Non-specific X linked mental retardation with aphasia exhibiting genetic linkage to chromosomal region Xp11

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Abstract

A new type of non-specific X linked mental retardation is described in a three generation family. The three affected males had severe mental retardation (IQ 20 to 30), mutism, growth failure, frequent infections, seizures, and the following minor anomalies: brachycephaly, frontal hair whorl, square face, large mouth, thick lips, and prognathism. There was not a characteristic facies. Normal laboratory studies on the proband included a karyotype with fragile X screening, skeletal survey, blood amino acid, urine organic acid, and HGPRT levels. Linkage analysis was performed with 10 X chromosome DNA probes of which probe DXS255 at chromosomal region Xp11.22 gave a maximal two point lod score of 2.10 if phase was inferred and 1.20 if it was not. Crossovers were shown with probes mapping to regions Xp22, Xp21, and Xq28. Comparison of these patients with 80 X linked causes of mental retardation, including 41 which might be classified as 'non-specific', showed no other disorders compatible with the phenotypic and linkage data.

(J Med Genet 1992;29:629-34)

mental function of hemizygous persons. Genes on the X chromosome may account for about a third of mental retardation in males¹ and numerous surveys document a 20 to 50% excess of males over females when selected for severe retardation.² While disorders such as the Lowe and Lesch-Nyhan syndromes are associated with definitive morphological or metabolic findings which aid delineation, many subjects with X linked mental retardation do not have striking phenotypes. These disorders have been grouped under the term 'non-specific' X linked mental retardation (XLMR) and have a cumulative incidence greater than 1 to 2 per 1000 male births.² Over 30 types of XLMR have now been defined and many have been mapped to specific regions of the X chromosome (fig 1).¹² Here we describe a new variety of XLMR which exhibits striking aphasia and linkage to the Xp11 region.

Case reports

Case 1 (IV.1, fig 2) was referred for evaluation at 15 months of age because of developmental delay. The height was 81 cm (75th centile), weight 11 kg (50th centile), and head circumference 46 cm (25th centile). At birth the patient weighed 3100 g with Apgar scores of 7 and 9 after a 37 week gestation to a 26 year old primigravida. There was hypertension and 'flu' in the last trimester, when antepartum amniocentesis to determine the L/S ratio showed meconium. After caesarian section, the

It is ironic that the human X chromosome, noted for its conservation in mammalian evolution, should wreak such havoc upon the

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Received 16 January 1992.
Revised version accepted 24 February 1992.

Figure 1 Idiogram of the human X chromosome showing the locations of mapped XLMR loci.³ The locations of informative DNA probes along with RFLP fragment sizes, allele designations, and frequencies in the general population are also shown.

Figure 2 Family pedigree summarising the RFLP alleles detected by Southern analysis. Boxes represent X chromosomes and a parenthesis around the allele indicates it was deduced by inheritance rather than experimentally determined. Subjects with a bar above the symbol were examined.

child was hypotonic and suffered from meconium aspiration. The mother immediately recognised a frontal hair whorl identical to that of her affected brother. Early developmental milestones were delayed and a single tonic-clonic seizure occurred at 10 months accompanied by a transient left hemiparesis. An MRI scan performed at that time showed an increased periventricular signal, delayed myelination, and slightly prominent lateral ventricles. Physical examination at 16 months (fig 3H) showed lip smacking, tongue thrusting, and self-stimulating behaviour with the minor anomalies listed in table 1. Laboratory findings included normal karyotype with fragile X analysis; normal haematological, thyroid, and liver functions; normal serum amino acids, urine organic acids, and urine mucopolysaccharides; normal skeletal survey; and normal levels of the enzyme HGPRT (1119 U/mg with controls of 635 and 938). Follow up examination at 3 years showed a developmental level of about 16 months with a vocabulary of five to 10 words.

Case 2 (III.5, fig 2) is 16 years old and lives in a developmental centre. Birth weight was 3150 g after an uncomplicated term pregnancy and a breech delivery with Apgar scores of 8 and 8. A 'peculiar' face was mentioned at birth and infancy was complicated by pylorospasm and frequent upper respiratory infections. He was hypotonic during infancy with frequent self-stimulating behaviour and intractable crying spells. Walking started at the age of 10½ years. Medical problems in childhood included chronic otitis, sinusitis, bilateral inguinal hernias, and a bowel biopsy for

Hirschsprung disease which was reportedly negative despite continued administration of laxatives. Developmental delay was recognised at 1 year and an eventual IQ of less than 30 was measured. The patient can imitate sounds, understand his name and simple commands, knows limited sign language, has mild myopia, and normal hearing, and no speech. Care givers describe a limited attention span, cold and reddened extremities, rhythmic breathing, frequent tongue protrusion with licking and tasting of objects, an expressionless face, and a good natured demeanour. Physical examination showed an extremely withdrawn and 'autistic' adolescent with the abnormalities listed in table 1. His height was 145 cm (below the 3rd centile, 50th centile for 11½ years), weight 27 kg (below the 3rd centile, 50th centile for 9 years), and head circumference 50 cm (below the 3rd centile, 50th centile for 3 years). Photographs at ages 8 months, 3½ years, and 9 years are shown in fig 3E–G, respectively. Normal laboratory findings included karyotype, serum amino acids, CBC and electrolytes, and SMAC 20 serum screen including hepatic enzymes.

Case 3 (III.3, fig 2) is 27 years old and resides in a state school for the retarded. Birth weight was 3650 g after a long labour; hypotonia, somnolence, and feeding problems were noted in infancy. Frequent infections including otitis and pneumonia occurred in early childhood. Developmental delay was recognised by the age of 6 months, with an IQ of 40 being measured in adulthood. He has inappropriate behaviour with self-injury and resistance requiring occasional constraints. This behaviour has improved somewhat on Tegretol[®], Serenitil[®], and Artane[®] therapy for a diagnosis of organic brain disorder, mixed type (DSM-IIIR). The patient can dress himself and maintain personal hygiene, function in a sheltered workshop, count up to 10 objects, but cannot handle small sums of money or keep a locker key. He is completely mute, has mild myopia, excellent comprehension of instructions, a 50 word vocabulary in sign language, and normal hearing. Much of his spare time is spent listening to the radio. Physical examination disclosed an extremely curious, interactive, and friendly young man with the minor anomalies listed in table 1. His height was 163 cm (5th centile), weight 57 kg (20th centile), and head circumference 54.5 cm (25th centile). His appearance is shown at ages 6 months, 14 years, and 27 years in fig 3A–D. Laboratory studies included normal karyotype with fragile X screening, normal serum amino acids, and normal haematological and liver functions.

The carrier females II.1, II.3, and III.2 (fig 2) were all examined and found to have normal intellectual function without evidence of dysmorphism.

Methods

DNA BANKING

Heparinised blood samples from family members were collected in Leucoprep[™] tubes,

Figure 3 Affected males III.3 (A, 16 months, B, 14 years, C, D, 27 years), III.5 (E, 8 months, F, 3 years, G, 9 years), and IV.1 (H, 10 months) as designated in fig 2.

centrifuged for 15 minutes at 1500 to 1800 *g* at room temperature, and the washed white cells (two 5 ml aliquots) incubated with equal volumes of supernatant medium (RPMI 1640 and 10% fetal calf serum, GIBCO) from an EB virus infected marmoset cell line. Phytohaemagglutinin (0.1 ml of GIBCO suspension) was added to both cultures followed by incubation for three to five days at 37°C in 5% CO₂. After successful transformation was indicated by visible cell aggregates, the lymphoblast cultures were expanded by decanting and replacing with fresh medium. The lymphoblast pellet from 100 ml of culture was washed with 0.9% NaCl; hand homogenised in 5 ml of 50 mmol/l Tris-HCl, pH 7.5, 25 mmol/l KCl, 5 mmol/l MgCl₂, 0.25 mol/l sucrose, 0.01% Triton X-100; incubated for 15 minutes at 4°C to accomplish cell lysis; and extracted by the procedure of Marmur.⁴ From 500 µg to 1 mg

of DNA was obtained after chloroform extraction, RNase and Pronase treatment, and ethanol spooling. DNA was stored frozen before use.

DNA ANALYSIS AND LINKAGE STUDIES

The DNA probe *DXYS14* was obtained from Lifecodes Corporation (New York),^{4,5} *DXS43*, *DXS41*, and *DXS270* from L Kunkel,⁶⁻⁸ *DXS28* from J Mandel, *DXS268* and *DXS84* from G van Ommen,⁹ *DXS255* from I Craig and Y Boyd,¹⁰ *PGK* from B Vogelstein,¹¹ and *F8C* from the Human Mutant Cell Repository, catalogue no 57204. Cloned DNA segments were separated from vector segments on 0.8% agarose minigels and purified using GeneClean (Bio 101 Inc, La Jolla CA). For RFLP analysis, 5 to 10 µg of DNA was restricted using the manufacturer's protocol and excess enzyme. DNA transfer to Hybond N+ membranes (Amersham) was accomplished by capillary action after electrophoresis on 0.8% agarose gels and alkali denaturation/neutralisation. Prehybridisation, hybridisation, and washing procedures were undertaken using the conditions of Church and Gilbert¹² with 50 ng of DNA segment labelled to a specific activity of 10⁹ cpm/µg with ³²P-dCTP by random hexanucleotide primer extension.¹³ Washed membranes were exposed to Kodak x ray film for one to two days at -70°C using an intensifying screen. Of the 10 X linked probes used (fig 1), seven gave informative results as displayed in table 2. Two point lod scores (Z) were calculated using the program MLINK as described by Ott.^{14,15}

Table 1 Clinical manifestations of affected males.

	IV.1	III.3	III.5	Total
Age (y)	3	27	16	
Severe MR (IQ)	(<50)	(<30)	(<30)	3/3
Growth failure	+	+	+	2/3
Microcephaly	+	+	+	1/3
Brachycephaly	+	+	+	3/3
Frontal whorl/upsweep	+	+	+	3/3
Square jaw	+	+	+	3/3
Hypertelorism	+	+	+	3/3
Thick lips	+	+	+	2/3
Large mouth	+	+	+	3/3
Tongue thrusting	+	+	+	3/3
Prognathism	+	+	+	3/3
Inguinal hernia/hydrocele	+	-	+	2/3
Seizures	+	-	+	2/3
Frequent infections	+	+	+	3/3
Decreased myelination	+	?	?	1/1

Table 2 Pair wise lod scores; putative XLMR gene versus X chromosome marker loci.

Locus	Location	Z at θ of						$\hat{\theta}$	$\hat{Z}$
		0.001	0.01	0.1	0.2	0.3	0.4		
<i>DXS14</i>	Xp22.2	-3.9	-1.9	-0.12	0.22	0.29	0.20	0.3	0.29
<i>DXS43</i>	Xp21	0.30	0.30	0.26	0.20	0.15	0.08	0.001	0.30
<i>DXS41</i>	Xp21	-4.1	-2.2	-0.38	0.020	0.14	0.12	0.3	0.14
<i>DXS28</i>	Xp21	-9.9	-5.9	-2.0	-0.98	-0.45	-0.15	0.4	-0.15
<i>DXS255</i>	Xp11.22	2.1	2.1	1.8	1.4	1.1	0.56	0.001	2.1
<i>PGK</i>	Xq13	-7.8	-4.8	-1.8	-0.99	-0.52	-0.21	0.4	-0.21
<i>F8C</i>	Xq28	-4.1	-2.2	-0.38	0.02	0.15	0.08	0.3	0.14

Results

The family pedigree (fig 2) and clinical summary (table 1) of the affected males are consistent with an X linked form of mental retardation which could be mapped to a specific X chromosome region by RFLP linkage analysis. Representative Southern analyses of DNA from 11 family members are shown in fig 4. Fig 4A shows three recombinations between the putative XLMR gene and the smaller *EcoRV* allele (c) shown by the probe *DXS28* (fig 1). Fig 4B shows cosegregation of the putative XLMR gene with allele M3 of the multiallelic probe *DXS255* (fig 1). In fig 2, the deduced alleles from these and other restriction analyses are displayed alongside X chromosomes of family members. The marker haplotypes were deduced assuming a minimum number of crossovers and implied that recombinations were shown by the DNA probes *DXS14* (alleles X1 to X4), *DXS28* (alleles C, c), and *F8C* (alleles H, h). Table 2 shows two

point lod scores (Z) as a function of recombination fraction (θ) with phase inferred from the pedigree and marker configuration. The maximal two point lod score ($\hat{Z}$) was 2.10 at a recombination fraction of 0.01 for the DNA probe *DXS255* located at Xp11.22. If phase was not inferred, then $\hat{Z}$ for *DXS255* was 1.20 at a $\hat{\theta}$ of 0.

Discussion

In 1943, Martin and Bell¹⁶ first described a family with XLMR. Two additional families with XLMR were soon reported,^{17,18} raising the question of whether one or many genes were involved. For a time, all types of XLMR were named 'Martin-Bell syndrome' or 'Rennpenning syndrome' after the authors of these first descriptions. This confusion began to lessen when a more specific phenotype of prominent jaw, large ears, lax connective tissue, and megalotestes was delineated for the Martin-Bell syndrome. Soon it was recognised that most patients with this phenotype had a fragile X marker which could be shown by culture of lymphocytes or fibroblasts in folate deficient medium. Improved analysis and widespread screening has now shown that the fragile X syndrome affects about 1 in 1000 males and accounts for most patients with Martin-Bell phenotype as well as 30 to 40% of families with XLMR.²

Review of the catalogue of genetic disorders updated periodically by McKusick¹⁹ shows 60 X linked conditions which cause mental retardation, many with distinctive associated features. An estimated 21 of these disorders (depending on the perspective of the reviewer) have been placed in the category of 'non-specific X linked mental retardation (XLMR)', that is, mental retardation without a striking metabolic or morphological phenotype. Recent surveys^{1,20} list an additional 20 conditions with XLMR defined in single families which have not been assigned a McKusick number. In many of these conditions classified as XLMR, careful assessment can establish a syndrome which allows separation from 'true' XLMR with normal appearance. Differentiating clinical features include a characteristic facies (Prieto XLMR,²¹ Atkin-Flaitz XLMR,²² Chudley-Lowry-Hoar XLMR,²³ Pettigrew XLMR,²⁴ Vasquez XLMR²⁵), palmoplantar hyperkeratosis (Fitzsimmons XLMR²⁶), macrotestes without fragile X (Clark-Baraitser XLMR,²⁷ Tranebjaerg II XLMR,²⁸ Tariverdian XLMR²⁹), Marfanoid habitus (Lujan-Fryns XLMR³⁰), and skeletal dysplasia (Christian XLMR³¹). Several forms of XLMR are associated with spastic paraplegia and ataxia,

Figure 4 Representative Southern blots showing (A) 8 and 7.5 kb RFLP alleles (C, c) detected with the enzyme *EcoRV* and DNA probe *DXS28*, (B) alleles M1-M4 detected with the enzyme *EcoRI* and DNA probe *DXS255*. Lane numbers correspond to the subjects in fig 2 as shown by the condensed pedigree.

including Allan-Herndon XLMR,¹⁸ Gareis-Mason XLMR,³² Paine-Seemanova XLMR,³³ Smith-Fineman-Myers XLMR,³⁴ Davis XLMR,³⁵ and Schimke XLMR.³⁶

In the present family, a characteristic facial appearance, metabolic abnormality, or chromosomal aberration could not be found. However, physical examination disclosed the minor anomalies listed in table 1 which suggest that this condition is different from previously reported types of XLMR. Prominent among the minor anomalies was a frontal hair whorl or upsweep; the presence of this manifestation allowed natal recognition of the condition by the proband's mother. This anomaly is found in two other types of X linked mental retardation, but in neither is the full spectrum of malformation compatible with that in the proband and his male relatives. The Opitz-Kaveggia FG syndrome³⁷ includes a frontal cowlick with a prominent anterior fontanelle, hypertelorism, long philtrum, abnormal ears, hypotonia, agenesis of the corpus callosum, and gastrointestinal defects. The Pallister W syndrome³⁸ includes a frontal cowlick with pugilistic facies, hypertelorism, midline notch of the upper lip, skeletal anomalies, and seizures. Comparison with the 39 other XLMR conditions showed no comparable malformation pattern either.

Linkage analysis of this family does not suggest a match with previously reported forms of XLMR. Coordinate segregation with the DNA marker DXS255 at chromosomal region Xp11.22 provided a maximal two point lod score ($\hat{Z}$) of 2.1 based on seven informative meioses in this family (table 2). Although the distal X short (p21-pter) and long arms (q28) are ruled out by crossovers, a gene location anywhere within the Xp11-Xq11 pericentromeric region would be compatible with the linkage data. Additional families with this disorder must be ascertained to refine the gene location and to provide a lod score above the value of 3 considered to establish linkage. Comparison with the X chromosome regions implicated in 13 other forms of XLMR³ (fig 1) indicates overlap with the Prieto,²¹ Carpenter,³⁹ Sutherland,⁴⁰ and Sammans⁴¹ forms of XLMR with phenotypes that are quite different from the present family. The Xp11-q11 region is also a candidate for gene localisation in two XLMR families^{42,43} where affected males lack even subtle anomalies. If these and the present family involve the same locus, then allelic heterogeneity or variable expressivity must be invoked to explain the different phenotypes.

The three affected males in the family were striking for their absent or delayed speech. The oldest affected subject (III.5) was particularly remarkable for aphasia despite an interactive personality and considerable facility with sign language. Speech is mentioned as delayed or abnormal in seven of the 41 XLMR disorders so far described. In one of them (Gareis-Mason XLMR³²), speech was absent while in others it was dysarthric^{18,35,44-46} or described as verbal disability.^{41,47} The severe mutism in the present family despite normal hearing

suggests a gene particularly involved with speech, that is, through control of brain asymmetry/lateralisation, rather than one which merely impacts speech along with other higher cortical functions. Such associations of X chromosome loci and particular cognitive or behavioural traits emphasise the insights these characterised genes should bring to neural development and mental function.^{48,49}

Support of a grant from the Biological Humanities Foundation, Dallas, TX to GNW is gratefully acknowledged.

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