European Journal of Human Genetics (1999) 7, 828–832

http://www.stockton-press.co.uk/ejhg

SHORT REPORT

Linkage mapping of a new syndromic form of X-linked mental retardation, MRXS7, associated with obesity

Wasim Ahmad[1], Maurizio De Fusco[1], Muhammad Faiyaz ul Haque[2], Paolo Aridon[1], Tiziana Sarno[1], Muhammad Sohail[3], Sayed ul Haque[4], Mahmud Ahmad[4], Andrea Ballabio[1,5], Brunella Franco[1] and Giorgio Casari[1]

[1]*Telethon Institute of Genetics and Medicine, Milan, Italy*
[2]*Department of Neurology, Cell and Molecular Biology, Northwestern University Medical School, Chicago, IL, USA*
[3]*Department of Biochemistry, University of Oxford, UK*
[4]*Department of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan*
[5]*Universita' Vita Salute, Milan, Italy*

A new syndromic form of X-linked mental retardation associated to obesity, MRXS7, has been localised to Xp11.3–Xq23 in a large Pakistani family. The ten affected males show clinical manifestations of mental retardation, obesity and hypogonadism. The family was genotyped by a set of microsatellite markers spaced at approximately 10 cM intervals on the X chromosome. Linkage to five adjacent microsatellite markers, mapping in the pericentromeric area, was established and a maximum two-point lod score of 3.86 was reached at zero recombination with marker DXS1106. Reduced recombination events around the centromere prevented precise mapping of the gene.

Keywords: X-linked mental retardation; obesity; linkage mapping

X-linked mental retardation (XLMR) is the most common cause of mental retardation in males. XLMR can be divided into syndromic and non-specific forms.[1] Both non-specific and non-syndromic forms of X-linked mental retardation (MRX) are genetically heterogeneous. Affected males in families segregating MRX have no consistent clinical or somatic manifestations, apart from their mental retardation, to distinguish them from unaffected family members. Several XLMR loci have already been mapped by linkage analysis. Lubs and colleagues[2] listed 147 XLMR conditions. Among these, 105 consisted of syndromic forms of MRXS and 42 were described as non-specific forms of mental retardation. However, only 18 genes responsible for MRXS and five genes for MRX (FRAXE,[3] GDI1,[4] PAK3,[5] oligophrenin-1,[6] and RSK2[7] have been cloned so far.

In the present study we describe a family with mild to moderate forms of mental retardation, which is associated with clinical manifestations such as obesity, hypogonadism, micropenis, tapering fingers, hairless body, eyesight and dental anomalies, speech disabilities, and diminished body strength. Linkage analysis localises the gene responsible for this form of mental retardation to Xp11.3–Xq23.

Correspondence: Dr Giorgio Casari, Telethon Institute of Genetics and Medicine, San Raffaele Biomedical Science Park, Via Olgettina 58, 20132 Milan, Italy. Tel: 39 02 21560201; Fax: 39 02 21560220; E-mail: casari@tigem.it
Received 21 October 1998; revised 21 May 1999; accepted 9 June 1999

Materials and Methods

Clinical Description

The pedigree is represented in Figure 1. Female members of the family, including obligate carriers, show no signs of mental deficiency. Patient III-2 is 50 years old, moderately mentally retarded, unable to read and write, and his speech is difficult to understand. His height is 145 cm and weight 120 kg, with normal facial appearance. Hair is present on the face but absent on the rest of the body, including the pubic area. He has a micropenis and small testes. Feet are normal but with *pes planus*, fingers are slightly tapered, and body strength is highly diminished. Patient IV-4 is a 20-year-old mildly affected male. He has never attended any type of school and is unable to read or write, although he can communicate with other people when required. His height is 150 cm and weight 83 kg. He has normal body and facial hair, although scanty in the pubic area; penis and testes are small, and feet and fingers are normal.

Patient IV-6, 18 years old, weight 87 and height 160 cm, is moderately affected and unable to read, write, or perform simple calculations; phallus is very small and testes are not descended; hair is present only on the face; feet are small, fingers tapered, and body strength is remarkably below average. The clinical history of patients IV-9 and IV-10 are not available. They were obese and died at the ages of 8 and 10, respectively, due to accidents. Patient IV-11, 25 years old, is moderately affected; his height is 165 cm and weight 85 kg. Facial hair is normal but absent on the rest of the body, including the pubic area. Like other affected members of the family, he presents severe micropenis; his speech is extremely difficult to understand; fingers are slightly tapered and body strength is diminished.

Patient IV-12, 24 years old, is mildly affected. He can follow commands and perform simple calculations. His height is 177 cm and weight 97 kg. Teeth are malpositioned and malformed; testes and phallus are small; foot size is normal but with *pes planus*; fingers are tapered; the speech is clear except for occasional slurring. Patient IV-17, 16 years old, is moderately mentally retarded with extreme speech disability; height 152 cm and weight 82 kg; tapered fingers, *pes planus*, and decreased muscular strength are present. Both maxillary and mandibular incisors are malformed and malpositioned. Patient IV-19, 13 years old, is severely mentally retarded and almost completely blind in both eyes; height is 137 cm and weight 75 kg. Besides common traits such as micropenis, non-descended testes, and absence of body hair, he presents the most severe dental anomalies of all patients, with mandibular incisors malpositioned and malformed and eight axillary incisors arranged in two rows.

The endocrinological evaluation (FSH, LH, testosterone concentration) of affected members III-2, IV-4, and IV-6 shows normal values. The IQ test performed on all affected members ranges between 40 and 50.

Genotype and Linkage Analysis

A set of fluorescence labelled markers (DXS1060, DXS987, DXS1226, DXS1202, DXS1214, DXS1068, DXS993, DXS1055, DXS991, DXS986, DXS990, DXS1106, DXS1001, DXS1047, and DXS1227) was used for primary screening.

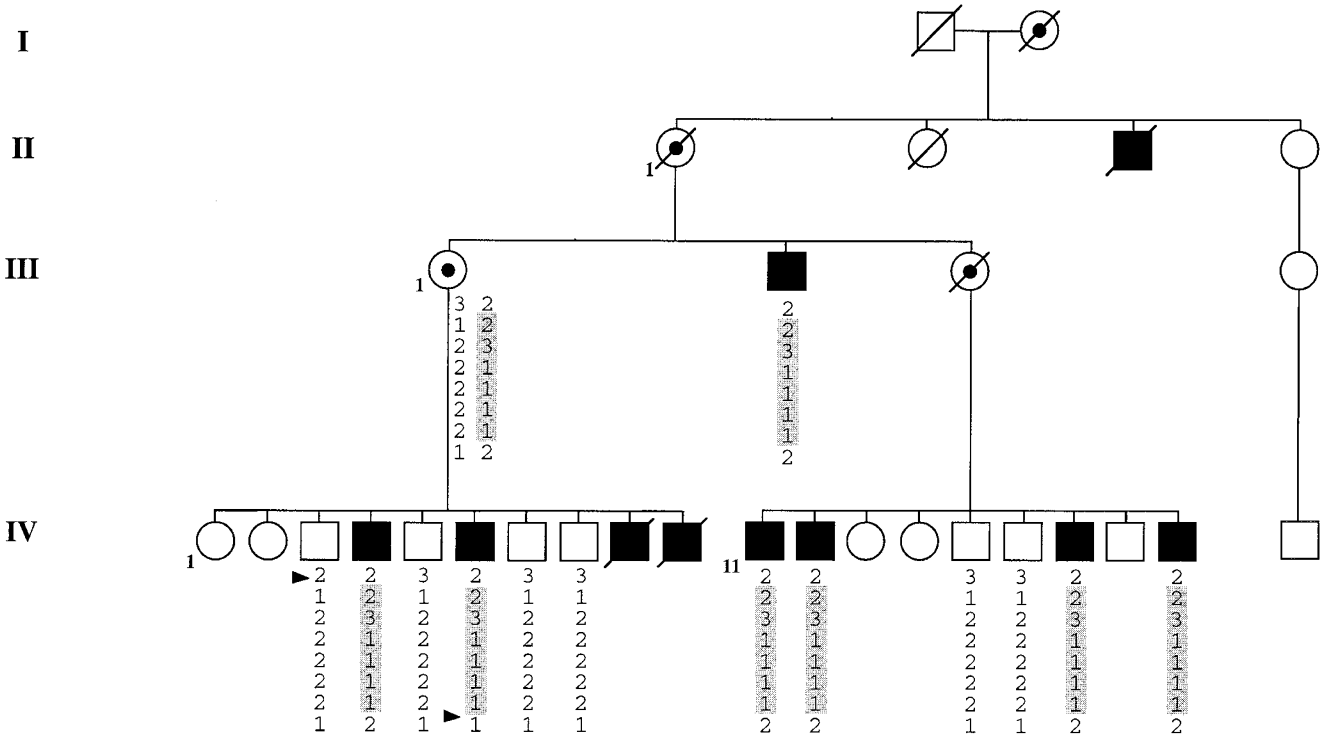

Figure 1 *MRXS7 pedigree. Haplotypes for selected markers in Xp11.3–q23 are shown. Markers DXS8083, DXS1055, DXS991, DXS986, DXS990, DXS1106, DXS8063, and DXS8112 are ordered pter (up) to qter (down). Arrows indicates the recombination events*

Further refinement of the localisation was carried out by locally increasing the marker map density. Two-point linkage analysis between each marker and the disease locus was performed using the computer program LINKAGE 5.1,[8] assuming X-linked recessive inheritance. The frequency of the disease allele was chosen arbitrarily as 0.00001. Genetic distances of the marker loci were used as described by Dib *et al*.[9]

Results

Fourteen family members were enrolled in a genetic linkage study, including seven affected and seven unaffected subjects. Twenty-two highly polymorphic markers (the fluorescence labelled set of markers, DXS8083, DXS8063, DXS8112, DXS1210, DXS1059, DXS8088, and DXS8055) spanning from Xpter to Xqter were genotyped. The two-point lod score table between the MRXS7 disease locus and markers is presented in Table 1. Evidence of linkage was observed with six markers (DXS1055, DXS991, DXS986, DXS990, DXS1106, and DXS8063) covering a 38 cM area with regional localisation at Xp11.3–Xq23. However, the chromosomal area spanning the two closest recombinant markers, DXS8083 and DXS8112, is 42 cM.

The maximum lod score value 3.86 was reached with DXS1106 at zero recombination. Multipoint linkage analysis was performed with markers DXS8083, DXS1055, DXS986, DXS1106, DXS8063 and DXS8112, resulting in a broad peak, which includes all the significant markers and reaches a maximum multipoint lod score of 4.20 (data not shown). Haplotype analysis presented in Figure 1 for markers DXS8083, DXS1055, DXS991, DXS986, DXS990, DXS1106, DXS8063, and DXS8112 showed recombination events defining the boundaries of the critical region. Unaffected male IV-3 recombines with marker DXS8083, 2.7 cM distant from DXS1055, defining the p arm boundary; affected member IV-6 shows with marker DXS8112 and therefore places the Xq boundary in the 2.9 cM between DXS8063 and DXS8112.

Discussion

Mental retardation associated with manifestation of obesity, hypogonadism, microphallus, tapering fingers, hairless body, speech disability, eyesight and dental anomalies, and decreased body strength in a family of 10 affected males supports the hypothesis of a new X-linked recessive mental retardation syndrome. None

Table 1 Two-point lod scores for MRXS7 family

θ	*0.00*	*0.01*	*0.05*	*0.10*	*0.20*	*0.30*	*0.40*
marker							
DXS1060	–inf	–1.63	–0.93	–0.63	–0.33	–0.16	–0.06
DXS987	–inf	–4.08	–2.05	–1.23	–0.50	–0.17	–0.03
DXS1226	–inf	–4.29	–1.63	–0.60	0.19	0.40	0.32
DXS1202	–inf	–5.99	–2.63	–1.30	–0.21	0.18	0.22
DXS1214	–inf	–2.37	–0.45	0.22	0.61	0.59	0.35
DXS1068	–inf	–2.60	–0.67	0.01	0.45	0.47	0.29
DXS993	–inf	–2.31	–0.39	0.27	0.65	0.61	0.36
DXS8083	–inf	1.62	2.10	2.12	1.82	1.32	0.70
DXS1055	3.67	3.61	3.37	3.06	2.39	1.66	0.85
DXS991	3.74	3.68	3.43	3.11	2.43	1.69	0.86
DXS986	3.67	3.62	3.38	3.08	2.42	1.69	0.87
DXS990	3.18	3.13	2.91	2.62	2.02	1.38	0.69
DXS1106	3.86	3.80	3.54	3.21	2.50	1.74	0.89
DXS8063	3.19	3.13	2.91	2.63	2.02	1.34	0.58
DXS8112	–inf	1.14	1.64	1.67	1.41	0.97	0.41
DXS1210	0.17	0.16	0.14	0.11	0.07	0.03	0.01
DXS1059	0.17	0.16	0.14	0.11	0.07	0.03	0.01
DXS8088	–inf	1.14	1.64	1.67	1.41	0.97	0.41
DXS8055	–inf	–2.31	–0.39	0.26	0.65	0.61	0.36
DXS1001	0.22	0.21	0.19	0.15	0.09	0.03	0.00
DXS1047	–inf	–7.70	–3.68	–2.10	–0.77	–0.22	–0.01
DXS1227	0.18	0.17	0.15	0.12	0.07	0.02	–0.01

of the observed manifestations are detected in any normal members of the family. Lubs and co-workers[2] provided a comprehensive list of all forms of X-linked mental retardation, altogether 147 entries, consisting of 105 syndromic and 42 non-specific forms. Some of the clinical anomalies observed in patients with various disorders overlap with the syndrome described in this study. The MEHMO syndrome (mental retardation, epilepsy, hypogonadism, microcephaly, and obesity[10]) locus maps on Xp21–22, external to the MRXS7 critical region. Wilson *et al*[11] describe 14 affected males through three successive generations in a large family with X-linked mental retardation, characterised by obesity, gynecomastia, speech difficulties, emotional lability, tapering fingers, small feet, and hypogonadism (Wilson-Turner syndrome).

However, the major clinical manifestation described in the affected subjects, gynecomastia, is a finding absent in our MRXS7 patients. The candidate region for the MRXS7 gene (Xp11.3–Xq23) overlaps with that of the Wilson-Turner syndrome, Xp21.1–Xq22.[11,12] Although clinical manifestation of gynecomastia is absent in our patients, the possibility that a single gene is involved in both MRXS7 and Wilson-Turner syndrome cannot be excluded. Two more XLMR syndromes associated with obesity, hypogonadism, and short stature exhibit some clinical overlap with patterns of MRXS7 patients. Vasquez *et al*[13] identified a family with five affected males through four generations with mental retardation, obesity, hypogonadism, and gynecomastia. The Borjeson-Forssman-Lehmann syndrome is characterised by mental retardation, unusually coarse face with large ears, obesity and epilepsy, and maps in Xp27.[14]

The MRXS7 critical region has been described as the most gene-dense region after the MHC class III cluster identified on chromosome 6.[15] Several disease genes have been mapped to this region. They include the androgen receptor gene,[16] the *XH2* gene, responsible for ATRX syndrome, an X-linked disorder comprising severe psychomotor retardation, genital abnormalities, and alpha-thalassaemia,[17] three genes responsible for eye diseases,[18–20] Wiskott-Aldrich syndrome,[21] one form of synovial sarcoma,[22] X-linked nephrolithiasis,[23] and zinc finger genes (ZXDA[24] and four Kruppel type[25]). These zinc finger genes could be considered candidates for the syndrome described in this paper, and possibly the Wilson syndrome, further supported by earlier findings, showing that disruption of zinc finger genes was involved in human development disorders such as Greig-cephalopolysyndactyly syndrome[26] and Wilms tumour.[27]

Acknowledgements

We gratefully acknowledge the family members. We thank Drs Mohammad Ayub and Mohammad Andaleeb for helping with clinical diagnosis. This work was supported by the Italian Telethon Foundation to TIGEM and WA (postdoctoral fellowship 205/bs). MA was supported by the Pakistan Science Foundation (PSF).

References

1 Neri G, Gurrieri F, Gal A, Lubs HA: *XLMR* genes: update 1990. *Am J Med Genet* 1991; **38**: 186–189.
2 Lubs HA, Chiurazzi P, Arena JF, Schwartz C, Tranebjærg L, Neri G: *XLMR* genes: Update 1996. *Am J Med Genet* 1996; **64**: 147–157.
3 Oostra BA, Verkerk AJ: The fragile X syndrome: isolation of the *FMR 1* gene and characterization of the fragile X mutation. *Chromosoma* 1992; **101**: 381–387.
4 D'Adamo P, Menegon A, Lo Nigro C *et al*: Mutations in GDI1 are responsible for X-linked non-specific mental retardation [see comments]. *Nat Genet* 1998; **19**: 134–139.
5 Allen KM, Gleeson JG, Bagrodia S *et al*: PAK3 mutation in nonsyndromic X-linked mental retardation. *Nat Genet* 1998; **20**: 25–30.
6 Billuart P, Bienvenu T, Ronce N *et al*: Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation. *Nature* 1998; **392**: 923–926.
7 Merienne K, Jcquott S, Pannetier S *et al*: A missense mutation in *RPS6KA3* (*RSK2*) responsible for non-specific mental retardation. *Nat Genet* 1999; **22**: 13–14.
8 Lathrop GM, Lalouel JM, Julier C, Ott J: Strategies for multilocus linkage analysis in humans. *Proc Nat Acad Sci USA* 1984; **81**: 3443–3446.
9 Dib C, Fauré S, Fizames C *et al*: A comprehensive genetic map of the human genome based on 5,264 microsatellites. *Nature* 1996; **380**: 152–154.
10 Steinmuller R, Steinberger D, Muller U: MEHMO (mental retardation, epileptic seizures, hypogonadism and genitalism, microcephaly, obesity), a novel syndrome: assignment of disease locus to xp21.1–p22.13. *Eur J Hum Genet* 1998; **6**: 201–206.
11 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**: 406–413.
12 Gedeon A, Mulley J, Turner G: Gene localisation for Wilson Turner syndrome (WTS:MIM 309585). *Am J Med Genet* 1996; **64**: 80–81.
13 Vasquez SB, Hurst DL, Sotos JF: X-linked hypogonadism, gynecomastia, mental retardation, short stature and obesity – a new syndrome. *J Pediatr* 1979; **94**: 56–60.
14 Turner G, Gedeon A, Mulley J *et al*: Borjeson-Forssman-Lehmann syndrome: clinical manifestations and gene localization to Xq26–27. *Am J Med Genet* 1989; **34**: 463–469.

15 Coleman MP, Nemeth AH, Campbell L, Raut CP, Weissenbach J, Davies KE: A 1.8 Mb YAC contig in Xp11.23: identification of CpG islands and physical mapping of CA repeats in a region of high gene density. *Genomics* 1994; **21**: 337–343.
16 Lubahn DB, Joseph DR, Sar M *et al*: The human androgen receptor: complementary deoxyribonucleic acid cloning, sequence analysis and gene expression in prostate. *Mol Endocrinol* 1988; **2**: 1265–1275.
17 Gibbons RJ, Picketts DJ, Villard L, Higgs DR: Mutations in a putative global transcriptional regulator cause X-linked mental retardation with a-Thalassemia (ATR-X syndrome). *Cell* 1995; **80**: 837–845.
18 Ott J, Bhattacharya S, Chen JD *et al*: Localizing multiple X chromosome linked retinitis pigmentosa loci using multilocus homogeneity tests. *Proc Natl Acad Sci USA* 1990; **87**: 701–704.
19 Bech-Hansen NT, Pearce WG: Manifestations of X linked congenital stationary night blindness in three daughters of an affected male: demonstration of homozygosity. *Am J Hum Genet* 1993; **52**: 71–77.
20 Alitalo T, Kruse TA, Forsius II, Eriksson AW, de la Chapelle A: Localization of the Åland Island eye disease locus to the pericentromeric region of the X chromosome by linkage analysis. *Am J Hum Genet* 1991; **48**: 31–38.
21 Kwan SP, Lehner T, Hagemann T *et al*: Localization of the gene for the Wiskott-Aldrich syndrome between two flanking markers, TIMP and DXS255, on Xp11.22 Xp11.3. *Genomics* 1991; **10**: 29–33.
22 de-Leeuw B, Suijkerbuijk RF, Balemans M *et al*: Sublocalization of the synovial sarcoma associated t(X-18) chromosomal breakpoint in Xp11.2 using cosmid cloning and fluorescence *in situ* hybridization. *Oncogene* 1993; **8**: 1457–1463.
23 Scheinman SJ, Pook MA, Wooding C, Pang JT, Frymoyer PA, Thakker RV: Mapping the gene causing X linked recessive to Xp11.22 by linkage studies. *J Clin Invest* 1993; **91**: 2351–2357.
24 Greig GM, Sharp CB, Carrel L, Willard HF: Duplicated zinc finger protein genes on the proximal short arm of the human X chromosome: isolation, characterization and X-inactivation studies. *Hum Mol Genet* 1993; **2**: 1611–1618.
25 Knight JC, Grimaldi G, Thiesen HJ, Bech-Hansen NT, Fletcher CD, Coleman MP: Clustered organization of Kruppel zinc finger genes at Xp11.23, flanking a translocation breakpoint at OATL1: a physical map with locus assignments for ZNF21, ZNF41, ZNF81, and ELK1. *Genomics* 1994; **21**: 180–187.
26 Vortkamp A, Gessler M, Grzeschik K-H: *GLI3* zinc finger gene interrupted by translocations in Greig syndrome families. *Nature* 1991; **352**: 539–540.
27 Haber DA, Buckler AJ, Glaser T *et al*: An internal deletion within an 11p13 zinc finger gene contributes to the development of Wilms' tumor. *Cell* 1990; **61**: 1257–1269.