Review article

X linked mental retardation

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Classification of mental retardation

Mental retardation (MR) can be classified within approximate IQ ranges assuming a population mean of 100 and a standard deviation of 15. Mild MR is defined as being within the IQ range 50 to 70 (-2.0 to -3.3 SD), moderate MR within the IQ range 35 to 50 (-3.3 to -4.3 SD), severe MR within the IQ range 20 to 35 (-4.3 to -5.3 SD) and profound MR within the IQ range 0 to 20 (less than -5.3 SD).¹ A simplification of this classification into two large groups is often used; severe mental retardation (SMR), which includes the profound, severe, and moderate categories, and mild mental retardation (MMR).² SMR has an estimated incidence of just less than 4 per 1000 live births.³⁻⁵ The MMR group comprises some 2 to 3% of the population but many of these persons, especially at the top end of this IQ range, will make satisfactory adjustments and not be regarded as abnormal.⁶ The estimates of the fraction of genetically determined handicap contributing to SMR range from 0.25⁷ to 0.52.³ In addition, a large idiopathic fraction (between 0.12⁷ and 0.51⁴) exists and this component almost certainly contains unrecognised genetic disease. Even for MMR, traditionally considered to represent the lower end of the multifactorial distribution of intelligence, pathological causes have been delineated which include genetic conditions.^{6, 8}

Historical perspective and frequency of X linked mental retardation

It has been long recognised that males consistently outnumber females in surveys of MR. Penrose⁹ noted a 16% excess of males in the 1280 cases of insti-

tutionalised mental defect he ascertained. Since no excess of retarded male sibs was observed he rejected this sex difference as being the result of X linked genes, attributing it to the greater susceptibility of males to environmental effects. Reed and Reed,¹⁰ using a population approach, found a 49% excess of MR males in their survey and provided indirect evidence for sex linkage of intelligence by showing that retarded females with a normal male partner were twice as likely to have retarded offspring as retarded males with a normal female partner. Further support for sex linkage of MR came by noting the disproportionate number of families with only male retarded children.^{11, 12} Similarly, in surveys of MMR ascertained from facilities for the MR, a male excess has been consistently observed.^{6, 8, 13} The breakdown, by level of MR, indicates that the contribution of X linked genes to MR is greatest in the mild-moderate MR categories.¹⁴ This is shown by the significantly greater recurrence risk for male sibs observed for mild-moderate MR in contrast to the findings for severe-profound MR.¹⁴ Lehrke¹⁵ hypothesised that, to account for this male excess of MR, between 25% and 50% of all retardation was attributable to sex linked genes.

Following Penrose's publication,⁹ sporadic reports of familial mental retardation segregating in an X linked fashion were described over the years before the delineation of fragile X syndrome.^{16, 17} Some of these families, notably the Martin-Bell pedigree (later syndrome),¹⁸ were subsequently shown to be fragile X syndrome.¹⁹ Others were apparently associated with a constellation of features which included MR (for example, Borjeson and Renpenning syndrome^{20, 21}), or were associated with an associated metabolic disturbance (for example, Menkes disease²²), or structural defects that appeared at first sight to be directly related to the MR (for example, X linked hydrocephalus²³). Lehrke¹⁵ had concluded independently, after studying 10 families with X linked segregation of MR who had no other identifiable metabolic or structural features, that a gene for lowered IQ was present in these kindreds. Davison²⁴

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had also ascertained five families with isolated MR in which either sex limitation or X linkage appeared to be the only possible explanation for the pattern of transmission of the MR. Lehrke,¹⁵ by recognising that MR itself could be inherited in an X linked fashion, postulated that major genetic loci related to human intellectual functioning were located on the X chromosome, the mutation of which would lead to mental impairment. The lag in recognising XLMR can, in retrospect, be attributed to surveys being confined to institutions whose occupants were largely within the SMR grouping. Hence mild-moderate MR, where XLMR predominates¹⁴ and which is in the main 'community based', was inadequately ascertained. In addition the presence of affected heterozygote females in XLMR conditions was not perceived and recurrence risks were not calculated for the MMR group until Reed and Reed¹⁰ attempted this by estimating the risks to offspring from retarded parent(s).

Following the discovery of the necessary culture conditions for fra(X) expression,¹⁷ a large number of reports followed delineating the fragile X phenotype and describing other XLMR conditions. This established the importance of X linked transmission of MR beyond doubt and culminated in the holding of the first of what subsequently turned out to be a series of meetings, 'International workshop on the fragile X and XLMR'.²⁵

Extrapolation from figures for the excess of brother-brother mentally retarded pairs over sister-sister retarded pairs gave an estimate for the frequency of XLMR of 1.83/1000 males with the carrier frequency estimated at 2.44/1000 females. This study included MMR in its ascertainment criteria but did not include neurological or syndromal conditions which lacked MR as the primary diagnosis.¹² Oritiz²⁶

went further, calculating the prevalence for all XLMR (both sexes) at 1/296 by using fragile X prevalence data and the assumption that fragile X comprises some 40% of XLMR.

Assuming a mutation rate for X linked loci of between 3 and 9×10^{-5} and by using their British Columbian prevalence estimates for XLMR, Herbst and Miller¹² estimated that between seven and 19 genes exist on the X chromosome, mutation of any of these genes being responsible for XLMR. The analysis of Morton *et al*²⁷ of the Colchester data assumed a similar mutation rate and concluded that at least 18 X linked loci could cause mental deficiency. At least one of these genes appeared to relate to verbal function, as verbal disability was observed in many cases of XLMR studied by Lehrke.²⁸

The nosology of X linked mental retardation

As the abnormal physical findings of fragile X and many of the other X linked conditions associated with MR have been documented, they have been reclassified as specific diagnostic entities, many with MIM listings, of which more than 70 now exist.²⁹ Non-specific or non-syndromal XLMR is now taken to include only those families with mental impairment without other distinguishing clinical abnormalities. The term originally encompassed many forms of XLMR, including fragile X syndrome (Renpenning syndrome has also been used to refer to fragile X syndrome or non-specific XLMR or both as well as the rare syndrome originally described by Renpenning *et al*²¹).

Difficulty may be encountered when the geneticist considers the possibility of an XLMR condition and is unable to decide easily whether the clinical features constitute a previously recognised condition. Table 1

Table 1 XLMR syndromes classified by clinical manifestation.

	MIM	Reference
1 XLMR and macrocephaly		
FG syndrome	305450	36, 37
Simpson-Golabi-Behmel syndrome	312870	38
X linked hydrocephalus (MR males exist from affected families with normal OFC and no evident hydrocephalus)	307000	39, 40
XLMR with Marfanoid habitus	309520	41
Fragile X syndrome	309550	42
Atkin-Flaitz syndrome	309530	43, 44
MR with skeletal dysplasia	309620	45
X linked basal ganglia disorder with MR	311510	46
2 XLMR with microcephaly		
Borjeson syndrome	301900	47, 48
Aicardi syndrome	304050	49
Focal dermal hypoplasia	305600	50
Incontinentia pigmenti	308300/308310	51
Renpenning syndrome	309500	52
*MR:Smith-Fineman-Meyers type	309580	53, 54
Rett syndrome	312750	55, 56
Chudley MR syndrome	309490	57, 58
Norrie disease	310600	34

(continued)

	MIM	Reference
*Branchial arch syndrome	301950	59
MRX2 (with brachycephaly)	309470	60
Paine syndrome	311400	61
Golabi-Ito-Hall syndrome	309530	62
Holmes-Gang syndrome	309530	63
MESD syndrome	309590	64
Seemanova syndrome	311400	65
Keratosis follicularis-MR syndrome	308830	66
Intrauterine growth retardation-MR	308400	67
Schimke syndrome	312840	68
XLMR with contractures		114
3 XLMR with macro-orchidism		
Fragile X syndrome	309550	42
XLMR with Marfanoid habitus	309520	41
Atkin-Flaitz syndrome	309530	43, 44
4 XLMR with hypogonadism		
Borjeson syndrome (microgenitalia, gynaecomastia, hypogonadotrophic hypogonadism)	301900	20, 47, 69
Aarskog syndrome (shawl scrotum, cryptorchidism)	305400	70, 71
FG syndrome (cryptorchidism, hypospadias)	305450	36, 37
Simpson-Golabi-Beihmel syndrome (cryptorchidism)	312870	38
Lowe syndrome (cryptorchidism)	309000	72
Juberg-Masardi syndrome (rudimentary scrotum, cryptorchidism, micropenis)	309590	73, 74
RUD syndrome (both hypo- and hypergonadotrophic hypogonadism)	308200	75, 76
Renpenning syndrome (micro-orchidism)	309500	52
Chudley MR syndrome (cryptorchidism, micro-orchidism)	309490	57, 58
Norrie disease (cryptorchidism)	310600	34
MRX2 (micro-orchidism)	309470	60
Vasquez family (microgenitalia, gynaecomastia, hypogonadotrophic hypogonadism)	309590	77
Young-Hughes family (microgenitalia, primary hypogonadism)		78
5 XLMR with skin disease		
Focal dermal hypoplasia (focal skin hypoplasia and depigmentation, adipose herniation, facio-oral papillomas, alopecia)	305600	50, 79, 80
Incontinentia pigmenti (neonatal linear vesicular rash, develop hypopigmented whorls, recedes in adulthood)	308300/308310	51
RUD syndrome (ichthyosis)	308200	75, 76
Keratosis follicularis-MR syndrome (with generalised alopecia)	308830	66
Fitzsimmons syndrome (plantopalmar hyperkeratosis)	309560	81
van den Bosch syndrome (acrokeratosis verruciformis, anhidrosis)	314500	82
XLMR with psoriasis	309480	83
6 XLMR with neurological features		
Borjeson syndrome (hypotonia, ptosis, nystagmus, seizures)	301900	20, 48, 69, 84
Aicardi syndrome (seizures, agenesis of corpus callosum)	304050	85
X linked partial agenesis of the corpus callosum (seizures)	304100	86, 87
FG syndrome (infantile hypotonia, constipation, seizures, agenesis of corpus callosum, strabismus)	305450	36, 37
Simpson-Golabi-Beihmel syndrome (infantile hypotonia)	312870	38
X linked hydrocephalus (absence of extensors pollicis brevis/longus with adducted thumbs, absent pyramids in medulla)	307000	40, 88
Incontinentia pigmenti (seizures, spasticity)	308300/308310	51
Lowe syndrome (areflexia, hypotonia, diffuse muscle atrophy, seizures)	309000	72, 89
MASA syndrome (aphasia, shuffling gait, spastic paraplegia, adducted thumbs)	303350	90, 91, 92
*MR:Smith-Fineman-Meyers type (seizures, ptosis, hypotonia)		
Rett syndrome (seizures, hyperventilation with apnoea, ataxia, later spasticity, autism, and regression, dystonic movements)	309580	53, 54
X linked cerebellar dysfunction with MR (congenital ataxia, hypotonia, nystagmus, normal reflexes)	312750	55, 56
Allan-Herndon syndrome (neck drop, muscle hypoplasia, ataxia, dysarthria, athetosis, spastic paraplegia, myoclonic fits)		93, 94
X linked motor-sensory neuropathy II (severe weakness and areflexia from infancy)	309600/312890	31, 95, 96
	310490	97
Fitzsimmons syndrome (spastic paraplegia, marked pes cavus)	309560	81
Ataxia-deafness syndrome (esotropias, progressive cerebellar dysfunction, severe bulbar problems)	301790	98
MRX2 (spastic diplegia)	309470	60
MR with spastic paraplegia (slowly progressive spastic quadriparesis)	309640	30
Paine syndrome (spastic diplegia, myoclonic fits)	311400	61
Barr Gabriel sex linked spastic paraplegia (spastic paraparesis of infantile onset, athetosis, nystagmus, no myoclonus)	312890	99
Goldblatt spastic paraplegia (upper limb ataxia, nystagmus)	312920	100
X linked basal ganglia disorder with MR (seizures, early onset extrapyramidal disease, strabismus)	311510	46
Wieacker-Wolff syndrome (foot and other joint contractures, progressive distal muscle atrophy, oculomotor and facial apraxias)	314580	101
Holmes-Gang syndrome (hypotonia, weakness with severe talipes equinovarus deformity)	309530	63
XLMR with psoriasis (ataxia, hypotonia, seizures)	309480	83
Partington syndrome (dysarthria, episodic dystonias of hands, ataxia, seizures)	309510	102

(continued)

	MIM	Reference
MESD syndrome (seizures, spasticity)	309590	64
Seemanova syndrome (spastic tetraplegia, clonic seizures)	311400	65
MR with skeletal dysplasia (abducens palsy)	309620	45
MR and scapuloperoneal muscular dystrophy and lethal cardiomyopathy (may be Emery-Dreifuss muscular dystrophy, however no contractures)	309660	103
Schimke syndrome (abducens palsy, infantile hypotonia, choreoathetosis from childhood with later spasticity)	312840	68
XLMR with Dandy-Walker malformation and basal ganglia disease (plus spasticity)		103a
7 XLMR with dysmorphic features		
Borjeson syndrome (prominent supraorbital ridges, deep set eyes, large fleshy ears)	301900	20, 48
Coffin-Lowry syndrome (prominent brow, antimongoloid slant, hypertelorism, broad nose, pouting lips, hypothernar crease)	303600	104, 105
Aarskog syndrome (hypertelorism, ptosis, downward slanting eyes, short anteverted nose, wide philtrum, linear chin dimple)	305400	70, 71
FG syndrome (drooping face, cowlicks of hairline, tall broad forehead, deep set eyes, structural anal anomalies)	305450	36, 37
Simpson-Golabi-Behmel syndrome (coarse facies, hypertelorism, notched lower lip, macrostomia, clefting, visceromegaly)	312870	38
Incontinentia pigmenti (hemifacial atrophy, alopecia, partial adontia, peg teeth, nail dystrophy)	308300/308310	51
Lowe syndrome (coarsening of facial features with age, frontal bossing, deep set eyes)	309000	106
XLMR with Marfanoid habitus (long face, small mandible, high arched palate, hypernasal voice)	309520	41, 107
Lenz microphthalmia syndrome (bat ears, crowded teeth, clefting, urogenital anomalies)	309800	108
Non-specific XLMR (minor dysmorphic features reported in some families)	309530	109
Fragile X syndrome (long face, large ears, prognathism)	309550	42
*MR: Smith-Fineman-Mayers type (narrow face, prominent maxilla, micrognathia, decreased frontonasal angle, patulous lips)	309580	53, 54
Juberg-Masardi syndrome (upward slanting palpebral fissures, flat nasal bridge, dysplastic nails)	309590	73, 74
OFD-I (sparse hair, aplasia of nasal alae, midline clefting lip/palate/tongue/jaw, tongue nodules)	311200	110
Atkin-Flaitz syndrome (square forehead, prominent supraorbital ridges, hypertelorism, broad nose, large ears)	309530	43, 44
RUD syndrome (hypoplastic teeth, hypoplastic deep set nails)	308200	76
Chudley MR syndrome (bitemporal narrowing, flat nasal bridge, high palate, lip tenting)	309490	57, 58
Allan-Herndon syndrome (long narrow face, large ears)	309600/312890	31, 95
Norrie disease (fine features, hypotelorism, large ears, narrow nasal bridge, flat malar region, thin upper lip)	310600	34
*Branchial arch syndrome (downward slanting palpebral fissures, low set protruding ears, high arched palate, webbed neck)	301950	59
XLMR with dysmorphism (prominent nose, malformed ears, retromicrognathia, double row lower incisors, sacral dimple)	309610	111
Pallister W syndrome (frontal prominence, anterior cowlick, hypertelorism, downward slanting eyes, flat nose, clefting)	311450	112
Golabi-Ito-Hall syndrome (narrow face, brittle hair, downward slanting eyes, laterally directed inner canthi, anteverted ears)	309530	62
Holmes-Gang syndrome (large anterior fontanelle, short nose with anteverted nares)	309530	63
X linked basal ganglia disorder with MR (frontal bossing, high arched palate, crowded teeth)	311510	46
Vasquez family (narrow forehead, upward slanted small eyes, varied structural anomalies of hands)	309590	77
*Scott craniodigital syndrome with MR (brachycephaly, small nose, startled look, extensive scalp/facial hair, syndactyly)	312860	113
8 XLMR with skeletal/stature anomalies		
Borjeson syndrome (short, obese, kyphoscoliosis, vertebral anomalies, tapered fingers, clawed toes, delayed bone age)	301900	20, 48, 69
Coffin-Lowry syndrome (short, kyphoscoliosis, broad hands, tapered fingers, joint laxity, hypodontia, delayed bone age)	303600	104, 105
Aicardi syndrome (fused and hemivertebrae)	304050	49, 85
Aarskog syndrome (short, pectus excavatum, clinobrachydactyly, webbing of fingers, metatarsus varus, delayed bone age)	305400	70, 71
FG syndrome (short, joint stiffness, contractures, camptodactyly, broad thumbs, ventral finger pads)	305450	36, 37
Focal dermal hypoplasia (short, missing digits or part of a limb, polysyndactyly, dysplastic teeth/nails)	305600	50, 80
Simpson-Golabi-Behmel syndrome (prenatal and postnatal overgrowth, postaxial polydactyly, advanced bone age)	312870	38
Lowe syndrome (short, kyphoscoliosis, renal tubular acidosis with vitamin D resistant rickets, fractures, joint laxity)	309000	72, 106
MASA syndrome (short, lumbar lordosis, camptodactyly)	303350	92
Renpenning syndrome (short)	309500	52
XLMR with Marfanoid habitus (tall, slender, exaggerated span)	309520	41, 107
Juberg-Masardi syndrome (small stature, retarded bone age)	309590	73, 74
Lenz microphthalmia syndrome (sloping shoulders, long thorax, duplication of thumbs, poly/syn/clinodactyly)	309800	108
OFD-I (skin and bony syndactyly of fingers, asymmetrical polydactyly, brachydactyly of toes)	311200	110
Atkin-Flaitz syndrome (short, obese)	309530	43
RUD syndrome (short stature)	308200	75, 76
Chudley MR syndrome (short stature, mild obesity)	309490	57, 58
*MR:Smith-Fineman-Mayer type (short stature)	309580	53, 54

(continued)

	MIM	Reference
*Branchial arch syndrome (short stature)	301950	59
Keratosis follicularis (proportionate dwarfing)	308830	66
MRX2 (short stature, lean habitus)	309470	60
MR with skeletal dysplasia (metopic ridging, cervical spine fusion, thoracic hemivertebrae, scoliosis, short middle phalanges)	309620	45
Pallister W syndrome (subluxed elbow, camptodactyly)	311450	112
Holmes-Gang syndrome (severe talipes equinovarus)	309530	63
XLMR and contractures (low fingertip arches, contractures, joint hypermobility)		114
Golabi-Ito-Hall syndrome (postnatal growth deficiency)	309530	62
MR with dysmorphism (patella subluxation, lower limb deformities)	309610	111
Young-Hughes family (short stature, obesity)		78
Vasquez family (short stature, obesity)	309590	77
9 XLMR with visual dysfunction		
Aicardi syndrome (bilateral chorioretinopathy with lacunae, coloboma of optic nerve/papilla/iris, microphthalmia)	304050	49, 85
Focal dermal hypoplasia (unilateral microphthalmia, coloboma of iris/choroid)	305600	50
Incontinentia pigmenti (strabismus, cataracts, visual loss)	308300/308310	51
Lowe syndrome (cataracts, glaucoma, buphthalmos)	309000	72, 106
Lenz microphthalmia syndrome (anophthalmos, microphthalmia, microcornea, coloboma, detached retina/lens)	309800	108
Norrie disease (bilateral retrolental mass/cataracts leading to phthisis bulbi)	310600	35
RUD syndrome (retinitis pigmentosa)	308200	75, 76
Ataxia deafness syndrome (optic atrophy)	301790	98
Paine syndrome (optic atrophy)	311400	61
van den Bosch syndrome (choroideremia)	314500	82
Goldblatt spastic paraplegia (optic atrophy)	312920	100
10 XLMR with deafness		
Coffin-Lowry syndrome	303600	104
FG syndrome	305450	36, 37
Juberg-Masardi syndrome	309590	73, 74
Norrie disease	310600	35
RUD syndrome	308200	76
X linked motor sensory neuropathy II	310490	97
Ataxia deafness syndrome	301790	98
*Branchial arch syndrome	301950	59
Golabi-Ito-Hall syndrome	309530	62
MESD syndrome	309590	64
Schimke syndrome	312840	68

Two groupings are made within each clinical manifestation. Families with two or more reports are followed by singly reported families that are either unique or who cannot be merged with other families from the available information. A gap separates the two groups.

A syndrome or family may be listed under several headings.

Important or useful differentiating features are listed in brackets, but not all features of a condition may be listed.

*Indicates that X linkage is equivocal.

outlines an approach to the diagnostic process and provides an aid in dealing with the published reports. Conditions that are either associated with frank regression (for example, adrenoleucodystrophy, Pelizeus-Merzbacher disease), a delineated metabolic defect (for example, glycerol kinase deficiency, ornithine transcarbamylase deficiency), or a well described myopathic condition (for example, Duchenne muscular dystrophy) are for the purposes of conciseness not included. It is apparent that a large number of individually described families exist and it seems improbable that they are all distinct entities. Differentiating information is not always available from the reports and merging of families under single entries has been avoided unless the evidence is convincing. Although the family reported by Davis *et al*³⁰ has features suggestive of MASA syndrome no comment concerning the thumbs was made to enable clarification.³⁰ Long term follow up, as in Allen-

Herndon syndrome,³¹ and 'second look' (S E Bunday, personal communication) can enable merging of families previously thought to be distinct. An invaluable proposal for accelerating the clinical classification of this large group of disorders has been made in which computer aided imaging and data processing would be used as an adjunct to the published reports.³² The documentation of clinical heterogeneity is vital as molecular investigation of these syndromes proceeds. In Norrie disease, it is not yet clear if males deleted for the sequence DXS7 (some of whom show disruption of monoamine oxidase genes³³) have a contiguous gene syndrome or represent a wider than previously appreciated clinical spectrum of Norrie disease,³⁴ which is supported by the wide intrafamilial variability observed in this condition.³⁵

Table 2 lists those XLMR conditions in which manifesting females have been described. Incontinentia pigmenti, focal dermal hypoplasia, orofacio-

Table 2 XLMR conditions with manifesting heterozygotes.

	Clinical features observed in females	Reference
<i>Multiply reported families</i>		
Non-specific XLMR	MR, specific psychometric anomalies	109, 115
FG syndrome	Facial dysmorphism	36, 37
X linked hydrocephalus (MR)	MR	40
Fragile X syndrome	MR, abnormal facies	42
Borjeson syndrome	MR, abnormal facies, short stature, tapering fingers	48, 69
Coffin-Lowry syndrome	MR, abnormal facies, tapered fingers with XR signs, short stature	104
Lowe syndrome	Fine lenticular opacities	116, 117
XLMR with Marfanoid habitus	Tall, macrocephaly, hypernasal voice, arched palate	41, 107
Atkin-Flaitz syndrome	MR, macrocephaly, coarse facies, diastema, tapered fingers	43, 44
Lenz microphthalmia syndrome	Microcephaly, short, digital anomalies	108
MASA syndrome	MR, shuffling gait, short, adducted thumbs	92
Aarskog syndrome	Abnormal facies, hand changes	71
<i>Single reported families</i>		
Ataxia deafness syndrome	Ataxia, cerebellar atrophy	98
Fitzsimmons syndrome	Plantar hyperkeratosis	81
MR with skeletal dysplasia	Glucose intolerance, abnormal vertebrae and phalanges	45
MESD syndrome	MR, microcephaly	64
MR and scapuloperoneal muscular dystrophy/ cardiomyopathy	Cardiomyopathy	103
Schimke syndrome	Hearing loss	68
XLMR with Dandy-Walker malformation and basal ganglia disease	MR	103a
XLMR with contractures	MR, facial asymmetry, low fingertip arches	114

digital I syndrome, and Rett syndrome appear almost exclusively in females (most likely as a result of X linked dominant mutations with male lethality in the first three conditions cited¹¹⁷).

Molecular studies of X linked mental retardation

A total of 19 X linked genes, mutation of which leads to MR,¹² appears to be an underestimate, as the depiction of the regional assignments to the X chromosome of conditions associated with or leading to XLMR in the figure shows. However, many of these assignments are overlapping with wide confidence intervals and cannot be assumed to be distinct. The large number of XLMR families with spastic paraplegia makes separate causative genes unlikely and it is probable that at least some of these pedigrees are allelic.

Progress in XLMR gene localisation has proceeded by a combination of cytogenetic and genetic mapping. In Lowe syndrome an X;autosome translocation in a manifesting female allowed regional localisation of the Lowe gene to Xq25¹³⁰ and provided material for a series of somatic cell hybrids that has enabled orientation of the locus and identification of flanking markers suitable for application to carrier detection.¹³¹ Comparisons of carrier status conferred by slit lamp examination with linkage analysis has verified the sensitivity and specificity of ophthalmological examination as a method of carrier detection.¹³¹ The molecular analysis of subjects with contiguous gene syndromes resulting from chromosomal rearrangements of Xp22-pter, using cDNA and genomic

probes, has assigned a gene responsible for MR to a specific interval in Xp22.¹¹⁹ It is of interest that a gene responsible for XLMR has also been assigned to Xp22 by linkage analysis,¹⁰⁹ but whether they are identical genes is not yet clear. The characterisation of the DNA of subjects manifesting the choroideremia-MR complex phenotype, who have X chromosomal rearrangements involving band Xq21, has assigned an MR gene to a specific interval in Xq21.¹²⁷ The overlap of several other putative XLMR localisations with this MR assigned interval suggests that further molecular investigation using Xq21 sequences may clarify whether an identical gene to that involved in the choroideremia-MR complex is mutated in those XLMR conditions. The report of cases of the non-deletional α thalassaemia-MR complex phenotype suggests that mutation in an unlinked, trans acting gene located on the X chromosome alters α globin expression and is responsible for the distinctive clinical features including MR.¹³⁷

Despite the limitations of single family linkage analyses, genetic heterogeneity is apparent for non-specific XLMR.^{109 115 124 125} The differing gene assignments for sporadic incontinentia pigmenti (assigned to pericentric Xp on the basis of Xp11 breakpoints¹²⁵) and familial incontinentia pigmenti (recombinant with Xp11 markers,¹³⁸ but linked to an Xq28 marker¹³⁶) also illustrate the importance of addressing this question before any clinical application of DNA technology. Combined linkage analysis of families with identical XLMR syndromes is desirable and may enable refinement of the tentative localisations of disease genes. However, the issue of genetic

Regional assignments of mental retardation to the human X chromosome. References in order from Xpter to Xqter: 118, 109, 119, 120, 102, 121, 34, 122, 123, 124, 60, 125, 97, 109, 126, 100, 127, 128, 114, 129, 130, 131, 69, 84, 115, 132, 133, 134, 135, 136.

heterogeneity has not yet been able to be realistically addressed for the majority of XLMR syndromes (many of which appear to be individually rare) and hence the implementation of DNA technology for genetic counselling purposes will inevitably be delayed. A recently developed method for providing tighter confidence limits in single pedigree linkage analyses has been applied to a single family with non-specific XLMR¹³⁹ and could conceivably act as an adjunct to fetal sexing, after successful gene localisation, in counselling a single family.

The genetic mapping of the fragile X mutation has recently received new impetus with several tightly linked markers now available. Genetic distances between markers and *FRAXA* may have been exaggerated owing to the inadvertent inclusion of phenocopies in past linkage analyses. This is most likely where either females have been scored as carriers,

attributing MMR as sufficient evidence of carrier status without establishing a complete heterozygote profile.¹⁴⁰ In addition, inclusion of subjects, as affected or carrier, with either low normal fra(X) expression or with the common fragile site at Xq27.2 (*FRAXD*)¹⁴¹ clearly introduces phenocopies into an analysis. The original segregation findings of incomplete penetrance in males was derived from the analysis of families reported by Sharman *et al*^{142 143} and appeared surprising for an X linked condition. Sved and Laird¹⁴⁴ argue that non-penetrant males exist at the same frequency as affected fragile X males and clearly an underestimation of the extent of incomplete penetrance to such a degree would exaggerate *FRAXA*-marker linkage interval estimates and may partially explain some of the discrepancies previously observed between genetic and physical distances in this region of the genome. However, by using newly available, tightly linked markers, which appear to identify non-penetrant males, the derived estimate of the degree of non-penetrance supports the results of the original segregation studies.¹⁴⁵ The polymorphic loci *DXS369*, *DXS296*, *DXS297*, *IDS*, and *DXS304* have been shown to map within a 0.06 recombination fraction of *FRAXA* in a large cohort of fragile X families.¹³² The demonstration of a lack of genetic heterogeneity for any of the linkage intervals and the observation that no differences exist in recombination rates between fragile X and normal families in this large data set¹⁴⁶ diminishes earlier fears of the unreliability of RFLPs for counselling purposes. For the majority of fragile X families at least one informative tightly linked marker is likely to be available¹³² and application of these RFLPs for carrier detection (in combination with cytogenetic examination) can now be undertaken. Prenatal diagnosis can be considered when informative flanking markers are available in a suitable family structure. However, both non-penetrance in males and the prediction of phenotype in carrier females represent problematic counselling issues. Penetrance data, related to the level of mental impairment in the mother, can aid in clarifying these phenotype predictions.¹⁴⁷

The resolving of the genetic map has enabled comparisons with the physical mapping data and appears now in closer agreement.¹⁴⁸ Fragile X appears to be the only XLMR condition in which cloning can be anticipated in the near future, with more rapid progress towards isolation of this intriguing mutation proceeding through a number of strategies to obtain candidate sequences, including microdissection¹⁴⁹ and contiguous yeast artificial chromosome cover of the region.¹⁵⁰

Genetic counselling of non-specific mental retardation

However, for the foreseeable future, the geneticist

Table 3 Isolated non-specific male mental retardation: recurrence risks to sibs.^{6 151}

Type of mental retardation in isolated male proband	Empirical recurrence risk		
	Brothers	Sisters	Overall
Severe idiopathic MR without fragile X syndrome	1 in 6	1 in 9	1 in 7
Mild idiopathic MR without fragile X syndrome	1 in 4	1 in 6	1 in 5

will continue to be asked to provide empirical recurrence risks for idiopathic MR in a male proband with no known family history. Caution is required in applying these figures to populations outside those from which they were derived, as is illustrated by the differences between the lower recurrence risk for MMR observed for Asian families when compared to non-Asian families.⁶ In addition, such data will always be subject to errors induced by an inevitable lack of complete ascertainment of MR. After exclusion of fragile X, the recurrence risk for sibs of an isolated fra(X) negative male proband are summarised in table 3.

When a pair of mentally retarded sibs who have neither fra(X) nor any other affected relatives is ascertained, an estimate of the chance of this being XLMR can be made. Frota-Pessoa *et al*¹⁵² gave theoretical reasons for stating that two similarly affected brothers were twice as likely to have an X linked condition rather than an autosomal recessive condition, and observations from British Columbia provide empirical data on sibs with non-specific MR which confirm these theoretical figures.¹² As fragile X syndrome may account for about one half of all cases of XLMR,²⁶ then it would be expected that about one half of all pairs of MR brothers (without fra(X) or other affected relatives) have XLMR and the remainder have autosomal recessive MR. This is consistent with the higher frequency of consanguinity observed in the parents with SMR offspring.²⁴

Although vital progress has been made in realising the contribution of X linked genes to the complex development of intelligence a vast amount of work remains both in extending the nosology of XLMR and in finely localising and ultimately defining the molecular pathology and the function of such genes.

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