6.0 (10)
Ear length, cm	7.5 (>98)	6.3 (35)	6.7 (80)	7.3 (97)	7.4 (98)	7.0 (90)	7.1 (90)	6.6 (65)
Height, cm	189 (98)	185.4 (90)	171.5 (40)	174 (40)	170.2 (20)	175.6 (50)	178.4 (65)	185.4 (90)
Span, cm	180.3 (40)	185.4 (65)	175.3 (?)	185.4 (65)	180.3 (40)	181 (45)	183 (55)	—
Weight, kg	118 (>98)	121 (>98)	86.4 (>98)	77.3 (50)	84 (70)	91 (85)	75 (40)	88.6 (80)
Hand length, cm	19.6 (60)	20.4 (85)	20.6 (>98)	19.4 (55)	19.1 (40)	19 (35)	19 (35)	22 (>98)
Shoe size	13	13	12	9	7.5	8.5	8.5	12
Facies								
Square configuration	+	+	+	0	0	0	0	0
Thick upper eyelids	+	+	+	0	0	0	0	0
Thick helices	±	+	+	0	0	0	0	0
Cupped ears	0	0	+	0	0	0	0	0
Thick alae/columella	+	+	+	0	0	0	0	0
Arched upper lip	0	+	+	0	0	0	0	0
Small teeth	+	+	0	0	0	0	0	0
Tapered fingers	+	+	+	0	0	0	0	0
Fingerprints								
Arches	5	1	7	0	0	0	0	0
Low loops	2	5	1	0	0	0	0	1
10 finger ridge count	37	NE	18	134	153	118	180	184
Muscle tone	↓	↓	↓	NI	NI	NI	NI	NI
Genu valgum	+	+	+	0	0	0	0	0
Reflexes	0	0	0	NI	NI	NI	NI	NI
Genitalia	NI	NI	NI	NE	NE	NE	NE	NE
IQ	40	51	40	NI	NI	NI	NI	NI

Measurement centiles given in parentheses. NE=observation not made. NI=normal.

Figure 2 Patient II.3 showing large and squarish face, heavy upper eyelids, thickened helices, and thickened alae nasi. (All photographs reproduced with permission.)

Figure 3 Patient III.4 showing large and squarish face, thickened alae nasi, thickened helices, arched upper lip, and small teeth.

Figure 4 Hands of patient III.4 showing tapered digits with small terminal phalanges.

show seven arches and three ulnar loops. The lower legs are thickened, deep tendon reflexes are absent, and genu valgum is present.

PREPARATION OF DNA

Genomic DNA was isolated from peripheral blood using a high salt precipitation method.⁶ Purified DNA was diluted to a concentration of

105 µg/ml and stored at 4°C in TE (10 mmol/l Tris-Cl, pH 7.6, 1 mmol/l EDTA).

MICROSATELLITE ANALYSIS

The conditions used to generate the specific di-, tri-, or tetranucleotide polymorphisms have been previously published.⁷ The forward primers for PCR products analysed by the Automated Laser Fluorescent Sequencer (ALF, Pharmacia, Upsala, Sweden) were synthesised with fluorescein amidite (Fluore-Prime, Pharmacia). Primers for the ALF were desalted through Sephadex G-25 (NAP-10 columns, Pharmacia). Polymorphisms were detected by the ALF using Fragment Manager (Pharmacia) and Automated Linkage Preprocessor (ALP) software.⁸ Earlier PCRs were performed with ³²P-dCTP (3000 Ci/mmol) and detected by manual polyacrylamide-urea gel electrophoresis.

VNTR ANALYSIS

Genomic DNA (5 µg) was digested, separated by agarose gel electrophoresis, transferred to a nylon membrane (MSI), prehybridised, and hybridised as described previously.⁹ DNA probes were labelled by primer extension to a specific activity of approximately 1 × 10⁹ cpm/µg.¹⁰

LINKAGE ANALYSIS

Two point disease to marker analysis was conducted using the program MLINK of the LINKAGE package.¹¹ The mutation rate and gene frequency were set at 3 × 10⁻⁶ and 0.0001, respectively.

Results

The maximal expected lod score for this family was calculated to be Z=2.53 at θ=0.00. Initial two point lod scores for the disease locus and numerous markers spanning the X chromosome were computed using MLINK. Suggestive linkage to Xq12-Xq21.1 was noted for ARA (Z=1.48 at θ=0.00) in Xq12, DXS1111 (Z=1.48 at θ=0.00) in Xq12, DXS453 (Z=1.03 at θ=0.00) in Xq12, DXS566 (Z=1.48 at θ=0.00) in Xq13.1, and DXS986 (Z=1.03 at θ=0.00) in Xq21.1 (table 2).

Once suggestive linkage was established to this region, additional markers were used and lod scores computed: DXS1162 (Z=1.16 at θ=0.11) in Xq12, DXS1166 (Z=2.53 at θ=0.00) in Xq13.2, and DXS995 (Z=2.53 at θ=0.00) in Xq21.1. Haplotype analysis indicated that recombination occurred between DXS1162 and DXS453 proximally (subject II.4 in fig 1). Distally, a recombination occurred between DXS995 and DXS326 (subjects II.8 and III.6 in fig 1). Thus, two point and haplotype analysis indicated a region of linkage extending from DXS453 in Xq12 to DXS995 in Xq21.1. The maximal expected lod score of 2.53 was observed at DXS1166 (Xq13.2) and DXS995 (Xq21.1).

Discussion

This syndrome is characterised by distinctive facies, poor muscle tone, absent deep tendon reflexes, tapered fingers with an excessive

Table 2 Two point lod scores between MR locus in K8035 and X chromosome loci

Marker	Locus	Location	Probe type	Recombination (θ)						θmax	Zmax
				0.001	0.01	0.05	0.1	0.2	0.3		
KAL 5'	KAL 5'	Xp22.32	(CA) _n	-10.45	-7.14	-3.75	-2.35	-1.06	-0.44	0.50	0.00
AFM120Xa9	DXS987	Xp22.31	(CA) _n	-7.94	-6.43	-3.81	-2.63	-1.46	-0.80	0.50	0.00
RX324	DXS443	Xp22.13	(CA) _n	-5.89	-4.15	-2.20	-1.39	-0.67	-0.32	0.50	0.00
5' DYS II	DXS1242	Xp21.1	(CA) _n	-12.77	-7.78	-4.34	-2.90	-1.54	-0.81	0.50	0.00
MAOA	MAOA	Xp11.4	(CA) _n	-3.77	-3.55	-2.59	-1.81	-0.98	-0.51	0.50	0.00
XL91B10	DXS426	Xp11.3	(CA) _n	-4.17	-2.16	-1.17	-0.49	-0.23	-0.01	0.34	0.07
M27β	DXS255	Xp11.23	VNTR	-1.07	-0.09	0.49	0.65	0.63	0.44	0.14	0.68
AFM151xf6	DXS991	Xp11.21	(CA) _n	-0.47	0.50	1.05	1.16	1.04	0.73	0.11	1.16
HumARA	AR	Xq12	(ACG) _n	1.48	1.45	1.35	1.20	0.90	0.56	0.00	1.48
A0352	DXS1111	Xq12	(CA) _n	1.48	1.45	1.35	1.20	0.90	0.56	0.00	1.48
E10	DXS1162	Xq12	(CA) _n	-0.47	0.50	1.05	1.16	1.04	0.73	0.11	1.16
Mfd66	DXS453	Xq12	(CA) _n	1.03	1.01	0.96	0.89	0.72	0.52	0.00	1.03
A20	DXS1166	Xq13.2	(CA) _n	2.53	2.49	2.33	2.12	1.64	1.10	0.00	2.53
HX60	DXS566	Xq13.3	(CA) _n	1.48	1.45	1.35	1.20	0.90	0.56	0.00	1.48
AFM116XgI	DXS986	Xq21.1	(CA) _n	1.03	1.01	0.96	0.89	0.72	0.52	0.00	1.03
AFM207zg5	DXS995	Xq21.1	(CA) _n	2.53	2.49	2.33	2.12	1.64	1.10	0.00	2.53
pQST38	DXS326	Xq21.2	RFLP	-1.50	-0.54	0.07	0.25	0.30	0.20	0.17	0.31
AFM249vh5	DXS1002	Xq21.31	(CA) _n	-3.46	-1.50	-0.22	0.21	0.47	0.44	0.23	0.48
AFM056yb8	DXS1196	Xq21.31	(CA) _n	-1.96	-0.98	-0.32	-0.07	0.12	0.15	0.29	0.16
Mfd72	DXS454	Xq21.33	(CA) _n	-5.19	-3.66	-2.68	-1.96	-1.52	-0.91	0.50	0.00
XG30B	DXS456	Xq22.1	(CA) _n	-7.50	-4.97	-2.33	-1.26	0.36	-0.01	0.40	0.09
XL5A	DXS424	Xq23	(CA) _n	-3.92	-2.74	-1.63	-1.10	-0.57	-0.29	0.67	0.07
XL90A3	DXS425	Xq25	(CA) _n	-4.97	-3.24	-1.35	-0.61	-0.04	0.13	0.34	0.03
HPRT	HPRT	Xq26.1	(AGAT) _n	-1.52	-0.54	0.07	0.25	0.30	0.20	0.17	0.31
46	DXS548	Xq27.3	(CA) _n	-3.20	-2.46	-1.21	-0.70	-0.28	-0.10	0.50	0.00
DXS1113	DXS1113	Xq28	(CA) _n	-1.54	-0.56	0.04	0.22	0.27	0.18	0.17	0.28
ST14	DXS52	Xq28	VNTR	1.48	1.45	1.34	1.20	0.90	0.56	0.00	1.48
sDF-2	DXS1108	Xq28	(GT) ₂ GC(GT) ₁₃	-4.67	-2.68	-1.33	-0.78	-0.31	-0.10	0.46	0.01

Table 3 Comparison of X linked entities with mental retardation and obesity

Reference	Hypotonia	Hypogonadism	Short stature	Other	Linkage
16	+	+	+	Microcephaly, coarse facies, large ears, gynaecomastia	Xq26
17	+	+	+	Microcephaly, normal hands/feet, gynaecomastia, genu valgum, cubitus valgus	-
18	+	+	+	Normocephalic, narrow palpebral fissures, skin abnormality, seizures, ocular abnormalities	-
15	+	+	+	Normocephalic, bitemporal narrowing, almond shaped eyes, tented upper lip, short hands/feet, excessive fingerprint arches, genu valgum	-
19	+	+	+	Genu valgum, small distal phalanges, small feet, stiff digits, cubitus valgus	-
20	+	+	-	Normocephalic, heavy eyebrows, small hands/feet, gynaecomastia, tapered fingers, emotional lability	Xq11.3-Xq21.3
Present cases	+	-	-	Excessive growth, normocephalic, square face, absent reflexes, excessive arches, tapered fingers, genu valgum, large hands/feet	Xq13.2-Xq21.1
21	-	-	+	Macrocephaly, square forehead, hypertelorism, broad nasal tip, prominent lower lip, macro-orchidism, incisor gap	-
22	-	-	-	Macrocephaly, square forehead, prominent supraorbital ridges, broad nasal tip, prominent lower lip, incisor gap, large ears, macro-orchidism	-
23	-	-	-	Macrocephaly, square forehead, prominent supraorbital ridges, prominent lower lip, large ears, incisor gap	-

number of digital arches, and mild-moderate mental retardation. No major malformations are present. Manifestations are present from birth and do not progressively worsen. Prenatal and postnatal growth appears comparable in affected and unaffected males except that affected males are heavier (table 1). Motor and language milestones are moderately delayed. Sexual maturation occurs at the appropriate time. Obligate carrier females lack any somatic features and have normal intelligence.

The face appears large in relation to the cranium and has a squarish configuration. Subcutaneous tissues of the upper eyelids, helices of the ears, alae nasi, and columella are thickened. The upper lip is arched, especially during childhood, and permanent teeth appear small in two affected males.

Overall decreased muscle tone is reflected in persistent drooling, cupped ears, arched upper lip, genu valgum, absent reflexes, and perhaps in the tapered fingers and thickened soft tissues of the eyelids, ears, and nose. Presumably decreased muscle tone contributed, in part, to the delay in motor milestones. The cause for decreased muscle tone and absent deep tendon reflexes was not identified. Creatine kinase was normal. Electromyograms, peripheral nerve conduction velocities, and muscle biopsies were not possible.

An excessive number of fingerprint arches and low loops were found in the three living males. The average ridge count was 28 in two affected males and 154 in five unaffected brothers. There was associated tapering of the digits and small distal phalanges. None of the five unaffected brothers or two obligate carrier females has excessive arches or low total ridge counts.

This syndrome has certain similarities (hypotonia, open mouth with arched upper lip, tapered digits) with X linked α thalassaemia-mental retardation (ATR-X) syndrome but

differs in many other manifestations (severity of mental retardation, absent speech, seizures, lack of bowel or bladder control, constipation, telecanthus or hypertelorism, small, triangular nose, spacing of teeth, small and simple ears, genital anomalies, short stature, brachydactyly) of that entity.¹² Dermatoglyphics have not been reported in ATR-X syndrome. Both syndromes map to Xq13. Our patient III.6 lacked haemoglobin H inclusions that have been found in ATR-X syndrome.

Excessive fingerprint arches have been found in several chromosomal and single gene disorders. Coffin-Lowry, Miles-Carpenter, and Chudley syndromes are distinctive XLMR syndromes in which excessive arches have been reported.¹³⁻¹⁵ Coffin-Lowry syndrome has distinctive facial and skeletal features, heterozygote manifestations, and gene localisation to Xp22.¹³ Miles-Carpenter syndrome maps close to the entity reported here, but may be distinguished by microcephaly, facial asymmetry, rockerbottom feet, contractures, and spastic paraplegia.¹⁴ There are a number of similarities between the syndromes reported here and the condition reported by Chudley *et al.*¹⁵ That condition, characterised by moderate-severe mental retardation, has bitemporal narrowing, almond shaped eyes, small nose, open mouth with arched upper lip, short stature, low fingerprint ridge count, obesity, hypogonadism, genu valgum, and brachydactyly. It has not been mapped nor investigated as an example of ATR-X syndrome.

A number of X linked entities with mental retardation and obesity have been described.¹⁵⁻²³ Often these entities are associated with hypotonia, hypogonadism, and short stature and may be distinguished from the syndrome reported here by the latter two manifestations (table 3).

Delineation of this entity adds to the list of X linked syndromes with mental retardation.²⁴⁻²⁵ In the process of studying these syndromes, the expectations that mutations in the same gene might cause different phenotypes (for example, PLP mutations resulting in Pelizaeus-Merzbacher syndrome and spastic paraplegia) and that similar phenotypes might be caused by mutations in different genes (for example, spastic paraplegia caused by mutations in PLP and L1CAM genes) have been realised.²⁶⁻²⁷ Further correlations of the phenotype and genotype will become possible with the cloning of additional responsible genes, a research activity now being pursued in a number of laboratories.

1 Online mendelian inheritance in man, OMIM (TM). Center for Medical Genetics, Johns Hopkins University (Balti-

- more, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 1996. World Wide Web URL: <http://www3.ncbi.nlm.nih.gov/omim/>.
- 2 Lubs HA, Chiurazzi P, Arena JF, Schwartz C, Tranebjærge L, Neri G. XLMR genes: update 1996. *Am J Med Genet* 1996;64:147-57.
- 3 Mulley JC, Kerr B, Stevenson R, Lubs H. Nomenclature guidelines for X-linked mental retardation. *Am J Med Genet* 1992;43:383-91.
- 4 Kerr B, Turner G, Mulley J, Gedeon A, Partington M. Non-specific X linked mental retardation. *J Med Genet* 1991;28:378-82.
- 5 Häne B, Schroer RJ, Arena JF, Lubs HA, Schwartz CE, Stevenson RE. Nonsyndromic X-linked mental retardation: review and mapping of MRX29 to Xp21. *Clin Genet* (in press).
- 6 Schwartz CE, Ulmer J, Brown A, Pancoast I, Goodman HO, Stevenson RE. Allan-Herndon syndrome. II. Linkage to DNA markers in Xq21. *Am J Hum Genet* 1990;47:454-9.
- 7 Willard HF, Cremers F, Mandel JL, Monaco AP, Nelson DL, Schlessinger D. Report of the fifth international workshop on human X chromosome mapping 1994. *Cytogenet Cell Genet* 1994;67:295-358.
- 8 Mansfield DC, Brown AF, Green DK, *et al.* Automation of genetic linkage analysis using fluorescent microsatellite markers. *Genomics* 1994;24:225-33.
- 9 Schwartz CE, McNally E, Leinward L, Skolnick MH. Linkage of a myosin heavy chain locus to an anonymous single copy locus (D17S1) at 17p13. *Cytogenet Cell Genet* 1986;43:117-20.
- 10 Feinberg AP, Vogelstein B. A technique for radiolabeling DNA restriction endonuclease fragments to high specific activity. *Anal Biochem* 1983;132:6-13.
- 11 Lathrop GM, Lalouel JM. Easy calculations of lod scores and genetic risks on small computers. *Am J Hum Genet* 1984;36:460-5.
- 12 Gibbons RJ, Brueton L, Buckle VJ, *et al.* Clinical and hematological aspects of the X-linked α -thalassaemia/mental retardation syndrome (ATR-X). *Am J Med Genet* 1995;55:288-99.
- 13 Gilgenkrantz S, Mujica P, Gruet P, *et al.* Coffin-Lowry syndrome: a multicenter study. *Clin Genet* 1988;34:230-45.
- 14 Miles JH, Carpenter NJ. Unique X-linked mental retardation syndrome with fingertip arches and contractures linked to Xq21.31. *Am J Med Genet* 1991;38:215-23.
- 15 Chudley AE, Lowry RB, Hoar D. Mental retardation, distinct facial changes, short stature, obesity, and hypogonadism: a new X-linked mental retardation syndrome. *Am J Med Genet* 1988;31:741-51.
- 16 Börjeson M, Forssman H, Lehmann O. An X-linked, recessively inherited syndrome characterized by grave mental deficiency, epilepsy and endocrine disorder. *Acta Med Scand* 1962;171:13-21.
- 17 Vasquez SB, Hurst DL, Sotos JF. X-linked hypogonadism, gynecomastia, mental retardation, short stature, and obesity - a new syndrome. *Pediatrics* 1979;94:56-60.
- 18 Young ID, Hughes HE. Sex-linked mental retardation, short stature, obesity and hypogonadism: report of a family. *J Ment Defic Res* 1982;26:153-62.
- 19 Stevenson RE, Richter B. Short stature, mental retardation, and hypogonadism in brothers. *Proc Greenwood Genet Center* 1990;9:7-11.
- 20 Wilson M, Mulley J, Gedeon A, Robinson H, Turner G. New X-linked syndrome of mental retardation, gynecomastia, and obesity is linked to DXS255. *Am J Med Genet* 1991;40:406-13.
- 21 Atkin JF, Flaitz K, Patil S, Smith W. A new X-linked mental retardation syndrome. *Am J Med Genet* 1995;21:697-705.
- 22 Clark RD, Baraitser M. A new X-linked mental retardation syndrome. *Am J Med Genet* 1987;26:13-15.
- 23 Baraitser M, Reardon W, Vijeratnam S. Nonspecific X-linked mental retardation with macrocephaly and obesity: a further family. *Am J Med Genet* 1995;57:380-4.
- 24 Schwartz CE. Invited editorial: X-linked mental retardation in pursuit of a gene map. *Am J Hum Genet* 1993;52:1025-31.
- 25 Saugier-Verber P, Munnich A, Bonneau D, *et al.* X-linked spastic paraplegia and Pelizaeus-Merzbacher disease are allelic disorders at the proteolipid protein locus. *Nat Genet* 1994;6:257-62.
- 26 Jouet M, Rosenthal A, Armstrong G, *et al.* X-linked spastic paraplegia (SPG1), MASA syndrome and X-linked hydrocephalus result from mutations in the L1 gene. *Nat Genet* 1994;7:402-7.