

Non-specific X linked mental retardation

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Abstract

Non-specific X linked mental retardation (MRX) is mental retardation in persons of normal physical appearance who have no recognisable features apart from a characteristic pedigree. Review of published reports shows that there is clinical variability in the degree of mental retardation within families and genetic heterogeneity, based on gene localisation, between families. We propose a classification based on genetic localisation and a set of minimal clinical features that should be recorded in the hope of identifying possible specific phenotypes.

Twenty-five years ago the contribution of mutant genes on the X chromosome to mental retardation was thought to be about 6%, proportional to the physical length of the X chromosome in relation to the total haploid length of the genome.^{1,2} A few years later this view was challenged by three independent investigators,³⁻⁷ all of whom stressed that X linked genes contributed disproportionately to the sum of mental retardation. Estimates varied from 10 to 20%^{3,8} to 25 to 50%.^{5,4}

A small part of all X linked mental retardation (XLMR) can be attributed to syndromes or diseases with specific biochemical, neurological, or morphological abnormalities. Sixty-nine such entities are listed in the McKusick catalogue⁹ but each of these is rare. The discovery of a cytogenetic test for the presence of a fragile site at Xq27.3 allowed a large number of males previously designated as affected by

non-specific XLMR to be reclassified as fragile X syndrome. However, it has been increasingly recognised that XLMR without conspicuous somatic manifestations may be equally or more common than the fragile X syndrome.

Non-specific X linked mental retardation (MRX) may be defined as non-progressive intellectual handicap segregating in an X linked manner without any consistent somatic or diagnostic features. The first name given to this entity was Renpenning syndrome³ in recognition of one of the first convincing published pedigrees.¹⁰ This family has been restudied. Their physical features constitute an X linked mental retardation syndrome^{11,12} and Renpenning syndrome is therefore reserved to describe subjects with the same clinical findings as the original family. Suthers *et al*¹³ introduced the MRX nomenclature (meaning non-syndromal mental retardation, X linked) to describe the chromosomal location of the genes responsible for non-specific X linked mental retardation.

Prevalence

There are difficulties in estimating the prevalence of MRX since individual cases cannot be recognised in the absence of a characteristic pedigree. Population surveys have attempted to estimate the contribution of X linked genes to mental retardation. Turner and Turner⁷ surveyed the moderately retarded population in New South Wales. Herbst and Miller¹⁴ considered the entire mentally retarded population in British Columbia. Both these surveys are likely to have been underestimates as, at that time, the contribution of heterozygous expression to mental retardation in females was not recognised and the number of families with only affected females was used in the calculations as representing the prevalence of genes on autosomes associated with familial mental retardation. In British Columbia the overall prevalence of XLMR was 1.83/1000 males.

The epidemiology of the fragile X syndrome has recently been reviewed by Webb *et al*.¹⁵ In populations of principally European extraction the prevalence varies from 0.4 to 0.9/1000 for males and 0.2 to 0.6/1000 for expressing females. MRX could therefore affect 0.9 to 1.4/1000 males.

An indirect estimate of the prevalence of MRX can be made from the data of Fishburn *et al*¹⁶ who

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reviewed 58 pairs of moderately retarded brothers, 54 of whom had first been identified by Turner and Turner.⁷ X linked conditions were found in 26 pairs of brothers or 45% of the whole series. X linked syndromes occurred in five pairs. The fragile X syndrome was present in 12 pairs, only seven (58%) of whom had a positive family history. MRX could be diagnosed on pedigree information in nine pairs. The ratio of fragile X to MRX using the raw figures would be 12:9. Using the assumption that, as with the fragile X syndrome, only 58% would have a positive family history, the ratio would be 12:16, a ratio consistent with the figure derived from Herbst *et al*¹⁴ and Webb *et al*.¹⁵

Clinical features

Before the clinical significance of the fragile X site was appreciated,^{17, 18} and the need to use a folic acid deficient medium to produce the phenomenon was established,^{19, 20} the fragile X syndrome was regarded as a form of MRX along with Renpenning syndrome¹⁰ and several other families that had been reported in the 1970s.^{21–24} Once it was possible to bring all those with a fragile site into a group, then a fairly characteristic clinical picture of the fragile X syndrome began to emerge.

To determine whether any subtle clinical characteristics may suggest the diagnosis of non-specific X linked mental retardation we have reviewed the published reports. We reviewed only the reports where X linked inheritance was confirmed by the presence of affected males either in two generations or in two sibships maternally related, and where the fragile site at Xq27.3 had been excluded.²⁵ Nineteen published pedigrees met these criteria and contained clinical information (table).

The degree of mental retardation within a sibship was consistent in only nine out of 19 families and could vary from mild to severe in the same family. No conclusion could be drawn concerning verbal performance discrepancy in intellectual function. Intellectual function in heterozygotes was mentioned in six families, in four of these as normal. In one family,³⁵ the three obligate carriers were described as slow in comparison to their sibs, and in one mild intellectual handicap had been confirmed by IQ testing.

Head circumferences and heights in affected males were most often in the normal range. Testicular volumes had been documented in at least one male in 17 kindreds, in six as enlarged and in 11 as normal. In one family,³² two affected males were stated to have a similar facial appearance (high forehead, sunken eyes, wide mouth, prognathism), and in two further families³⁰ affected males were described as having an awkward gait.

The amount of clinical information varied widely from publication to publication without any uniform

reporting of clinical data. The only possible suggestive feature that emerged was testicular enlargement.

Genetic classification

Gene localisation by linkage has established MRX as a genetically heterogeneous disorder.^{13, 37, 39} Families must be of sufficient size to localise the MRX gene using that family alone. Lod scores cannot be added among families because of genetic heterogeneity and the absence of diagnostic clinical features.

Gene localisation in X linked disorders entails the estimation of recombination frequencies using markers spread along the X chromosome. A lod score of +2 or greater represents a significant result for establishment of linkage to a particular X linked marker locus when recombinants are detected using markers spread along the remainder of the X chromosome.⁴⁰ Boundaries to any unambiguous gene localisation based on a single family can be defined by the physical location of the closest informative flanking markers with which there is recombination.

Suthers *et al*¹³ undertook a linkage analysis in a three generation pedigree. No recombination was observed between the disease gene and *DXS14*, located at Xp11.21, with a lod score of 2.12 at a recombination frequency of 0. Recombination was observed with the flanking markers, *DXS7* and *DXYS1*, located at Xp11.4–11.3 and Xq21.31, respectively. This locus, near Xcen, was designated *MRX1*. The highly polymorphic *DXS255* within the *DXS7* to *DXS14* interval was not informative in reducing this localisation (unpublished data), but inclusion of additional family members subsequently increased the lod score with *DXS14* to 2.90.⁴¹

In family 3 of Arveiler *et al*,³⁷ a lod score of 2.53 was obtained at a recombination fraction of 0 with *DXS159* at Xq12. At present this localisation is indistinguishable from *MRX1* of Suthers *et al*.¹³

The clinical details for family 1 of Arveiler *et al*³⁷ have been published by Proops *et al*.³⁵ In this family, a lod score of 2.62 at a recombination frequency of 0.05 was found with *DXS85* which localises to Xp22.2–p22.3. This locus can be designated *MRX2*. The proximal limit to the localisation for *MRX2* was not defined by recombination close to the *MRX2* gene. The closest marker with negative lods was *DXYS1* at Xq21.31. Family 1 of Arveiler *et al*³⁷ requires re-examination using markers in the Xp21 region in order to detect a recombination point defining a proximal boundary to *MRX2*.

Gedeon *et al*³⁹ have reported localisation of *MRX3* to Xq28–qter, distal to the fragile site at Xq27.3 and *DXS304* at Xq28. The maximum lod score was 2.89 with *DXS52* (St14) at a recombination frequency of 0. A recombinant was observed at *DXS304* (U6.2) defining the proximal limit for this regional localisation on Xq28.

Clinical reports of kindreds with non-specific XLMR. Normal standards are those of Hall *et al.*²⁶

Authors	Kindred	No of males with some clinical detail	Level of MR in males*	Affected carriers specified†	Affected females of unknown carrier status‡	Head circumference †	Height ‡	Testicular volume §	Development ¶	Neurological signs	Phenotype**
Lehrke (1974) ²⁷	a b	22	S/Mod/M	?	—	<(3)	?	N(1)	?	—	N
Howard-Peebles <i>et al.</i> (1979) ³⁰	Ac B C	9 3 2	P/Mod/M M Mod/M	N ? ?	—	?	?	N(1) N(1) N(1)	U U U	+ — +	N N N
Jennings <i>et al.</i> (1980) ³²	d	2	P/Severe	?	—	>(1)	<(1)	>(2)	?	—	+
Herbst <i>et al.</i> (1981) ³⁴	J M GJ	1 4 3	? Mod/M Mod/M/B	? 2 ?	—	N N >(1)	N N <(1)	>(1) >(2) >(1)	? ? ?	— — —	N N N
Proops <i>et al.</i> (1983) ³⁵	F	5	?M	3	1	?	?	>(3)	U	—	N
	O	2	M	?	—	?	?	N(2)	?	—	N
Archidiacono <i>et al.</i> (1987) ³⁶	10 13	1 6	? ?	? ?	1 —	N <(1)	<(1) <(1)	>(1) N	? ?	? ?	? ?
Arveiler <i>et al.</i> (1988) ³⁷	2 3	5 7	?Mod/M ?Mod	N N	—	? ?	? ?	? N	? U	? —	? N
Suthers <i>et al.</i> (1988) ¹³	1	11	Mod	N	—	N	?	N	?	N	N
Thode <i>et al.</i> (1988) ³⁸	S B G R	3 2 3 3	?M ?M S/Mod/M Mod	? ? ? ?	—	N N N N	N N N N	N N N N	? ? ? ?	? ? ? ?	N N N N

a Originally published as abstract by Optiz *et al.*²⁸ b Howard-Peebles and Roberts²⁹; fragile site negative. c Originally published by Yarborough and Howard-Peebles.³¹ d Previously published by Ruvalcaba *et al.*³³

†If specified in text.

‡Recorded as increased (>), or decreased (<) if recorded by author as above 97th or less than 3rd centile; number of males in brackets.

§Normal (N), increased (>), or decreased (<); number of males in brackets.

¶U=uniform delay, V=verbal delay, P=performance delay if described in any affected male.

||+ if present in all affected males, — not necessarily uniform.

**Recorded as + if consistent in all affected males.

The MRX2 designation was initially applied by Sutherland *et al*⁴² to a previously undescribed XLMR syndrome. This designation is now rescinded (G R Sutherland, personal communication), reserving the MRX nomenclature for non-specific X linked mental retardation.

Conclusion

Linkage analysis in large pedigrees provides an objective method for genetic classification of MRX. By correlating gene location and clinical findings, new syndromes may emerge, enabling diagnosis in pedigrees where linkage analysis is unable to provide a genetically based classification owing to the size of the pedigree.

Determination of prevalence, the magnitude of heterozygote manifestations, and suggestive clinical features require consistent reporting. We propose that:

- (1) The definition of non-specific X linked mental retardation (MRX) as mental retardation in persons of normal physical appearance, who have no recognisable features apart from a characteristic pedigree, should be adhered to. The label non-specific X linked mental retardation (MRX) should replace such terms as 'simple XLMR',⁴³ 'non syndromic XLMR', 'bland XLMR',⁴⁴ and 'XLMR without the fragile X' and be limited to those without any consistent physical feature.
- (2) Only pedigrees which meet the criteria of Herbst,²⁵ that is, where inheritance has been shown by the presence of affected males in either two generations or in two sibships maternally related, and where the presence of the fragile site at Xq27.3 has been excluded, should be described as MRX. Until the presence or absence of heterozygote expression has been determined the presence of affected females should not be a basis for exclusion of families.⁴⁵
- (3) Clinical information should include, if possible, (1) birthweight, (2) developmental history, (3) body measurements, (4) testicular size, (5) somatic characteristics with photographs, (6) personality characteristics, (7) IQ tests and measurements of scatter, (8) neuroradiological investigations.
- (4) The symbol MRX should be reserved for gene localisations in families with non-specific X linked mental retardation. Syndromal forms of XLMR should have a different nomenclature; this could be a descriptive title or else the name of the first author. If subsequent refinements to mapping establish non-overlapping localisations within loci, by either demonstration of deletions or detection of recombination points with flanking markers, then the first described family could be labelled MRX1.1 and the second MRX1.2. New families mapping to the pericentromeric region which cannot be separated

into the MRX1.1 or MRX1.2 subgroups would retain the MRX1 nomenclature pending refinement to their gene localisation.

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