

## REVIEW

## X linked mental retardation: a clinical guide

F L Raymond



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Mental retardation is more common in males than females in the population, assumed to be due to mutations on the X chromosome. The prevalence of the 24 genes identified to date is low and less common than expansions in FMR1, which cause Fragile X syndrome. Systematic screening of all other X linked genes in X linked families with mental retardation is currently not feasible in a clinical setting. The phenotypes of genes causing syndromic and non-syndromic mental retardation (NLGN3, NLGN4, RPS6KA3(RSK2), OPHN1, ATRX, SLC6A8, ARX, SYN1, AGTR2, MECP2, PQBP1, SMCX, and SLC16A2) are first discussed, as these may be the focus of more targeted mutation analysis. Secondly, the relative prevalence of genes causing only non-syndromic mental retardation (IL1RAPL1, TM4SF2, ZNF41, FTSJ1, DLG3, FAFL4, PAK3, ARHGEF6, FMR2, and GDI) is summarised. Thirdly, the problem of recurrence risk where a molecular genetics diagnosis has not been made and what proportion of the male excess of mental retardation is due to monogenic disorders of the X chromosome are discussed.

evaluation and educational, developmental, and medical history, they are extremely useful in assessing children. In the UK, the ICD-10 Classification of Mental and Behavioural Disorders<sup>7</sup> is used, while in the USA the DSM-IV diagnostic classification, which is similar to the WHO classification, is used.<sup>8</sup>

IQ across the population is normally distributed with the mean set at 100 and an IQ of <70 classified as mental retardation. Mild mental retardation is defined as an IQ of 50–70, moderate as an IQ of 35–49, severe as an IQ of 20–34, and profound as an IQ of <20. Approximately 2–3% of the population have mild to moderate intellectual disability and 0.5–1% of the population have moderate to severe mental retardation.

The publication in 1943 of the study by Martin and Bell<sup>9</sup> subsequently led to the identification of the first single gene defect where the phenotype was predominantly mental retardation, Fragile X syndrome.<sup>10</sup>

In 1991 Kerr *et al* identified families where no clinical features other than mental retardation were observed and where Fragile X syndrome was not the cause of disease. This phenomenon was termed non-specific X linked mental retardation (XLMR).<sup>11</sup> This then led to the classification of families with XLMR where a family was given an individual MRX number if linkage was performed and a LOD score >2.0 was obtained. The term MRX25 or MRX11 therefore has a precise meaning. To date MRX1 to MRX81 are recorded as individual families with XLMR, some of whom now have precise mutations identified in the literature ([http://xlmr.interfree.it/5\\_non.htm](http://xlmr.interfree.it/5_non.htm)).

#### DIAGNOSIS OF XLMR

The clinical diagnosis of XLMR is usually a diagnosis of exclusion of other causes of developmental delay in a male (table 1).<sup>12</sup> Only rarely does a new family present with sufficient affected males for a confident clinical diagnosis of XLMR to be made. All patients where XLMR is suspected should have the benefit of contemporary karyotype analysis at >550 banded resolution, as unbalanced autosomal translocations from balanced carriers can be misclassified as X linked if no male-to-male transmission is observed. Similarly, with the advent of subtelomeric analysis approximately 3–4% of familial mental retardation will be found to be due to submicroscopic telomeric deletions.<sup>13–16</sup> Mutation analysis for Fragile X syndrome is also essential.

Having excluded a karyotype abnormality and Fragile X syndrome by seeking an expansion in

In 1938 Lionel Penrose first observed that more males than females in the population are mentally retarded in a survey and classification of those in institutional care and their relatives.<sup>1</sup> The ratio of males to females was 1.25:1. This figure has been substantiated by numerous subsequent studies in the USA, Canada, Australia, and Europe and all agree with the observation of an approximately 30% excess of males being affected with mental retardation.<sup>2–6</sup>

The definition of mental retardation requires there to be significant sub-average general intellectual functioning (criterion A) that is accompanied by limitations in adaptive functioning in at least two of the following skill areas: communication, self care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety (criterion B). The onset must also occur before 18 years of age (criterion C). General intellectual functioning is defined by the intelligence quotient (IQ). Adaptive functioning refers to how effectively individuals cope with common life demands. Although these observations are less objective measures and rely on information gathered from independent sources, for example, teacher

Correspondence to:  
F Lucy Raymond,  
Cambridge Institute of  
Medical Research,  
Department of Medical  
Genetics, University of  
Cambridge,  
Addenbrooke's Hospital,  
Cambridge, CB2 2XY, UK;  
[flr24@cam.ac.uk](mailto:flr24@cam.ac.uk)

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**Table 1** Investigation of a male child with possible XLMR based on Shevell *et al*<sup>2</sup>

Obtain three generation pedigree and details of development of all possibly affected individuals  
 Obtain a detailed clinical history of maternal health pre-pregnancy  
 Pregnancy history  
 Birth history and birth height, weight and head circumference  
 Developmental milestones and growth rates  
 Neonatal PKU and hypothyroidism  
 Educational history and IQ  
 Examination for dysmorphic features and neurological signs  
 Karyotype analysis (550 banded resolution)  
 Fragile X  
 Telomere screen  
 Brain MRI if abnormal neurological findings or head circumference indicates microcephaly or macrocephaly  
 EEG to assist definition of epilepsy phenotype  
 Metabolic screen if clinically indicated. Consider urine and plasma screen of creatine/creatinine ratio where indicated and possible.  
 Consider free T<sub>3</sub> thyroid function tests if spastic paraplegin is present.

**Table 2** Additional clinical features found in syndromic XLMR

Characteristic	Gene
Microcephaly	ATRX, MECP2, PQBP1, SMCX
Cleft lip and palate	PQBP1
Congenital heart disease	PQBP1
Spastic paraplegia	SLC16A2, ATRX, SMCX, MECP2
Seizures	AGTR2, SYN1, ATRX, SLC6A8, ARX, SMCX
Absent speech	ATRX, SLC16A2, SLC6A8
Cerebellar hypoplasia	OPHN1
Short stature	PQBP1, SMCX
Autistic behaviour	NLGN3, NLGN4, AGTR2, SLC6A8
Dystonia	ARX
Hypertelorism	RSK2
Scoliosis	RSK2, ATRX
Abnormal thyroid function	SLC16A2

FMR1, 23 X linked genes remain where mutations have been described that result in either syndromic or non-syndromic mental retardation (fig 1). The decision as to which gene(s) to analyse depends on the identification of additional clinical features that could categorise the condition as syndromic (table 2) and the relative prevalence of the gene abnormality in the study population.

In this review a number of genes, the clinical features associated with the gene abnormality, and the prevalence of the disease gene will be discussed. Genes that are associated only with a syndrome are not discussed, for example LICAM, PLP1, and DCX, as the review is limited to those genes where both non-syndromic and syndromic phenotypes have been described, due to limitations of space. The original separation of genes causing syndromic disease from those causing non-syndromic mental retardation was useful in the early days of identifying new genes that cause mental retardation. Increasingly, this divide is becoming blurred and somewhat arbitrary as the range of phenotypes associated with any one gene, for example ARX (see below), is becoming increasingly varied. Nevertheless, this distinction still has some limited merit when categorising genes associated with mental retardation.

## SYNDROMIC XLMR

### Autism

A mutation was identified in NLGN3 (neuroligin 3; OMIM 300366) and NLGN4 (neuroligin 4, X linked; OMIM 300427) in two brother pairs with severe mental retardation and autism.<sup>17</sup> Since then a further family has been described, but mutations have not been identified in any large cohort of autistic children to date, suggesting that abnormalities in this gene are a rare cause of autism. In addition, all cases have been associated with severe mental retardation.<sup>18–20</sup> Routine testing is of unproven utility to date.

### Coffin Lowry

Mutations in RPS6KA3 (ribosomal protein S6 kinase, 90 kDa polypeptide 3; OMIM 300075), previously known as RSK2, are associated with Coffin Lowry syndrome.<sup>21</sup> Short stature, distinctive facies with a prominent forehead and coarse facies, hypertelorism, prominent lips, large soft hands with thickened tapering fingers, hypotonia, hyperextensibility, and skeletal changes are characteristic.<sup>22</sup> A single family with non-syndromic mental retardation has been reported with mutations in this gene, but recently mutations have been identified in three further families who did not meet the diagnostic criteria for Coffin Lowry syndrome (Raymond *et al*,

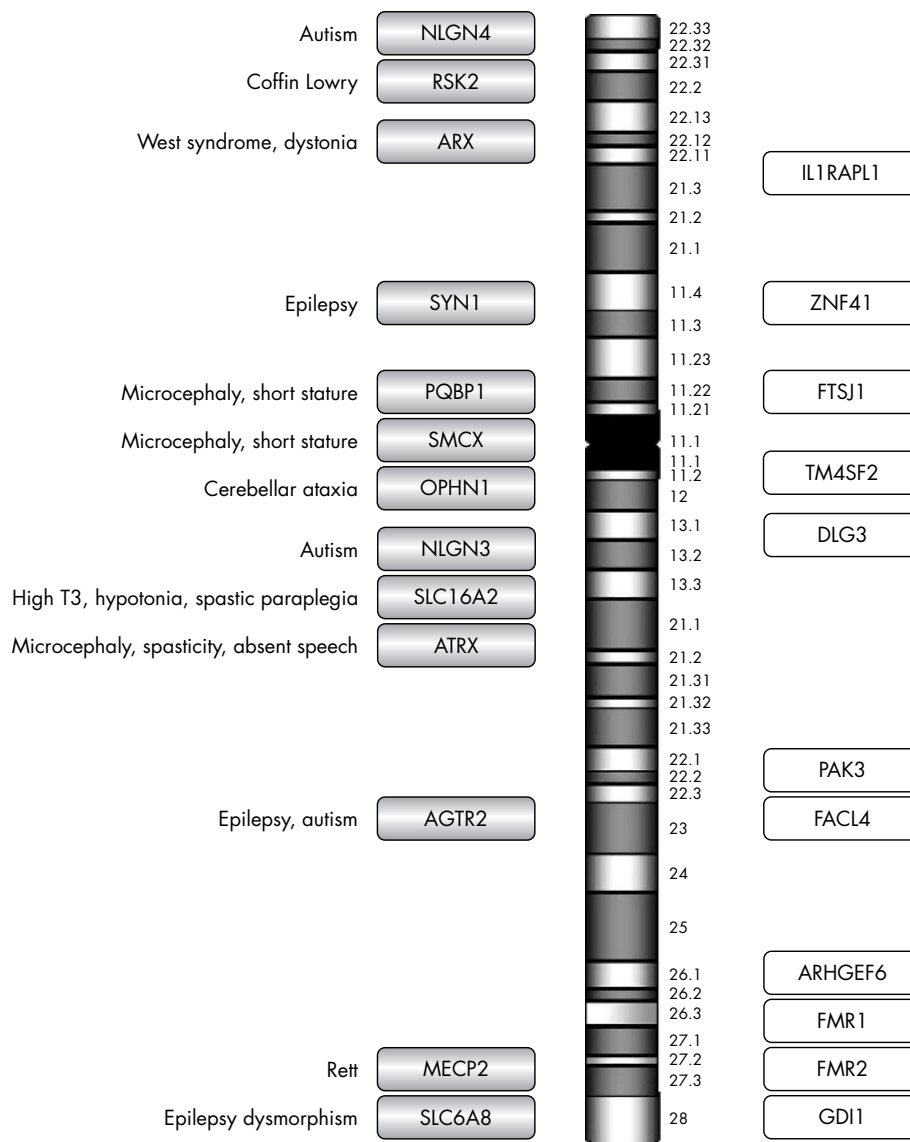
unpublished data).<sup>23</sup> This suggests that mutations in RPS6KA3 will prove to be a more common cause of XLMR and should be considered where the phenotype has some similarities. Testing therefore may yield further families.

### Cerebellar ataxia

Families with mutations in OPHN1 (oligophrenin 1; OMIM 300127) were initially described as having a non-syndromic mental retardation phenotype, but on re-evaluation the affected males were found to have significant reduction in the size of the cerebellum. None of the families presented with significant ataxia or cerebellar signs clinically and the subtle cerebellar phenotype was only revealed on closer investigation. Obligate females also have reduced cerebellar size and this condition is now regarded as a syndrome.<sup>24–25</sup> The prevalence of mutations in this gene is low, however systematic screening of this gene has not been performed in any large cohorts of patients with cerebellar hypoplasia or non-syndromic mental retardation. To date mutations have been described in two families, a patient with a translocation and a singleton with a similar phenotype to that of the familial cases.<sup>24–25</sup> Testing in non-syndromic mental retardation alone is of unproven utility, but screening this gene in families with X linked cerebellar hypoplasia may be considered.

### ATRX

X linked alpha thalassaemia was initially thought to be clinically homogenous, but mutation analysis of ATRX (alpha thalassaemia, mental retardation syndrome X linked; OMIM 300032) has found that the following conditions are all allelic: Juberg-Marsidi, Chudley-Lowry, Smith-Fineman-Myers, Carpenter-Waziri, Holmes-Gang, and Martinez. The phenotype is usually associated with severe mental retardation, commonly with absent speech, microcephaly, hypotonia, spasticity or seizures, and growth retardation with midface hypoplasia and skeletal abnormalities. A single large family has been reported with non-syndromic mental retardation alone where the proband did not have the characteristic facial features and profound intellectual disability associated with ATRX syndrome. Other affected members of the family did have the characteristic phenotype, suggesting that abnormalities of this gene show some intra-familial variation.<sup>26</sup> Testing for this gene abnormality initially by screening for the presence of HbH bodies is certainly valuable where there is a syndromic phenotype, but routine screening of this gene in non-syndromic mental retardation is not useful.



**Figure 1** Summary of genes on the X chromosome reported to cause XLMR. Shaded bars are syndromic XLMR genes; open bars are non-syndromic XLMR genes.

**Epilepsy**

Mental retardation in combination with epilepsy is relatively common, which means that the list of differential diagnoses remains long in cases that present with these two features. However, mutations in SLC6A8 (solute carrier family 6 (neurotransmitter transporter, creatine), member 8; OMIM 300036) are usually associated with epilepsy, severe mental retardation, and autistic spectrum behavioural problems with particular deficits in expressive speech and language often resulting in absent speech.<sup>27</sup> Recently, a systematic screen of 288 families with mental retardation and either with proven X linked inheritance or having two or more affected male family members revealed mutations in 6/288 (2.1%) families, suggesting that mutations in this gene are a relatively common cause of mental retardation, although still 10 times less frequent than Fragile X syndrome in familial cases.<sup>28-29</sup> The clinical features of these six families were not described in detail, so the presence or absence of epilepsy as a diagnostic criterion is not entirely clear. Patients with this condition have altered creatine/creatinine ratios and reduced creatine uptake. In future, the detection of this

condition using biochemical assays of plasma and urine will be an invaluable screen and mutation analysis will then be used as confirmation of disease in affected individuals.<sup>30-32</sup>

The identification of ARX (aristaless related homeobox; OMIM 300382) as a cause of West syndrome, mental retardation and either hypsarrythmia, myoclonic epilepsy, dystonia (Partington syndrome), lissencephaly, and abnormal genitalia or mental retardation alone has altered the previous somewhat rigid delineation of conditions as syndromic or non-syndromic, as the same mutation within this gene can lead to a wide variety of phenotypes.<sup>33-34</sup> Intracerebral cysts have also now been reported.<sup>35</sup> Problems associated with mood including aggression or depression were also a feature in some families. Within families where XLMR is highly suspected, the prevalence of mutations in this gene is relatively high at 9/136 (6.6%), but systematic screening of a larger cohort of smaller possible X linked families has revealed no mutations (0/151) and in further screening of affected singletons the prevalence is low (2/1501).<sup>36-38</sup> Testing is useful in syndromic mental retardation

and in familial cases of non-syndromic mental retardation but not in singleton cases.

A truncating mutation in *SYN1* (synapsin 1; OMIM 313440) has been reported in a single family with mental retardation and epilepsy.<sup>39</sup> This is not a common cause of mental retardation as more than 300 families with X linked or possible XLMR have now been screened and no new mutations have been identified to date (Raymond *et al*, unpublished data).

Mutations in *AGTR2* (angiotensin II receptor, type 2; OMIM 300034) have been described in 10 patients to date, but the same mutation p.G21V found in three patients appears to be a rare polymorphism and unlikely to be disease causing.<sup>40-42</sup> Severe mental retardation associated with epilepsy was present in the other cases reported with likely pathological mutations and two families had autistic behaviour. Testing is of unproven value to date.

### MECP2

The clinical spectrum seen in males with mutations in *MECP2* (methyl CpG binding protein 2 (Rett syndrome); OMIM 300005) include neonatal encephalopathy, Angelman syndrome, Rett syndrome, severe mental retardation with or without progressive spasticity, and manic depression as in PPM-X (mental retardation, psychosis, pyramidal signs, and macroorchidism X syndrome). Orrico *et al* reported a family where a mother had mild intellectual problems, a daughter had classic Rett syndrome, and four affected boys had severe mental retardation.<sup>43</sup> All family members have a missense mutation A140V in *MECP2*, suggesting that mutations in *MECP2* may be a common cause of mental retardation in males. Two further families were then reported, one with progressive spasticity and the other with PPM-X syndrome, where Q406X and A140V, respectively, were found to be the causative mutations.<sup>44-45</sup> This stimulated screening of male patients with severe mental retardation for mutations in *MECP2*. Many sequence changes have been identified, but few are disease causing as this gene is highly polymorphic. Recent cohort studies have identified one pathological mutation in almost 1000 samples (1/475 in a European consortium study, 0/300 in the Cambridge GOLD study cohort, and 0/>200 samples referred for testing of males with mental retardation to Wessex Clinical Genetics Laboratory, UK).<sup>46</sup> Mutations in *MECP2* are rare causes of non-syndromic mental retardation and sequence analysis should not be routinely offered but remains invaluable in the diagnosis of Rett syndrome and related disorders with a high diagnostic yield.

### SHORT STATURE AND MICROCEPHALY

Mutations in *PQBPI* (polyglutamine binding protein 1; OMIM 300463) have been published as a cause for XLMR, but all patients described to date have a range of syndromic features. Microcephaly, short stature, and mental retardation are common features, together with a variety of mid-line defects including anal atresia, situs inversus, congenital heart disease, cleft palate, ocular coloboma, and small testes. One patient had spastic paraplegia. The phenotypes in Renpenning syndrome, cerebropalatocardiac (Hamel) syndrome, and Sutherland Hann syndrome are similar and mutations in *PQBPI* have also been identified in these conditions, suggesting they are allelic.<sup>47-49</sup> No non-syndromic mental retardation patients have yet been described, but screening patients with the above clinical features would be useful.

Mutations in *SMCX* (Smcy homolog, X linked (mouse); OMIM 314690), previously known as *JARIDIC*, are also associated with short stature and microcephaly.<sup>50</sup> Of the seven families described, only one family has a normal head

circumference. Other frequent clinical features of this syndrome are small testes, prognathism or micrognathia, strabismus, myopia, facial hypotonia, progressive spastic paraplegia, epilepsy, and aggressive behaviour. Only one family had non-syndromic mental retardation and was relatively mildly affected compared to the others.<sup>50</sup>

### HIGH TRIIODOTHYRONINE CONCENTRATIONS (T<sub>3</sub>)

Mutations in *SLC16A2* (solute carrier family 16 (monocarboxylic acid transporter), member 2; OMIM 300095), also known as *MCT8*, a thyroid hormone transporter gene, were first reported in five unrelated boys with severe mental retardation and high triiodothyronine T<sub>3</sub> concentrations.<sup>51</sup> Two of the boys had partial deletions of the gene with a 24 kb deletion that encompassed exon 1 and a 2.4 kb deletion which resulted in a deletion of exon 3 and exon 4. The other three boys had missense mutations and a nonsense mutation.<sup>51</sup> Subsequently, two further families were reported with abnormal triiodothyronine (T<sub>3</sub>) levels, global developmental delay, central hypotonia, spastic paraplegia, dystonic movements, rotary nystagmus, and impaired hearing and gaze.<sup>52</sup> Children with Allan-Herndon-Dudley syndrome have a similar phenotype to that of the families reported by Dumitrescu *et al* and six large families have all been found to carry mutations, five missense and one 3 bp pair deletion.<sup>53</sup> These patients were all subsequently found to have associated abnormal T<sub>3</sub> levels although the neonatal Guthrie screens for hypothyroidism were normal. Abnormalities in this gene appear to be relatively common and suggest that in the diagnosis of profound mental retardation with neurological features detailed and continued surveillance of thyroid function tests may be helpful. This will aid the early identification of families who have mutations in this gene.

In the differential diagnosis of X linked spastic paraplegia (*SMCX*), *SCL16A2* should be considered together with *L1CAM* (OMIM 308840), *PLP1* (OMIM 300401), *MECP2*, and *ARX*.

### NON-SYNDROMIC MENTAL RETARDATION GENES

Nine genes have been identified where the clinical feature of the families is mental retardation alone: *IL1RAPL1*, *TM4SF2*, *ZNF41*, *FTSJ1*, *DLG3*, *FACL4*, *PAK3*, *ARHGEF6*, *FMR2*, and *GDI*. To date, no detailed comparative prevalence studies have been published for abnormalities in these genes. The prevalence of Fragile X syndrome in affected sib pairs and X linked families is approximately 12/45 (27%), although this figure predates molecular genetic analysis and is likely to be an overestimate.<sup>29-54</sup> The prevalence of each of the non-syndromic genes is 1-2% in selected research samples where at least two males are affected in the family pedigree.

*IL1RAPL1* (interleukin 1 receptor accessory protein-like 1; OMIM 300206) was first identified as a candidate gene for mental retardation after the finding of deletions in families with mental retardation, adrenal hypoplasia, Duchenne muscular dystrophy, and glycerol kinase deficiency. Initially, a mutation was identified in 1/20 small XLMR families screened and no mutations were found in five large X linked families.<sup>55</sup> Since then a complex rearrangement of this gene has been described, but no new mutations have been found.<sup>56</sup>

A translocation disrupting *TM4SF2* (OMIM 300096), now known as *TSPAN7* (tetraspanin 7), identified this gene as a potential cause of mental retardation. Mutations in this gene were also identified in 2/33 small families and 0/3 large families, but no further mutations have been reported since.<sup>57</sup> More recently, the significance of the missense mutation p.P172H in one of the families has been questioned, although it has been reported in another case of a singleton with mild

to moderate mental retardation but without family follow-up studies being carried out.<sup>58 59</sup>

Disruption of ZNF41 (zinc finger protein 41; OMIM 314995) in a child with mental retardation and a balanced X autosome translocation identified this as a candidate gene. Screening of a panel of 210 families with XLMR identified one missense and one splice site mutation which are likely to be pathological.<sup>60</sup>

Mutations in FTSJ1 (Fts J homolog (*Escherichia coli*); OMIM 300499) have been found in 2/219 small X linked families and 2/30 linked families. Three mutations affect splicing and one is a missense mutation.<sup>61 62</sup>

Four truncating mutations in DLG3 (discs, large homolog 3 (neuroendocrine-dlg, *Drosophila*); OMIM 300189) have been identified in a cohort of 328 families with XLMR.<sup>63</sup> All the affected males in the families had moderate to severe mental retardation while female carriers were usually of normal intellect. X inactivation studies showed no skewing of lymphocytes in obligate female carriers.<sup>63</sup>

Mutations in FAFL4 (renamed ACSL4, acyl-CoA synthetase long-chain family member 4; OMIM 300157) have been reported. These are two missense and one splice site mutation that reduce the enzymatic activity.<sup>64 65</sup> The gene was originally localised by characterising genomic deletions in patients with Alport's syndrome and mental retardation.<sup>66 67</sup>

Since the identification of a truncating mutation in PAK3 (p21(CDKN1A) activated kinase 3; OMIM 300142), two further missense mutations have been described.<sup>68-70</sup> Only a few families have been screened to date. The initial study screened 18 families, all of whom had positive linkage data that mapped the gene abnormality in the family to Xq21, but no systematic prevalence data are available for this gene.

Disruption of ARHGEF6 (Rac/Cdc42 guanine nucleotide exchange factor (GEF) 6; OMIM 300267) in a balanced translocation patient and the identification of a single intronic IVS1-11T>C mutation in 1/119 mentally retarded patients have been described to date.<sup>71</sup>

FMR2 was identified by characterising the genomic structure around the folate sensitive fragile site, FRAXE.<sup>72 73</sup> The official name for this gene is AFF2 (AF4/FMR2 family, member 2; OMIM 309548). Two unrelated boys with mental retardation had submicroscopic deletions in this region and facilitated the localisation of the gene. Subsequently, two families were identified, one of whom was also found to have FRAXA. The penetrance of FMR2 is variable and the phenotype can be mild or borderline mental retardation. Currently most diagnostic laboratories offer a PCR based screen for expansions in this gene. Specific Southern blot analysis can then be performed if the diagnosis is suspected. The prevalence is rare compared to Fragile X syndrome and interpretation of results is sometimes difficult.<sup>74-77</sup>

Three mutations in GDI1 (GDP dissociation inhibitor 1; OMIM 300104) have been characterised. Two out of five X linked families with linkage data mapping to Xq28 have mutations and 1/164 males with non-familial mental retardation have been screened and found to carry a mutation.<sup>78 79</sup>

Finally, Fragile X syndrome should be considered as a frequent cause of non-syndromic mental retardation as the classic phenotype of mental retardation, macrocephaly, frontal bossing, large ears, prominent mandible with prognathism, and enlarged testes is rarely seen. The prevalence of an expansion in the 5'CGG repeat of FMR1 (fragile X mental retardation 1; OMIM 309550) in the population in an unselected sample of mainly singletons is 1/3500-1/9000 and many of the affected individuals have a non-syndromic phenotype.<sup>80 81</sup>

**RECURRENCE RISKS FOR MENTAL RETARDATION**

Where a molecular genetic diagnosis has been made, accurate genetic advice can usually be given. Unfortunately, this is still rarely the case when a family presents in a clinic and recurrence risks need to be quantified. Much of the available data were published between 1971 and 1987<sup>82-86</sup> (table 3) and although the observations of recurrence risks of 2-14% are still valid, the quality of chromosome analysis, the advent of molecular genetic testing for Fragile X syndrome, and the improved clinical expertise in syndromic identification question the validity of some of these data.<sup>87</sup> A recent population based study in Atlanta, USA discusses contemporary recurrence risks for developmental delay although the sample was relatively old by contemporary molecular and cytogenetic standards. The sample was based on children born to mothers between 1981 and 1991 and the total number of cases with a disability was 3685. Recurrence risks for isolated mental retardation were 8.4% if the first child had isolated mental retardation as compared with recurrence risks for cerebral palsy of 2.9-3.6%, hearing loss of 4.7-5.7%, and vision impairment of 5.3-6.9%. If the first child had mild mental retardation, recurrence risks for mild and severe mental retardation were 7.1% and 4.7%, respectively.<sup>88</sup>

Where detailed clinical assessment is possible and current molecular genetic and cytogenetic analysis is available, the calculations of Turner and Partington are an additional useful guide for calculating recurrence risks.<sup>89</sup> These authors observed recurrence risks for mental retardation in the siblings of index cases referred to a genetics centre. Observed recurrences were 1:7.5 (11/83) for brother pairs and 1:20 (3/60) for sister pairs. These figures are comparable to those of Herbst and Miller from 1980 and those from the Colchester cohort collected by L Penrose and revisited by Morton *et al.*<sup>90 91</sup> The calculated offspring risk to intellectually normal siblings of a single affected male were 1-2% for the offspring of a normal male sibling and 2-5% for the offspring of a sister. The figures include the risk of an undetected familial cryptic translocation and, for the sister, the estimated risk that disease in a singleton male brother is due to an X linked disease (~25%). If there are two affected males in a family, the assumption is that ~80% (the male excess) is due to X linked disease. The offspring risk to a normal brother remains the same as the risk of an undetected familial cryptic translocation, as above, whereas the offspring risk to an unaffected sister if there are two affected males is

**Table 3** Summary of published recurrence risks for mental retardation by sex of proband

Reference	Affected male			Affected female		
	Brother	Sister	All siblings	Brother	Sister	All siblings
Turner <i>et al</i> <sup>82</sup>			2-9%			3.5-4%
Bundey <i>et al</i> <sup>83</sup>	6.7%	3.2%	5%	4.4%	6.3%	5.4%
Herbst <i>et al</i> <sup>84</sup>	6%	2.3%	4.3%	2.9%	5.6%	4.2%
Bundey <i>et al</i> <sup>85</sup>	10%	5%	7.5%			
Costeff <i>et al</i> <sup>86</sup>	14%	14%	14%	9.6%	9.6%	9.2%
Van Naarden Braun <i>et al</i> <sup>88</sup>			8.4%			8.4%

significantly higher at 10% to include the X linked disease risk. Although this guide is useful, the calculations are inevitably inaccurate as they are biased by ascertainment of families in a clinical genetics setting and assume that the majority of male sib pairs have X linked disease.

Mandel and Chelly have addressed the issue of whether the observed male excess of patients with mental retardation is due entirely to mutations in monogenic disease genes on the X chromosome or not.<sup>37</sup> Observing the prevalence of a 24 bp expansion in ARX, they observed that 6.6% (9/136) of families with XLMR pedigrees but only 0.13% (2/1501) of singleton cases were found to carry this mutation. Based on this observation, they calculate that only ~10% of the excess males observed are due to X linked genes. This observation does not alter the practical clinical recurrence risks we inform patients about, but suggests that the identification of the cause of mental retardation in some families, especially where a single generation is affected, will be even harder to elucidate. Accurate genetic counselling of those families where no mutation is identified will continue to be challenging in the future. The use and predictive value of predisposing alleles or polymorphisms in clinical practice is extremely limited and this situation is not likely to change. Furthermore, this suggests that genetic counselling should clearly distinguish families with an X linked pedigree from those where a single generation is affected and provide appropriate recurrence risks based on the probability of there being an X linked condition in the family.

To date more than 20 genes have been identified that cause XLMR. Estimates of the number of genes that remain to be identified vary considerably from 30 to 50.<sup>92-94</sup> Until all the genes on the X chromosome have been scrutinised in a large sample cohort, the exact number of XLMR genes will remain unknown, as will the prevalence and importance of each gene as a cause of human mental retardation. The future challenge is to understand the molecular genetic basis of the observed excess of mentally retarded males, discover the autosomal causes of mental retardation, and determine the biological basis of this disease in each gene abnormality identified.

In summary, Fragile X syndrome remains the most common XLMR gene discovered so far. Syndromic features should always be sought in possible XLMR as this can lead to molecular diagnosis. The discovery of the plethora of genes that cause a small proportion of non-syndromic XLMR has clinical value for those families where mutations are detected, but awaits the arrival of high throughput, cheap, and reliable sequence analysis methods that can be readily introduced to clinical service.

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## ELECTRONIC-DATABASE INFORMATION



The names and symbols used in this review are those agreed by the HUGO nomenclature committee (<http://www.gene.ucl.ac.uk/nomenclature>). MRX families are listed at [http://xlmr.interfree.it/5\\_non.htm](http://xlmr.interfree.it/5_non.htm).

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## REFERENCES

- 1 Penrose L. *A clinical and genetic study of 1280 cases of mental defect*, vol 229. London: HMSO, 1938.
- 2 Drillien CM. The incidence of mental and physical handicaps in school age children of very low birth weight. II. *Pediatrics* 1967;**39**(2):238-47.
- 3 McLaren J, Bryson SE. Review of recent epidemiological studies of mental retardation: prevalence, associated disorders, and etiology. *Am J Ment Retard* 1987;**92**(3):243-54.
- 4 Baird PA, Sadovnick AD. Mental retardation in over half-a-million consecutive livebirths: an epidemiological study. *Am J Ment Defic* 1985;**89**(4):323-30.
- 5 Stevenson RE, Schwartz C, Schroer R. Mental retardation in South Carolina. I. Characteristics of the study population. *Proc Greenwood Genet Center* 1996;**15**:26.
- 6 Stoller A. Epidemiology of mental deficiency in Victoria. In: JD Van Zelt, ed. *Proceedings of the Fourth Interstate Conference on Mental Deficiency*. Melbourne, Australia: Australian Group for the Scientific Study of Mental Deficiency, 1965:18-28.
- 7 WHO. *The ICD-10 classification of mental and behavioural disorders*. Geneva: WHO, 1992.
- 8 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders DSM-IV*. Washington, DC: American Psychiatric Association, 1994.
- 9 Martin JP, Bell J. A pedigree of mental defect showing sex-linkage. *J Neurol Psychiatry* 1943;**6**:154.
- 10 Oberle I, Rousseau F, Heitz D, Kretz C, Devys D, Hanauer A, Boue J, Bertheas MF, Mandel JL. Instability of a 550-base pair DNA segment and abnormal methylation in fragile X syndrome. *Science* 1991;**252**(5010):1097-102.
- 11 Kerr B, Turner G, Mulley J, Gedeon A, Partington M. Non-specific X linked mental retardation. *J Med Genet* 1991;**28**(6):378-82.
- 12 Shevell M, Ashwal S, Donley D, Flint J, Gingold M, Hirtz D, Majnemer A, Noetzel M, Sheth RD. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. *Neurology* 2003;**60**(3):367-80.
- 13 Knight SJ, Regan R, Nicod A, Horsley SW, Kearney L, Homfray T, Winter RM, Bolton P, Flint J. Subtle chromosomal rearrangements in children with unexplained mental retardation. *Lancet* 1999;**354**(9191):1676-81.
- 14 Slavotinek A, Rosenberg M, Knight S, Gaunt L, Fergusson W, Killoran C, Clayton-Smith J, Kingston H, Campbell RH, Flint J, Donnai D, Biesecker L. Screening for submicroscopic chromosome rearrangements in children with idiopathic mental retardation using microsatellite markers for the chromosome telomeres. *J Med Genet* 1999;**36**(5):405-11.
- 15 Koolen DA, Nillesen WM, Versteeg MH, Merckx GF, Knoers NV, Kets M, Vermeer S, van Ravenswaaij CM, de Kovel CG, Brunner HG, Smeets D, de Vries BB, Sistermans EA. Screening for subtelomeric rearrangements in 210 patients with unexplained mental retardation using multiplex ligation dependent probe amplification (MLPA). *J Med Genet* 2004;**41**(12):892-9.
- 16 Flint J, Knight S. The use of telomere probes to investigate submicroscopic rearrangements associated with mental retardation. *Curr Opin Genet Dev* 2003;**13**(3):310-16.
- 17 Jamain S, Quach H, Betancur C, Rastam M, Colineaux C, Gillberg IC, Soderstrom H, Giros B, Leboyer M, Gillberg C, Bourgeron T, Paris Autism Research International Sibpair Study. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat Genet* 2003;**34**(1):27-9.
- 18 Laumonnier F, Bonnet-Brilhault F, Gomot M, Blanc R, David A, Moizard MP, Raynaud M, Ronce N, Lemonnier E, Calvas P, Laudier B, Chelly J, Fryns JP, Ropers HH, Hamel BC, Andres C, Barthelemy C, Moraine C, Briault S. X-linked mental retardation and autism are associated with a mutation in the NLGN4 gene, a member of the neuroligin family. *Am J Hum Genet* 2004;**74**(3):552-7.
- 19 Gauthier J, Bonnel A, St-Onge J, Karemera L, Laurent S, Mottron L, Fombonne E, Jaober R, Rouleau GA. NLGN3/NLGN4 gene mutations are not responsible for autism in the Quebec population. *Am J Med Genet B Neuropsychiatr Genet* 2005;**132**(1):74-5.
- 20 Vincent JB, Kolozsvari D, Roberts WS, Bolton PF, Gurling HM, Scherer SW. Mutation screening of X-chromosomal neuroligin genes: no mutations in 196 autism probands. *Am J Med Genet B Neuropsychiatr Genet* 2004;**129**(1):82-4.
- 21 Trivier E, De Cesare D, Jacquot S, Pannetier S, Zackai E, Young I, Mandel JL, Sassone-Corsi P, Hanauer A. Mutations in the kinase Rsk-2 associated with Coffin-Lowry syndrome. *Nature* 1996;**384**(6609):567-70.
- 22 Hanauer A, Young ID. Coffin-Lowry syndrome: clinical and molecular features. *J Med Genet* 2002;**39**(10):705-13.
- 23 Merienne K, Jacquot S, Pannetier S, Zeniou M, Bankier A, Geçez J, Mandel JL, Mulley J, Sassone-Corsi P, Hanauer A. A missense mutation in RPS6KA3 (RSK2) responsible for non-specific mental retardation. *Nat Genet* 1999;**22**(1):13-14.
- 24 Billuart P, Bienvu T, Ronce N, des Portes V, Vinet MC, Zemni R, Roest Crollius H, Carrie A, Fauchereau F, Cherry M, Briault S, Hamel B, Fryns JP, Beldjord C, Kahn A, Moraine C, Chelly J. Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation. *Nature* 1998;**392**(6679):923-6.
- 25 Philip N, Chabrol B, Lissi AM, Cardoso C, Guerrini R, Dobyns WB, Raybaud C, Villard L. Mutations in the oligophrenin-1 gene (OPHN1) cause X linked congenital cerebellar hypoplasia. *J Med Genet* 2003;**40**(6):441-6.
- 26 Guerrini R, Shanahan JL, Carrozzo R, Bonanni P, Higgs DR, Gibbons RJ. A nonsense mutation of the ATRX gene causing mild mental retardation and epilepsy. *Ann Neurol* 2000;**47**(1):117-21.

- 27 **Salomons GS**, van Dooren SJ, Verhoeven NM, Cecil KM, Ball WS, Degrauw TJ, Jakobs C. X-linked creatine-transporter gene (SLC6A8) defect: a new creatine-deficiency syndrome. *Am J Hum Genet* 2001;**68**(6):1497–500.
- 28 **Rosenberg EH**, Almeida LS, Kleefstra T, deGrauw RS, Yntema HG, Bahi N, Moraine C, Ropers HH, Fryns JP, deGrauw TJ, Jakobs C, Salomons GS. High prevalence of SLC6A8 deficiency in X-linked mental retardation. *Am J Hum Genet* 2004;**75**(1):97–105.
- 29 **Mandel JL**. Comparative frequency of fragile-X (FMR1) and creatine transporter (SLC6A8) mutations in X-linked mental retardation. *Am J Hum Genet* 2004;**75**(4):730–1; author reply, 731–2.
- 30 **Carducci C**, Birarelli M, Leuzzi V, Carducci C, Battini R, Cioni G, Antonozzi I. Guanidinoacetate and creatine plus creatinine assessment in physiologic fluids: an effective diagnostic tool for the biochemical diagnosis of arginine:glycine amidinotransferase and guanidinoacetate methyltransferase deficiencies. *Clin Chem* 2002;**48**(10):1772–8.
- 31 **Arias A**, Garcia-Villoria J, Ribes A. Guanidinoacetate and creatine/creatinine levels in controls and patients with urea cycle defects. *Mol Genet Metab* 2004;**82**(3):220–3.
- 32 **Cognat S**, Cheillan D, Piraud M, Roos B, Jakobs C, Vianey-Saban C. Determination of guanidinoacetate and creatine in urine and plasma by liquid chromatography-tandem mass spectrometry. *Clin Chem* 2004;**50**(8):1459–61.
- 33 **Stromme P**, Mangelsdorf ME, Shaw MA, Lower KM, Lewis SM, Bruyere H, Lutchera V, Gedeon AK, Wallace RH, Scheffer IE, Turner G, Partington M, Frints SG, Fryns JP, Sutherland GR, Mulley JC, Gezcz J. Mutations in the human ortholog of *Aristaless* cause X-linked mental retardation and epilepsy. *Nat Genet* 2002;**30**(4):441–5.
- 34 **Kitamura K**, Yanazawa M, Sugiyama N, Miura H, Iizuka-Kogo A, Kusaka M, Omichi K, Suzuki R, Kato-Fukuyui Y, Kamiirisa K, Matsuo M, Kamijo S, Kasahara M, Yoshioka H, Ogata T, Fukuda T, Kondo I, Kato M, Dobyns WB, Yokoyama M, Morohashi K. Mutation of ARX causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. *Nat Genet* 2002;**32**(3):359–69.
- 35 **Stromme P**, Bakke SJ, Dahl A, Gezcz J. Brain cysts associated with mutation in the *Aristaless* related homeobox gene, ARX. *J Neural Neurosurg Psychiatry* 2003;**74**(4):536–8.
- 36 **Bienvenu T**, Poirier K, Friocourt G, Bahi N, Beaumont D, Fauchereau F, Ben Jeema L, Zemni R, Vinet MC, Francis F, Couvert P, Gomot M, Moraine C, van Bokhoven H, Kalscheuer V, Frints S, Gezcz J, Ohzaki K, Chaabouni H, Fryns JP, Desportes V, Beldjord C, Chelly J. ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation. *Hum Mol Genet* 2002;**11**(8):981–91.
- 37 **Mandel JL**, Chelly J. Monogenic X-linked mental retardation: is it as frequent as currently estimated? The paradox of the ARX (*Aristaless X*) mutations. *Eur J Hum Genet* 2004;**12**(9):689–93.
- 38 **Gronskov K**, Hjalgrim H, Nielsen IM, Brondum-Nielsen K. Screening of the ARX gene in 682 retarded males. *Eur J Hum Genet* 2004;**12**(9):701–5.
- 39 **Garcia CC**, Blair HJ, Seager M, Coulthard A, Tennant S, Buddles M, Curtis A, Goodship JA. Identification of a mutation in synapsin I, a synaptic vesicle protein, in a family with epilepsy. *J Med Genet* 2004;**41**(3):183–6.
- 40 **Vervoort VS**, Beachem MA, Edwards PS, Ladd S, Miller KE, de Mollerat X, Clarkon K, DuPont B, Schwartz CE, Stevenson RE, Boyd E, Srivastava AK. AGTR2 mutations in X-linked mental retardation. *Science* 2002;**296**(5577):2401–3.
- 41 **Ylisaukko-oja T**, Rehstrom K, Vanhala R, Tengstrom C, Lahdetie J, Jarvela I. Identification of two AGTR2 mutations in male patients with non-syndromic mental retardation. *Hum Genet* 2004;**114**(2):211–3.
- 42 **Erdmann J**, Dahmlow S, Guse M, Helzer R, Regitz-Zagrosek V. The assertion that a G21V mutation in AGTR2 causes mental retardation is not supported by other studies. *Hum Genet* 2004;**114**(4):369; author reply, 397.
- 43 **Orrico A**, Lam C, Galli L, Dotti MT, Hayek G, Tong SF, Poon PM, Zappella M, Federico A, Sorrentino V. MECP2 mutation in male patients with non-specific X-linked mental retardation. *FEBS Lett* 2000;**481**(3):285–8.
- 44 **Meloni I**, Bruttini M, Longo I, Mari F, Rizzolio F, D'Adamo P, Denriendt K, Fryns JP, Toniolo D, Renieri A. A mutation in the *ret* syndrome gene, MECP2, causes X-linked mental retardation and progressive spasticity in males. *Am J Hum Genet* 2000;**67**(4):982–5.
- 45 **Klauck SM**, Lindsay S, Beyer KS, Splitt M, Burn J, Poustka A. A mutation hot spot for nonspecific X-linked mental retardation in the MECP2 gene causes the PPM-X syndrome. *Am J Hum Genet* 2002;**70**(4):1034–7.
- 46 **Poirier K**, Francis F, Hamel B, Moraine C, Fryns JP, Ropers HH, Chelly J, Bienvenu T. Mutations in exon 1 of MECP2B are not a common cause of X-linked mental retardation in males. *Eur J Hum Genet* 2005;**13**(5):523–4.
- 47 **Kalscheuer VM**, Freude K, Musante L, Jensen LR, Yntema HG, Gezcz J, Sefiani A, Hoffmann K, Moser B, Haas S, Gurok U, Haesler S, Aranda B, Nshedian A, Tzschach A, Hartmann N, Roloff TC, Shoichet S, Hagens O, Tao J, Van Bokhoven H, Turner G, Chelly J, Moraine C, Fryns JP, Nuber U, Hoelzenbein M, Scharff C, Scherthan H, Lenzner S, Hamel BC, Schweiger S, Ropers HH. Mutations in the polyglutamine binding protein 1 gene cause X-linked mental retardation. *Nat Genet* 2003;**35**(4):313–5.
- 48 **Lenski C**, Abidi F, Meindl A, Gibson A, Platzer M, Frank Kooy R, Lubs HA, Stevenson RE, Ramser J, Schwartz CE. Novel truncating mutations in the polyglutamine tract binding protein 1 gene (PQBP1) cause Renpenning syndrome and X-linked mental retardation in another family with microcephaly. *Am J Hum Genet* 2004;**74**(4):777–80.
- 49 **Kleefstra T**, Franken CE, Arens YH, Ramakers GJ, Yntema HG, Sistermans EA, Hulsman CF, Nillesen WN, van Bokhoven H, de Vries BB, Hamel BC. Genotype-phenotype studies in three families with mutations in the polyglutamine-binding protein 1 gene (PQBP1). *Clin Genet* 2004;**66**(4):318–26.
- 50 **Jensen LR**, Amende M, Gurok U, Moser B, Gimmel V, Tzschach A, Janecke AR, Tariverdian G, Chelly J, Fryns JP, Van Esch H, Kleefstra T, Hamel B, Moraine C, Gezcz J, Turner G, Reinhardt R, Kalscheuer VM, Ropers HH, Lenzner S. Mutations in the *JARID1C* gene, which is involved in transcriptional regulation and chromatin remodeling, cause X-linked mental retardation. *Am J Hum Genet* 2005;**76**(2):227–36.
- 51 **Frie sema EC**, Grueters A, Biebertmann H, Krude H, von Moers A, Reeser M, Barrett TG, Mancilla EE, Svensson J, Kester MH, Kuiper GG, Balkasmi S, Uitterlinden AG, Koehle J, Rodien P, Haleshtar AP, Visser TJ. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. *Lancet* 2004;**364**(9443):1435–7.
- 52 **Dumitrescu AM**, Liao XH, Best TB, Brockmann K, Refetoff S. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. *Am J Hum Genet* 2004;**74**(1):168–75.
- 53 **Schwartz CE**, May MM, Carpenter NJ, Rogers RC, Martin J, Bialer MG, Ward J, Sanabria J, Marsa S, Lewis JA, Echeverri R, Lubs HA, Voeller K, Simensen RJ, Stevenson RE. Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene. *Am J Hum Genet* 2005;**77**(1):41–53.
- 54 **Fishburn J**, Turner G, Daniel A, Brookwell R. The diagnosis and frequency of X-linked conditions in a cohort of moderately retarded males with affected brothers. *Am J Med Genet* 1983;**14**(4):713–24.
- 55 **Carrie A**, Jun L, Bienvenu T, Vinet MC, McDonnell N, Couvert P, Zemni R, Cardona A, Van Buggenhout G, Frints S, Hamel B, Moraine C, Ropers HH, Strom T, Howell GR, Whittaker A, Ross MT, Kahn A, Fryns JP, Beldjord C, Marynen P, Chelly J. A new member of the IL-1 receptor family highly expressed in hippocampus and involved in X-linked mental retardation. *Nat Genet* 1999;**23**(1):25–31.
- 56 **Wheway JM**, Yau SC, Nihalani V, Ellis D, Irving M, Splitt M, Roberts RG. A complex deletion-inversion-deletion event results in a chimeric IL1RAPL1-dystrophin transcript and a contiguous gene deletion syndrome. *J Med Genet* 2003;**40**(2):127–31.
- 57 **Zemni R**, Bienvenu T, Vinet MC, Sefiani A, Carrie A, Billuart P, McDonnell N, Couvert P, Francis F, Chafey P, Fauchereau F, Friocourt G, des Portes V, Cardona A, Frints S, Meindl A, Brandau O, Ronce N, Moraine C, van Bokhoven H, Ropers HH, Sudbrak R, Kahn A, Fryns JP, Beldjord C, Chelly J. A new gene involved in X-linked mental retardation identified by analysis of an X;2 balanced translocation. *Nat Genet* 2000;**24**(2):167–70.
- 58 **Gomot M**, Ronce N, Dessay S, Zemni R, Ayrault AD, Moizard MP, Nivelon A, Gilgenkrantz S, Dourlens J, Des Portes V, Chelly J, Moraine C. TM4SF2 gene involvement reconsidered in an XLMR family after neuropsychological assessment. *Am J Med Genet* 2002;**112**(4):400–4.
- 59 **Maranduba CM**, Sa Moreira E, Muller Orabona G, Pavanello RC, Vianna Morgante AM, Passos-Bueno MR. Does the P172H mutation at the TM4SF2 gene cause X-linked mental retardation? *Am J Med Genet A* 2004;**124**(4):413–15.
- 60 **Shoichet SA**, Hoffmann K, Menzel C, Trautmann U, Moser B, Hoelzenbein M, Echenne B, Partington M, Van Bokhoven H, Moraine C, Fryns JP, Chelly J, Rott HD, Ropers HH, Kalscheuer VM. Mutations in the ZNF41 gene are associated with cognitive deficits: identification of a new candidate for X-linked mental retardation. *Am J Hum Genet* 2003;**73**(6):1341–54.
- 61 **Freude K**, Hoffmann K, Jensen LR, Delatycki MB, des Portes V, Moser B, Hamel B, van Bokhoven H, Moraine C, Fryns JP, Chelly J, Gezcz J, Lenzner S, Kalscheuer VM, Ropers HH. Mutations in the FTSJ1 gene coding for a novel S-adenosylmethionine-binding protein cause nonsyndromic X-linked mental retardation. *Am J Hum Genet* 2004;**75**(2):305–9.
- 62 **Ramser J**, Winnepenninckx B, Lenski C, Errigiers V, Platzer M, Schwartz CE, Meindl A, Kooy RF. A splice site mutation in the methyltransferase gene FTSJ1 in Xp11.23 is associated with non-syndromic mental retardation in a large Belgian family (MRX9). *J Med Genet* 2004;**41**(9):679–83.
- 63 **Tarpey P**, Parnau J, Blow M, Woffendin H, Bignell G, Cox C, Cox J, Davies H, Edkins S, Holden S, Kornly A, Mallya U, Moon J, O'Meara S, Parker A, Stephens P, Stevens C, Teague J, Donnelly A, Mangelsdorf M, Mulley J, Partington M, Turner G, Stevenson R, Schwartz C, Young I, Easton D, Bobrow M, Futreal PA, Stratton MR, Gezcz J, Wooster R, Raymond FL. Mutations in the DLG3 gene cause nonsyndromic X-linked mental retardation. *Am J Hum Genet* 2004;**75**(2):218–324.
- 64 **Meloni I**, Muscettola M, Raynaud M, Longo I, Bruttini M, Moizard MP, Gomot M, Chelly J, des Portes V, Fryns JP, Ropers HH, Maggi B, Bellan C, Volpi N, Yntema HG, Lewis SE, Schaffer JE, Renieri A. FAFL4, encoding fatty acid-CoA ligase 4, is mutated in nonspecific X-linked mental retardation. *Nat Genet* 2002;**30**(4):436–40.
- 65 **Longo I**, Frints SG, Fryns JP, Meloni I, Pescucci C, Ariani F, Borghgraef M, Raynaud M, Marynen P, Schwartz C, Renieri A, Froyen G. A third MRX family (MRX68) is the result of mutation in the long chain fatty acid-CoA ligase 4 (FAFL4) gene: proposal of a rapid enzymatic assay for screening mentally retarded patients. *J Med Genet* 2003;**40**(1):11–17.
- 66 **Jonsson JJ**, Renieri A, Gallagher PG, Kashtan CE, Cherniske EM, Bruttini M, Piccini M, Vitelli F, Ballabio A, Pober BR. Alport syndrome, mental retardation, midface hypoplasia, and elliptocytosis: a new X linked contiguous gene deletion syndrome? *J Med Genet* 1998;**35**(4):273–8.
- 67 **Piccini M**, Vitelli F, Bruttini M, Pober BR, Jonsson JJ, Villanova M, Zollo M, Borsani G, Ballabio A, Renieri A. FAFL4, a new gene encoding long-chain acyl-CoA synthetase 4, is deleted in a family with Alport syndrome, elliptocytosis, and mental retardation. *Genomics* 1998;**47**(3):350–8.
- 68 **Allen KM**, Gleeson JG, Bagrodia S, Partington MW, MacMillan JC, Cerione RA, Mulley JC, Walsh CA. PAK3 mutation in nonsyndromic X-linked mental retardation. *Nat Genet* 1998;**20**(1):25–30.
- 69 **Bienvenu T**, des Portes V, McDonnell N, Carrie A, Zemni R, Couvert P, Ropers HH, Moraine C, van Bokhoven H, Fryns JP, Allen K, Walsh CA, Boue J,

- Kahn A, Chelly J, Beldjord C. Missense mutation in PAK3, R67C, causes X-linked nonspecific mental retardation. *Am J Med Genet* 2000;**93**(4):294–8.
- 70 **Gedeon AK**, Nelson J, Geetz J, Mulley JC. X-linked mild non-syndromic mental retardation with neuropsychiatric problems and the missense mutation A365E in PAK3. *Am J Med Genet* 2003;**120A**(4):509–17.
- 71 **Kutsche K**, Yntema H, Brandt A, Jantke I, Nothwang HG, Orth U, Boavida MG, David D, Chelly J, Fryns JP, Moraine C, Ropers HH, Hamel BC, van Bokhoven H, Gal A. Mutations in ARHGEF6, encoding a guanine nucleotide exchange factor for rho GTPases, in patients with X-linked mental retardation. *Nat Genet* 2000;**26**(2):247–50.
- 72 **Geetz J**, Gedeon AK, Sutherland GR, Mulley JC. Identification of the gene FMR2, associated with FRAXE mental retardation. *Nat Genet* 1996;**13**(1):105–8.
- 73 **Gu Y**, Shen Y, Gibbs RA, Nelson DL. Identification of FMR2, a novel gene associated with the FRAXE CCG repeat and CpG island. *Nat Genet* 1996;**13**(1):109–13.
- 74 **Mazzocco MM**, Myers GF, Hamner JL, Panoscha R, Shapiro BK, Reiss AL. The prevalence of the FMR1 and FMR2 mutations among preschool children with language delay. *J Pediatr* 1998;**132**(5):795–801.
- 75 **Faradz SM**, Leggo J, Murray A, Lam-Po-Tang PR, Buckley MF, Holden JJ. Distribution of FMR1 and FMR2 alleles in Javanese individuals with developmental disability and confirmation of a specific ACG-interruption pattern in Asian populations. *Ann Hum Genet* 2001;**65**(Pt 2):127–35.
- 76 **Patsalis PC**, Sismani C, Hettinger JA, Boumba I, Georgiou I, Stylianidou G, Anastasiadou V, Koukoulli R, Pagoulatos G, Syrrou M. Molecular screening of fragile X (FRAXA) and FRAXE mental retardation syndromes in the Hellenic population of Greece and Cyprus: incidence, genetic variation, and stability. *Am J Med Genet* 1999;**84**(3):184–90.
- 77 **Sharma D**, Gupta M, Thelma BK. Expansion mutation frequency and CCG/GCC repeat polymorphism in FMR1 and FMR2 genes in an Indian population. *Genet Epidemiol* 2001;**20**(1):129–44.
- 78 **D'Adamo P**, Menegon A, Lo Nigro C, Grasso M, Gulisano M, Tamanini F, Bienvenu T, Gedeon AK, Oostra B, Wu SK, Tandon A, Valtorta F, Balch WE, Chelly J, Toniolo D. Mutations in GDI1 are responsible for X-linked non-specific mental retardation. *Nat Genet* 1998;**19**(2):134–9.
- 79 **Bienvenu T**, des Portes V, Saint Martin A, McDonell N, Billuart P, Carrie A, Vinet MC, Couvert P, Toniolo D, Ropers HH, Moraine C, van Bokhoven H, Fryns JP, Kahn A, Beldjord C, Chelly J. Non-specific X-linked semidominant mental retardation by mutations in a Rab GDP-dissociation inhibitor. *Hum Mol Genet* 1998;**7**(8):1311–15.
- 80 **de Vries BB**, van den Ouweland AM, Mohkamsing S, Duivenvoorden HJ, Mol E, Gelsema K, van Rijn M, Halley DJ, Sandkuijl LA, Oostra BA, Tibben A, Niermeijer MF. Screening and diagnosis for the fragile X syndrome among the mentally retarded: an epidemiological and psychological survey. Collaborative Fragile X Study Group. *Am J Hum Genet* 1997;**61**(3):660–7.
- 81 **Crawford DC**, Acuna JM, Sherman SL. FMR1 and the fragile X syndrome: human genome epidemiology review. *Genet Med* 2001;**3**(5):359–71.
- 82 **Turner G**, Collins E, Turner B. Recurrence risk of mental retardation in sibs. *Med J Aust* 1971;**1**(22):1165–7.
- 83 **Bundey S**, Carter CO. Recurrence risks in severe undiagnosed mental deficiency. *J Ment Defic Res* 1974;**18**(2):115–34.
- 84 **Herbst DS**, Baird PA. Sib risks for nonspecific mental retardation in British Columbia. *Am J Med Genet* 1982;**13**(2):197–208.
- 85 **Bundey S**, Webb TP, Thake A, Todd J. A community study of severe mental retardation in the West Midlands and the importance of the fragile X chromosome in its aetiology. *J Med Genet* 1985;**22**(4):258–66.
- 86 **Costeff H**, Weller L. The risk of having a second retarded child. *Am J Med Genet* 1987;**27**(4):753–66.
- 87 **Crow YJ**, Tolmie JL. Recurrence risks in mental retardation. *J Med Genet* 1998;**35**(3):177–82.
- 88 **Van Naarden Braun K**, Autry A, Boyle C. A population-based study of the recurrence of developmental disabilities—Metropolitan Atlanta Developmental Disabilities Surveillance Program, 1991–94. *Paediatr Perinat Epidemiol* 2005;**19**(1):69–79.
- 89 **Turner G**, Partington M. Recurrence risks in undiagnosed mental retardation. *J Med Genet* 2000;**37**(12):E45.
- 90 **Herbst DS**, Miller JR. Nonspecific X-linked mental retardation II: the frequency in British Columbia. *Am J Med Genet* 1980;**7**(4):461–9.
- 91 **Morton NE**, Rao DC, Lang-Brown H, Maclean CJ, Bart RD, Lew R. Colchester revisited: a genetic study of mental defect. *J Med Genet* 1977;**14**(1):1–9.
- 92 **Chelly J**. MRX review. *Am J Med Genet* 2000;**94**(5):364–6.
- 93 **Geetz J**, Mulley J. Genes for cognitive function: developments on the X. *Genome Res* 2000;**10**(2):157–63.
- 94 **Ropers HH**, Hoeltzenbein M, Kalscheuer V, Yntema H, Hamel B, Fryns JP, Chelly J, Partington M, Geetz J, Moraine C. Nonsyndromic X-linked mental retardation: where are the missing mutations? *Trends Genet* 2003;**19**(6):316–20.