X-linked Mental Retardation: a clinical guide

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Running title: XLMR review

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Abstract

Mental retardation is more common in males than females in the population and the predominant cause of this is the presence of mutations in any one of 24 genes on the X chromosome. The prevalence of each gene as a cause of mental retardation is low and less common than Fragile X syndrome. Expansions in FMR1 are still the most common cause of X-linked mental retardation. Systematic screening of all other X-linked genes in X-linked families with mental retardation is currently not feasible in a clinical setting. This review discusses the phenotypes of genes that cause syndromic and non-syndromic mental retardation, as these may be the focus of more targeted mutation analysis: NLGN3, NLGN4, RPS6KA3(RSK2), OPHN1, ATRX, SLC6A8, ARX, SYN1, AGTR2, MECP2, PQBP1, SMCX and SLC16A2. Secondly, it summarises the relative prevalence of genes that cause only non-syndromic mental retardation: IL1RAPL1, TM4SF2, ZNF41, FTSJ1, DLG3, FAACL4, PAK3, ARHGEF6, FMR2 and GDI. Thirdly, this review addresses the problem of recurrence risk where a molecular genetics diagnosis has not been made and, finally, returns to the problem of what proportion of the male excess of mental retardation is due to monogenic disorders of the X chromosome.
Historical Overview
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. 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 ~30% excess of males being affected with mental retardation (MR).

The definition of Mental Retardation (MR) requires there to be significant sub-average general intellectual functioning (Criterion A) that is accompanied by limitations in adaptive functioning in at least 2 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 age 18 years (Criterion C). General intellectual functioning is defined by the intelligence quotient, IQ. Adaptive functioning refers to how effectively individuals cope with common life demands. These are less objective measures and rely on information gathered from independent sources e.g. teacher evaluation and educational, developmental and medical history, nevertheless these observation are extremely useful in assessing children. In the UK, the ICD-10 Classification of Mental and Behavioural Disorders, WHO, Geneva 1992 is used whilst in the USA the DSM-IV diagnostic classification is used which is similar to the WHO classification.

IQ across the population is normally distributed with the mean set at 100 and an IQ <70 classified as mental retardation. Mild mental retardation is defined as an IQ 50-70, moderate as an IQ 35-49, severe as IQ 20-34 and profound <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.

In 1943 Martin and Bell published ‘A pedigree of mental defect showing sex-linkage’. This subsequently lead to the identification of the first single gene defect where the phenotype was predominantly mental retardation, Fragile X syndrome.

In 1991 Kerr et al. identified families where no clinical features other than mental retardation were observed and Fragile X syndrome was not the cause of disease. This phenomenon were termed non-specific mental retardation abbreviated to XLMR. This then lead to the classification of families with X-linked mental retardation where an individual family was given an MRX numbers 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.

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

**Table 1**
Investigation of a male child with possible XLMR based on Shevell et al 2003

<table>
<thead>
<tr>
<th>Investigation of a male child with possible XLMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 3 generation pedigree and details of development of all possibly affected individuals</td>
</tr>
<tr>
<td>• Obtain a detailed clinical history of maternal health pre-pregnancy</td>
</tr>
<tr>
<td>• Pregnancy history</td>
</tr>
<tr>
<td>• Birth history and birth height, weight and head circumference</td>
</tr>
<tr>
<td>• Developmental milestones and growth rates</td>
</tr>
<tr>
<td>• Neonatal PKU and hypothyroidism</td>
</tr>
<tr>
<td>• Educational history and IQ</td>
</tr>
<tr>
<td>• Examination for dysmorphic features and neurological signs</td>
</tr>
<tr>
<td>• Karyotype (550 banded resolution)</td>
</tr>
<tr>
<td>• Fragile X</td>
</tr>
<tr>
<td>• Telomere screen</td>
</tr>
<tr>
<td>• Brain MRI if abnormal neurological findings or head circumference indicates microcephaly or macrocephaly</td>
</tr>
<tr>
<td>• EEG to assist definition of epilepsy phenotype</td>
</tr>
<tr>
<td>• Metabolic screen if clinically indicated. Consider urine and plasma screen of creatine/creatinine ratio where indicated and possible. Consider repeat thyroid function tests where appropriate.</td>
</tr>
</tbody>
</table>

Having excluded a karyotype abnormality and Fragile X syndrome by seeking an expansion in FMR1, there are some 23 X-linked genes where mutations have been described that either result in syndromic or non-syndromic mental retardation. The decision as to which gene(s) to analyse depends on the identification of additional clinical features that could categorise the condition as syndromic and the relative prevalence of the gene abnormality in the study population.

In this review a number of genes will be discussed, the clinical features associated with the gene abnormality and the prevalence of the disease gene. Genes that are only associated with a syndrome have not been discussed here e.g. L1CAM, PLP1, DCX as the review is limited to those genes where a non-syndromic phenotype has also been described as well as a syndromic phenotype due to limitations of space. The original separation between genes that cause syndromic disease from those that cause 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 is becoming increasingly varied e.g ARX (see below). Nevertheless this distinction still has some limited merit when categorising genes associated with mental retardation.

**Syndromic X-linked Mental Retardation**
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\(^1\). 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 and all cases have been associated with severe mental retardation \(^18\)-\(^20\). Routine testing is of unproven utility to date.

Coffin Lowry
Mutations in RPS6KA3 (ribosomal protein S6 kinase, 90kDa polypeptide 3) OMIM: 300075 previously known as RSK2 are associated with Coffin Lowry syndrome \(^21\). 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 \(^22\). A single family with non-syndromic mental retardation has been reported with mutations in this gene but recently mutations in 3 further families have been identified who did not meet the diagnostic criteria for Coffin Lowry syndrome (Raymond et al. unpublished data)\(^23\). This suggests that mutations in RPS6KA3 will prove to be a more common cause of X-linked mental retardation 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 have significant reduction in size of the cerebellum. None of the family presented with significant ataxia or cerebellar signs clinically but 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 \(^24\), \(^25\). The prevalence of mutations in this gene is low although 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 2 families, a patient with a translocation and a singleton with a similar phenotype to that of the familial cases\(^24\), \(^25\).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 homogeneous 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, 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. There is a single family reported with non-syndromic mental retardation alone where the proband in the large family 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\(^26\). 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 MR is not useful.
Epilepsy

Mental retardation in combination with epilepsy is relatively common which means that the list of differential diagnoses remain long is 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, autistic spectrum behaviour problems with particular deficits in expressive speech and language often resulting in absent speech\textsuperscript{27,27}. Recently, a systematic screen of 288 families with mental retardation and either proven X-linked inheritance or where there were 2 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\textsuperscript{28,29}. The clinical features of these 6 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 a confirmation of affected individuals\textsuperscript{30-32}. The identification of ARX (aristaless related homeobox) OMIM:300382 as a cause of West syndrome, mental retardation and either hypersarrhythmia, myoclonic epilepsy, dystonia (Partington syndrome), lissencephaly and abnormal genitalia or mental retardation alone has altered the previous somewhat rigid delineation of conditions as syndromic and non-syndromic as the same mutation within this gene can lead to a wide variety of phenotypes\textsuperscript{33,34}. Intracerebral cysts have also now been reported\textsuperscript{35}. Problems associated with mood including aggression or depression were also a feature in some of the families. Within families where X-linked mental retardation 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 further screening of affected singletons the prevalence is low (2/1501)\textsuperscript{36-38}. Testing is useful in syndromic MR and in familial cases of non-syndromic MR 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\textsuperscript{39}. This is not a common cause of mental retardation. >300 families with X-linked or possible X-linked mental retardation 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 3 patients appears to be a rare polymorphism and unlikely to be disease causing\textsuperscript{40-42}. 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 range from: 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. (2000) reported a family where a mother had mild intellectual problems, a daughter had classical Rett syndrome and 4 affected boys had severe mental retardation\textsuperscript{43}. 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. 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 1 pathological mutation in almost 1,000 samples (1/475 European consortium, 0/300 in Cambridge GOLD study cohort, 0/>200 samples referred for testing of males with mental retardation to Wessex Clinical Genetics Laboratory, UK). Mutations in MECP2 are rare causes of non-syndromic mental retardation and sequence analysis should not be routinely offered but it remains invaluable in the diagnosis of Rett syndrome and related disorders with a high diagnostic yield.

**Short stature and microcephaly**

Mutations in PQBP1 (polyglutamine binding protein 1) OMIM:300463 have been published as a cause for X-linked mental retardation 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, small testes. One patient had spastic paraplegia. The phenotype in syndromes: Renpenning, Cerebropalatocardiac (Hamel) syndrome and Sutherland Hann syndrome are similar and mutations in PQBP1 have also been identified in these conditions suggesting they are allelic. 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 JARID1C are also associated with short stature and microcephaly. Of the 7 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 MR and was relatively mildly affected compared to the others.

**High Triiodothyronine concentrations (T₃)**

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 5 unrelated boys with severe mental retardation and high triiodothyronine T₃ concentrations. Two of the boys had partial deletions of the gene with a 24kb deletion that encompassed exon 1 and a 2.4 kb deletion which resulted in a deletion of exon 3 and exon 4. The other 3 boys had missense mutations and a nonsense mutation. Subsequently, two further families were reported with abnormal T₃ levels, global developmental delay, central hypotonia, spastic paraplegia, dystonic movements, rotary nystagmus and impaired hearing and gaze. Children with Allan-Herndon-Dudley syndrome have a similar phenotype to that of the families reported by Dumitrescu et al. and 6 large families have all been found to carry mutations, 5 missense and one 3 base pair deletion. These patients were all subsequently found to have associated abnormal T₃ levels although the neonatal Guthrie screens for hypothyroidism were normal. Abnormalities in this gene appear to be relatively common and suggests 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.

Table 2
Additional clinical features found in syndromic XLMR

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcephaly</td>
<td>ATRX, MECP2, PQBP1, SMCX</td>
</tr>
<tr>
<td>Cleft lip and palate</td>
<td>PQBP1</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>PQBP1</td>
</tr>
<tr>
<td>Spastic paraplegia</td>
<td>SLC16A2, ATRX, SMCX, MECP2, SMCX</td>
</tr>
<tr>
<td>Seizures</td>
<td>AGTR2, SYN1, ATRX, SLC6A8, ARX, SMCX</td>
</tr>
<tr>
<td>Absent speech</td>
<td>ATRX, SLC16A2, SLC6A8</td>
</tr>
<tr>
<td>Cerebellar hypoplasia</td>
<td>OPHN1</td>
</tr>
<tr>
<td>Short stature</td>
<td>PQBP1, SMCX</td>
</tr>
<tr>
<td>Autistic behaviour</td>
<td>NLGN3, NLGN4, AGTR2, SLC6A8</td>
</tr>
<tr>
<td>Dystonia</td>
<td>ARX</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>RSK2</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>RSK2, ATRX</td>
</tr>
<tr>
<td>Abnormal thyroid function</td>
<td>SLC16A2</td>
</tr>
</tbody>
</table>

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. Currently, no detailed comparative prevalence studies are 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 \(^{29,54}\). The prevalence of each of the non-syndromic genes is 1-2% in selected research samples where at least 2 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 MR 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 X-linked mental retardation families screened and no mutations were found in 5 large X-linked families\(^{55}\). Since then a complex rearrangement of this gene has been described but no new mutations have been found \(^{56}\).

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 \(^{57}\). 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 done 58, 59. Disruption of ZNF41 (zinc finger protein 41) OMIM:314995 in a child with mental retardation and a balanced X-autosome translocation identified this gene as a candidate gene. Screening of a panel of 210 families with X-linked mental retardation identified one missense and one splice site mutation which are likely to be pathological60.

Mutations in FTSJ1 (Fts J homolog (E. 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 61, 62. Four truncating mutations in DLG3 (discs, large homolog 3 (neuroendocrine-dlg, Drosophila)) OMIM:300189 have been identified in a cohort of 328 families with X-linked mental retardation 63. All the affected males in the families had moderate to severe mental retardation whilst female carriers were usually of normal intellect. X inactivation studies showed no skewing of lymphocytes in obligate female carriers63. Mutations in FACL4 renamed ACSL4 (acyl-CoA synthetase long-chain family member 4) OMIM:300157 have been reported. These are 2 missense and one splice site mutation that reduce the enzymatic activity 64, 65. The gene was originally localised by characterising genomic deletions in patients with Alport’s syndrome and MR 66, 67.

Since the identification of a truncating mutation in PAK3 (p21(CDKN1A)-activated kinase 3) OMIM:300142, 2 further missense mutations have been described 68-70. The number of families that have been screened are few to date. The initial publication 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 is 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 71.

FMR2 was identified by characterising the genomic structure around the folate sensitive fragile site, FRAXE 72, 73. 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 which 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 the interpretation of results is sometimes difficult74-77.

Three mutations in GD11 (GDP dissociation inhibitor 1) OMIM:300104 have been characterised. 2/5 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 mutation78, 79.

Finally, Fragile X syndrome should be considered as a frequent cause of non-syndromic mental retardation as the classical 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.

Recurrent 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 presented with a family in clinic and empiric recurrence risks are needed. Much of the available data was published between 1971-1987 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 questions the validity of some of this data. A recent population based study of Atlanta, USA provides contemporary recurrence risks for developmental delay although the sample was still relatively old by contemporary molecular and cytogenetic standards. The sample was based on children born to mothers between 1981-1991 and the total number of cases with a disability was 3,685. Recurrence risks for isolated mental retardation was 8.4% if the first child had isolated MR as compared recurrence risks for cerebral palsy (2.9-3.6%), hearing loss (4.7-5.7%) and vision impairment (5.3-6.9%). Recurrence risks for mild MR was 7.1% if the first child had mild MR whereas recurrence for severe MR was 4.7%

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Affected Male</th>
<th>Affected Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brother</td>
<td>Sister</td>
</tr>
<tr>
<td>Turner et al 1971</td>
<td>6.7%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Bundey et al 1974</td>
<td>6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Herbst et al 1982</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Costeff et al 1987</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Van Naarden Braun et al 2005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Where the possibility of detailed clinical assessment and when current molecular genetics and cytogenetics are available the calculations of Turner and Partington add an additional useful guide to recurrence risks calculations. This group observed recurrence risks for mental retardation in the siblings of index cases referred to a genetics centre. Observed recurrences were (11/83) 1:7.5 for brother pairs and (3/60) 1:20 for sister pairs. These figures are comparable to that of Herbst.
and Miller in 1980 and those from the Colchester cohort collected by L Penrose and revisited by Morton et al. 1977\(^90\),\(^91\). 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 2 affected males in the family the assumption is that ~80% (the male excess) are 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 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 (2004) 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\(^37\). Observing the prevalence of a 24bp expansion in ARX they observed that 6.6% (9/136) of families with X-linked mental retardation pedigrees were found to carry mutations whereas 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 give to patients, 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 to 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 in future. Furthermore, it 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 X-linked mental retardation. Estimates of the number of genes that remain to be identified vary considerably from 30-50 genes \(^92\)-\(^94\). 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. Syndromic features should always be sought in possible XLMR as it can lead to a molecular diagnosis. The discovery of the plethora of genes that cause a small proportion of non-syndromic XLMR has clinical value to those families where mutation are detected, but awaits the arrival of high throughput, cheap, and reliable sequence analysis methods that can be readily introduced to the clinical service.

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**Conflict of interest:** None

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


42. Erdmann J, Dahmlow S, Guse M, et al. The assertion that a G21V mutation in AGTR2 causes mental retardation is not supported by other studies. Hum Genet 2004;114(4):396; author reply 397.


<table>
<thead>
<tr>
<th>Condition</th>
<th>Genes</th>
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<tbody>
<tr>
<td>Autism</td>
<td>NR3C1</td>
</tr>
<tr>
<td>Coffin-Lowry</td>
<td>EEF2</td>
</tr>
<tr>
<td>West syndrome, dystonia</td>
<td>ANO1</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>PTEN</td>
</tr>
<tr>
<td>Microcephaly, short stature</td>
<td>CEP25, LMX2</td>
</tr>
<tr>
<td>Microcephaly, short stature</td>
<td>CEP25, LMX2</td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
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<tr>
<td>Autism</td>
<td>NR3C1, NR3C1</td>
</tr>
<tr>
<td>High T3, hypotonia, spastic paraplegia</td>
<td>MIF, MIF2</td>
</tr>
<tr>
<td>Microcephaly, spasticity, absent speech</td>
<td>MIF, MIF2</td>
</tr>
<tr>
<td>Epilepsy, autism</td>
<td></td>
</tr>
<tr>
<td>Re11</td>
<td>MLC1, P2</td>
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<tr>
<td>Epilepsy dysmorphism</td>
<td></td>
</tr>
</tbody>
</table>

- NR3C1: Nuclear receptor subfamily C, group 1
- EEF2: Elongation factor 2
- ANO1: Ankyrin G protein
- PTEN: Phosphatase and Tensin Homolog
- CEP25: Cerebral cortex-specific open reading frame
- LMX2: Limb homeobox 2
- MIF: Macrophage Migration Inhibitory Factor
- MIF2: Macrophage Migration Inhibitory Factor 2
- MLC1: Myosin light chain 1
- P2: P2A

Diagram:
- Represents a molecular or genetic analysis
- Showcases various conditions and their associated genes
- A color code may be present to indicate different levels or statuses
X-linked Mental Retardation: a clinical guide

F Lucy Raymond

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