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REVIEW

XLMR genes: update 2007

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X-linked mental retardation (XLMR) is a common cause of inherited intellectual disability with an estimated prevalence of ~1/1000 males. Most XLMR conditions are inherited as X-linked recessive traits, although female carriers may manifest usually milder symptoms. We have listed 215 XLMR conditions, subdivided according to their clinical presentation: 149 with specific clinical findings, including 98 syndromes and 51 neuromuscular conditions, and 66 nonspecific (MRX) forms. We also present a map of the 82 XLMR genes cloned to date (November 2007) and a map of the 97 conditions that have been positioned by linkage analysis or cytogenetic breakpoints. We briefly consider the molecular function of known XLMR proteins and discuss the possible strategies to identify the remaining XLMR genes. Final remarks are made on the natural history of XLMR conditions and on diagnostic issues.
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Introduction

Mental retardation (MR) is a complex phenotype characterized by suboptimal functioning of the central nervous system (CNS) resulting in 'significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social and practical adaptive skills,' originating before 18 years of age.[1] It is estimated that from 1 to 3% of the general population is affected with MR.[2,3] Increasingly, the term 'intellectual disability' is being used instead of 'mental retardation.'[4] MR/intellectual disability can be caused by genetic as well as environmental causes that act on the development and functioning of the CNS prenatally, perinatally or postnatally.[5] Genetic causes of MR include chromosome aneusomies, chromosome structural abnormalities, genomic disorders and monogenic diseases. Such causes account for up to 50% of moderate-to-severe MR, while environmental factors (eg malnutrition, cultural deprivation) play a larger role in the pathogenesis of mild MR.[6] An extended discussion of genes involved in the pathogenesis of MR has been recently provided by Inlow and Restifo[6] and by Chelly *et al*,[7] while Francis *et al*[8] concentrated on genes underlying CNS malformations, which may cause MR and/or epilepsy.

X-linked mental retardation (XLMR) is a common cause of monogenic intellectual disability affecting mostly males, partly accounting for the higher prevalence of MR among males relative to females.[9] However, female carriers may manifest (usually milder) symptoms, possibly because of skewed X-inactivation.[10–11] A differential expression of X-linked genes in males and females also appears to play a role in mental functioning, as discussed by Skuse.[12] A prevalence of 1.83/1000 males with XLMR had been estimated in 1980 by Herbst and Miller,[13] with the fragile X syndrome being by far the most prevalent condition (~20% of all XLMR cases).[14] However, the finding of a much smaller contribution of individual genes, other than *FMR1*, to XLMR has recently led to a reduced prevalence estimate of 10–12% of all MR cases in males.[15–17]

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This review represents the eight edition of the XLMR update, first compiled in 1990 by Neri *et al*.[18] Tables and maps presented here are also available at the XLMR update web site (http://xlmr.interfree.it/home.htm) and complementary information can be found at the Greenwood Genetic Center web site (http://www.ggc.org/xlmr.htm).

Conditions listed in the present update have been identified either by searches of PubMed (http://www.pubmed.gov) or of the Online Mendelian Inheritance in Man (OMIM) database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM). Only few entries have been included based on conference abstracts.

It has been suggested that the concentration of genes causing MR (number of MR genes per megabase) may be twice as high on the X chromosome compared to autosomes.[6] These estimates will be confirmed or disproved only when all MR genes will have been cloned. In any case, one should keep in mind that the identification of X-linked conditions is easier due to the hemizygosity of males, who inevitably manifest a phenotype when harboring a mutant allele. There is only one X-linked condition known that contradicts this inheritance pattern, that is, EFMR or epilepsy and MR limited to females.[19] In this condition, heterozygous females are affected, while hemizygous males are apparently unaffected. The gene responsible for this condition and the mechanism leading to sparing of mutant males are still unknown.

Nosology and classification

Classification of MR can be based on the underlying causes (genetic, environmental or a combination thereof) and/or on their timing (pre-, peri- and postnatal), as discussed by Moog.[20] A more practical subdivision is based on clinical presentation, irrespective of the identification of the causal gene or of the pathogenetic mechanism. In the first edition of the XLMR update,[18] there was already a clinical distinction between specific and nonspecific conditions, the latter being characterized by MR only. Over the years, specific XLMR conditions were subdivided into four classes,[21–26] namely (a) syndromes, with concurrent physical anomalies in various combinations, (b) neuromuscular conditions, with associated neurologic and/or muscular symptoms, (c) metabolic conditions and (d) dominant conditions. However, classes (c) and (d) are not based on a clinical presentation, but on the biochemical mechanism (c) or on the mode of inheritance (d). Furthermore, genes involved in causing dominant XLMR conditions (like *MECP2*) have often been found to cause X-linked recessive conditions in some families. Therefore in this update, we decided to categorize XLMR conditions into three classes based on their clinical presentation: (a) syndromes, characterized by multiple congenital anomalies and defects in organs/tissues other than (but also including) the brain; (b) neuromuscular disorders, characterized by neurological or muscular symptoms (epilepsy, dystonia, spasticity, muscle weakness, and so on) but no malformations and (c) nonspecific conditions (MRX), where MR is the only consistent clinical manifestation among the affected individuals.[27] This distinction has mostly practical value. Specific XLMR conditions (ie syndromes and neuromuscular conditions) can exist as separate nosological entities, recognizable on the basis of a distinctive clinical presentation, even if the causative gene or locus is unknown. On the contrary, nonspecific (MRX) conditions can only be distinguished based on the knowledge of their causative gene.

Table 1 summarizes all 215 XLMR conditions subdivided by clinical presentation and according to their mapping status (97 mapped and 82 cloned genes). Details on each condition are tabulated in Supplementary Tables S1–S3 (available online), where the total number of entries appears to be higher than 215, because all allelic conditions are counted separately.

Table 1 Count of XLMR conditions by clinical presentation: syndromes (listed in Supplementary Table S1), neuromuscular conditions (listed in Supplementary Table S2) and nonspecific/MRX conditions (listed in Supplementary Table S3)

	Total count	*Mapped*	*Cloned*
Syndromes	98	31	38
Neuromuscular	51	16	28
Nonspecific/MRX	66	50	16
Total conditions	215	97	82

For each category and for the total count, mapped conditions and cloned genes are also indicated.

Localization of XLMR genes and conditions

Figure 1 contains an ideogram of the X chromosome with the position of the 82 known XLMR genes. All these genes carry mutations in at least a single family with multiple affected individuals. The three most recent genes were reported at the 13th International Workshop on Fragile X and XLMR and were associated with an Angelman-like syndrome (SLC9A6),[28] with a neurological condition, that is, hyperekplexia and epilepsy (ARHGEF9)[29–30] and with both a syndromic condition in one family (Supplementary Table S1, entry 95) and MRX in two families (HUWE1),[31] respectively. Figures 2 and 3 illustrate the localization by linkage analysis or cytogenetic markers (translocation or inversion breakpoint, microdeletion or duplication) of mapped syndromes and neuromuscular conditions or MRX families, respectively. XLMR genes are spread over the entire X chromosome with a higher density in two

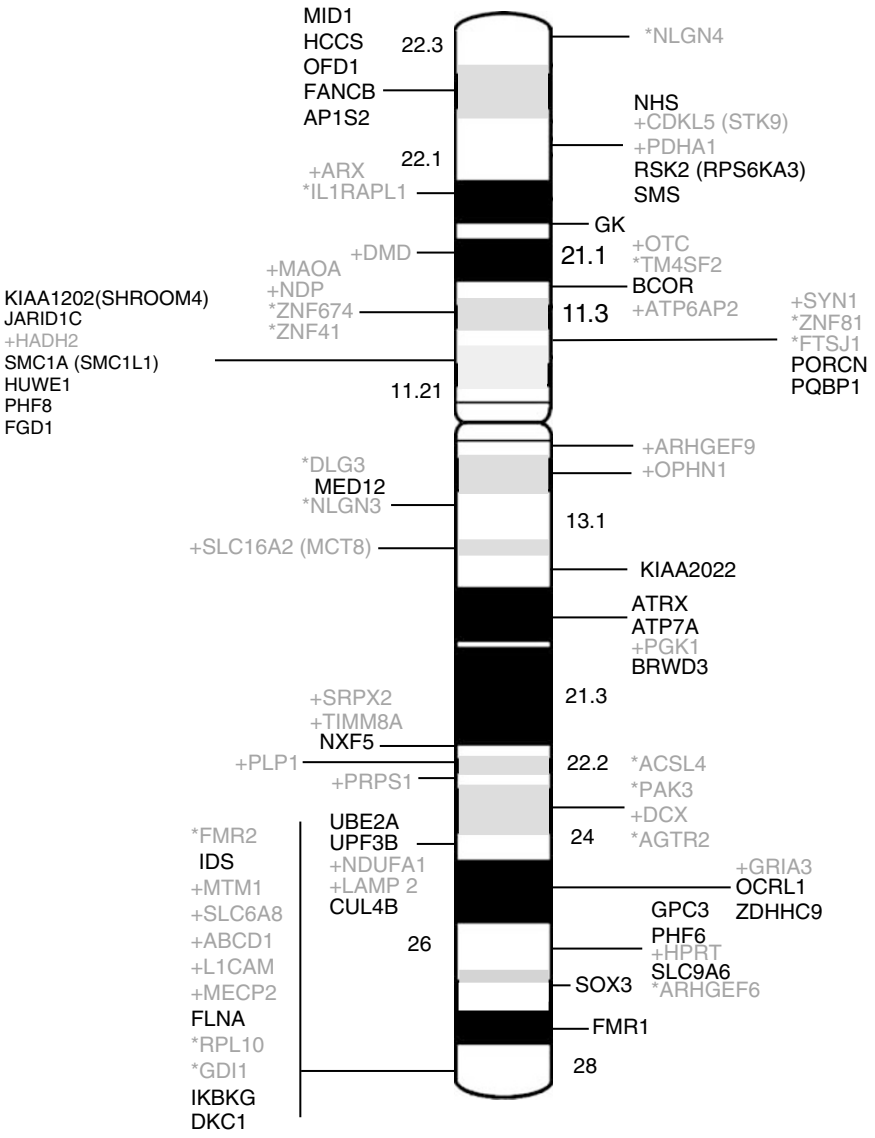


Figure 1 Ideogram of the X chromosome with the position of the 82 known XLMR genes. Genes written in black cause syndromes (Supplementary Table S1), those in gray preceded by a + sign cause neuromuscular disorders (Supplementary Table S2), while those written in gray preceded by an asterisk are involved in nonspecific (MRX) conditions (Supplementary Table S3).

G-negative bands at Xp11.2 (12 genes) and at Xq28 region (12 genes).

The actual role of a few XLMR genes is still uncertain because (a) they were identified in a single family with a missense mutation (eg *CASK*, *EFHC2* and *OST6*), (b) they were found interrupted by the breakpoint of a balanced translocation or inversion in a single patient (eg *KLF8* and *ZDHHC15*) or (c) they were deleted together with other genes (eg *ZNF673*, *ZNF630*, *SLC38A5* and *BRAF2*). Details on these unconfirmed candidate genes have been listed in Supplementary Table S4. Some of these were presented at the 13th International Workshop on Fragile X and XLMR held in Venice October 3–6, 2007.

Genomic duplications have also been identified in at least four different entries: (1) FG syndrome locus 5 in Supplementary Table S1 (OMIM %300581; ~5 Mb duplication in Xq22.3, including the *PRPS1* and the *MID2* genes); (2) panhypopituitarism in Supplementary Table S1 (OMIM %312000; ~1–4 Mb duplication in Xq26–q27 including the *SOX3* gene); (3) Pelizaeus–Merzbacher disease in Supplementary Table S2 (OMIM #312080; often due to small duplications encompassing the *PLP1* gene) and (4) severe MR with hypotonia, progressive spasticity and recurrent infections (OMIM +300005.0030). This latter clinical entity is listed in Supplementary Table S2 and has been identified in several XLMR families linked to

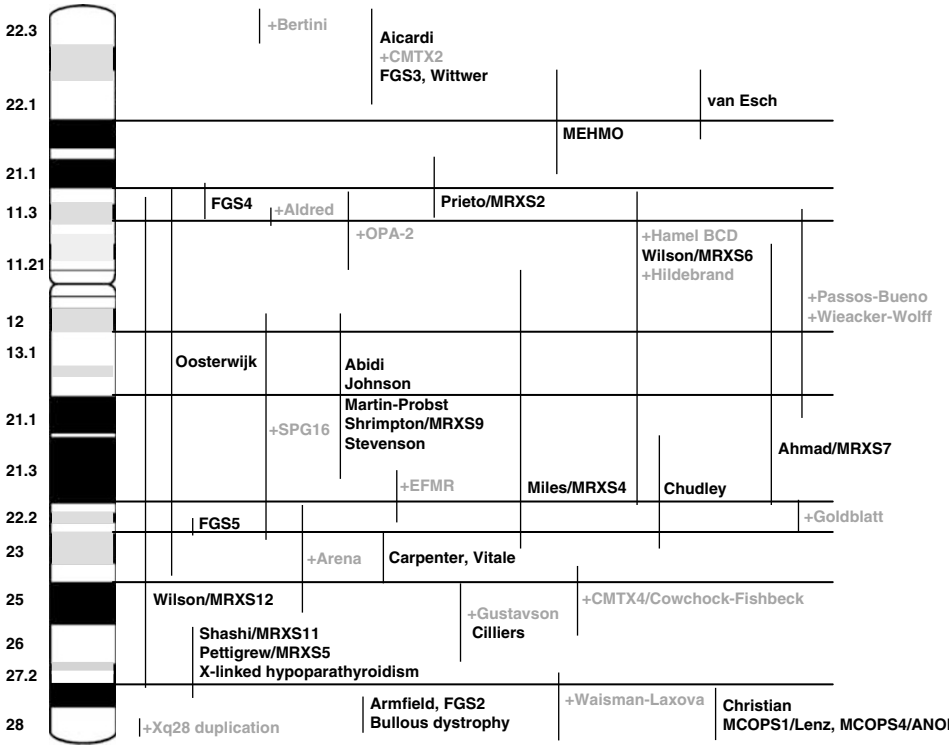


Figure 2 Ideogram of the X chromosome with the position of the 47 specific conditions that were mapped on the X chromosome. Vertical bars indicate the linkage/cytogenetic interval. The 31 syndromes are indicated in black (see Supplementary Table S1), while the 16 neuromuscular disorders are written in gray preceded by a + sign (see Supplementary Table S2).

Xq28.[32–35] Although several other genes are included in the duplication, *MECP2* is the only one to be present in all cases.[33] Recent observations suggest that duplications are quite common in XLMR patients.[36] For example, a recurrent duplication in Xp11.22 that harbors at least three genes (*RIBC1*, *HADH2* and *HUWE1*) has been characterized by Froyen *et al*[31] in six different pedigrees, including MRX17 and MRX31 (see Supplementary Table S3c). However, in such cases, the pathogenic role of individual genes included in the duplication is difficult to sort out. Functional studies and the establishment of animal models (eg mice overexpressing PLP[37]) will eventually clarify these issues.

Molecular function of XLMR gene products

Table 2 lists the 82 known XLMR genes, ordered by physical position on the X chromosome, that is, megabases from the Xp telomere. This table provides the name of the corresponding proteins as well as their subcellular localization and biological function, where known or predicted. Protein information was obtained partly from the Gene Ontology Web site (http://www.geneontology.org/) and partly from peer-reviewed publications. Figure 4 summarizes (a) the subcellular localization and (b) the biological function of XLMR gene protein products. These proteins can be found in all cell compartments: 30% in the nucleus, 28% in the cytoplasm and 16% in the organelles, while 22% are either membrane bound or secreted (Figure 4a). Their function is mainly related to signal transduction (19%) and regulation of transcription (22%), which may be considered the last step in the signaling cascade (Figure 4b). Many of the proteins indicated as 'membrane component' (15%) are also likely to play a role in signal transduction. However, a relevant portion of XLMR proteins is involved in different biological pathways, such as core metabolism (15%), DNA and RNA processing (6%), protein synthesis (3%), regulation of cell cycle and ubiquitin pathway (7%). These fundamental processes may disproportionately affect cognition because of a brain-specific expression pattern of the corresponding genes. It is important to note that XLMR genes may be expressed in the brain but not in neurons; for example, *PLP1* encodes for the proteolipid protein 1, a major component of myelin that is expressed exclusively in oligodendrocytes, that is, in the supporting cells belonging to the glia.[37]

The last column in Table 2 indicates whether a given protein localizes to synapses, according to data recently published by Laumonnier *et al*[38] and also available at the Web site of the Genes to Cognition Programme of the Wellcome Trust (http://www.genes2cognition.org/).

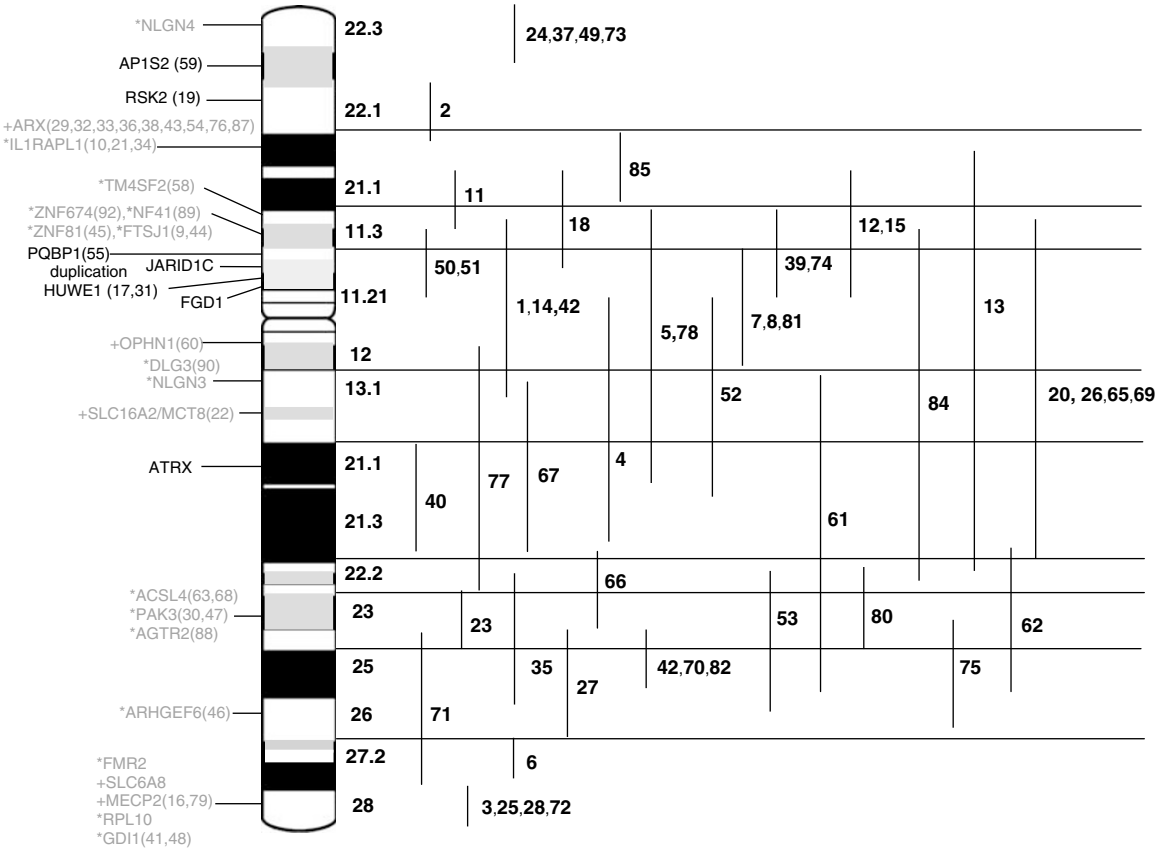


Figure 3 Ideogram of the X chromosome with the position of the 50 MRX pedigrees with mapping information available (see Supplementary Table S3). Vertical bars indicate the linkage/cytogenetic intervals and numbers next to them correspond to individual MRX families/cases. Known MRX genes are indicated on the left side of the X chromosome and numbers in parentheses next to gene names correspond to the original MRX pedigrees.

Laumonnier *et al*[38] list 39 proteins encoded by X-linked genes that belong to the synaptic proteome and indicate that 19 of these are known XLMR genes. It is important to note that, according to these authors, synaptosome preparations appear to include mitochondrial proteins (PDHA1 and HADH2), but surprisingly also a nuclear protein such as the DNA helicase ATRX. In contrast, some less represented transmembrane proteins may have gone undetected in the synaptic proteome (eg TM4SF2/TSPAN7) and were therefore not listed. One final note should be made about microRNAs (miRNA) and noncoding RNAs (ncRNA) transcribed by X-chromosomal loci, because their mutation may also potentially cause XLMR or other X-linked inherited disorders. miRNA plays a role in controlling the expression of target genes at the post transcriptional level, and their deletion may affect the stability of several target RNA molecules. Chen *et al*[39] selected 13 brain-expressed X-chromosomal miRNA genes and looked for mutations or deletions in a cohort of 464 XLMR patients. These authors identified only four nucleotide substitutions in the precursors of three miRNAs, but one was absent in the patient's affected brother and another one was found in 1 out of 183 normal control males, while two variants cosegregating with the disease in the third pedigree did not appear to have a significant effect on mir-222 processing.[39] Gecz[40] identified *FMR3*, a noncoding RNA transcribed from the same CpG island containing the promoter of the *FMR2* gene, but in the opposite direction. Transcription of this ncRNA is also abolished in the presence of CCG triplet repeat expansion in patients expressing the FRAXE fragile site.[40] Recently, while screening 441 Brazilian males with MR for FRAXE expansion, Santos-Reboucas *et al*[41] described a 58-bp deletion immediately distal to the CCG repeat that abolishes *FMR3* but not *FMR2* transcription, suggesting a role of this ncRNA in normal mental functioning. Currently, these miRNA and ncRNA genes, possibly involved in or contributing to XLMR, are not listed in this catalogue.

Strategies for candidate gene identification

The search for XLMR genes is going to continue and it is difficult to estimate how many of the ~900 X-linked protein-coding genes listed in the ENSEMBL database

Table 2 Listing of the 82 known XLMR genes, ordered by physical distance (megabases) from the Xp telomere

Gene name	*Megabases from Xpter*	*Cytoband*	*OMIM*	*Protein name*	*Cellular component*	*Biological function*	*Synaptic localization*
*NLGN4	5.82–6.15	Xp22.32–.31	*300427	Neuroligin 4	Membrane, plasma	Cell adhesion	Yes
MID1	10.37–10.76	Xp22.2	*300000	Midin (midline 1 protein)	Cytoplasm, cytoskeleton	Ubiquitin cycle, microtubule-associated complex	
HCCS	11.03–11.05	Xp22.2	*300056	Holocytochrome C synthase	Mitochondrion	Metabolism, energy production, cytochrome *c* heme-lyase)	
OFD1	13.66–13.69	Xp22.2	*300170	Oral-facial-digital syndrome 1 protein	Cytoplasm	Cytoskeleton, centrosome function	
FANCB	14.80–14.77	Xp22.2	*300515	Fanconi anemia complementation group B protein	Nucleus	DNA repair	
AP1S2	15.78–15.75	Xp22.2	*300629	Adaptor-related protein complex 1, sigma 2 subunit	Cytoplasm, Golgi	Membrane transporter-receptor mediated endocytosis vesicle-mediated transport	
NHS	17.30–17.66	Xp22.2–22.13	*300457	Nance–Horan syndrome protein	Nucleus	?	
+CDKL5/ STK9	18.35–18.58	Xp22.13	*300203	cyclin-dependent kinase-like 5	Nucleus?	Transcription regulation, serine/threonine kinase, MECP2 phosphorylation	Yes
+PDHA1	19.27–19.29	Xp22.12	*312170	Pyruvate dehydrogenase (lipoamide) α 1	Mitochondrion	Metabolism, glycolysis, acetyl-CoA, oxidoreductase activity	Yes
RPS6KA3/ RSK2	20.08–20.19	Xp22.12	*300075	Ribosomal protein S6 kinase, 90 kDa, polypeptide 3	Cytoplasm, ribosome	Signal transduction, protein serine/threonine kinase	Yes
SMS	21.87–21.92	Xp22.11	*300105	spermine synthase	Cytoplasm?	Metabolism, methionine metabolism, polyamine metabolism	
+ARX	24.93–24.94	Xp22.11	*300382	Aristaless-related homeobox protein	Nucleus	Transcription regulation	
*IL1RAPL1	28.51–29.88	Xp21.2	*300206	Interleukin 1 receptor accessory protein-like 1	Membrane, plasma	Signal transduction	Yes
GK	30.58–30.66	Xp21.2	*300474	Glycerol 3-phosphotransferase	Mitochondrion	Metabolism, glycerol uptake	
+DMD	31.05–33.26	Xp21.2–p21.1	*300377	Dystrophin (muscular dystrophy, Duchenne and Becker types)	Cytoplasm, cytoskeleton	Cytoskeleton component, Dp260	Yes
+OTC	38.10–38.16	Xp11.4	*300461	Ornithine carbamoyltransferase	Mitochondrion	Metabolism, urea cycle, amino acid	
*TM4SF2	38.30–38.43	Xp11.4	*300096	Tetraspanin 7	Membrane, plasma	Membrane component, cell surface glycoprotein	
BCOR	39.79–39.92	Xp11.4	*300485	BCL6 corepressor	Nucleus	Transcription regulation, corepressor activity, transcription factor and histone deacetylase binding	
+ATP6AP2	40.32–40.35	Xp11.4	*300556	ATPase, H+ transporting, lysosomal accessory protein 2	Lysosome membrane	Membrane transporter, lysosome	
+MAOA	43.40–43.49	Xp11.3	*309850	Monoamine oxidase A	Mitochondrion	Metabolism, neurotransmitter catabolism	Yes
+NDP	43.69–43.72	Xp11.3	*310600	Norrin (Norrie disease protein)	Extracellular, secreted	Signal transduction, growth factor	
*ZNF674	46.29–46.24	Xp11.3	+300573	Zinc-finger protein 674	Nucleus	Transcription regulation	
*ZNF41	47.19–47.23	Xp11.3	*314995	Zinc-finger protein 41	Nucleus	Transcription regulation	
+SYN1	47.31–47.36	Xp11.23	*313440	Synapsin I	Cytoplasm, membrane associated?	Membrane transporter, neurotransmitter exocytosis, actin binding, synaptic vesicle	Yes
*ZNF81	47.58–47.66	Xp11.23	*314998	Zinc-finger protein 81	Nucleus	Transcription regulation	
*FTSJ1	48.22–48.23	Xp11.23	*300499	FtsJ homolog 1	(Nucleolus, cytoplasm, mitochondria)?	Protein synthesis, rRNA processing, tRNA processing, RNA methylation	
PORCN	48.25–48.26	Xp11.23	*300651	*Drosophila* porcupine homolog	Cytoplasm, endoplasmic reticulum	Wnt receptor signaling pathway, Acyltransferase activity, integral to membrane of endoplasmic reticulum	
PQBP1	48.64	Xp11.23	*300463	Polyglutamine-binding protein 1	Nucleus	Transcription regulation	
KIAA1202/ SHROOM4	50.35–50.57	Xp11.22	*300579	KIAA1202 protein	Cytoplasm?	Cytoskeleton component, actin associated	

Table 2 (*Continued*)

Gene name	*Megabases from Xpter*	*Cytoband*	*OMIM*	*Protein name*	*Cellular component*	*Biological function*	*Synaptic localization*
JARID1C/ SMCX	53.24–53.27	Xp11.22	*314690	Jumonji/ARID domain-containing protein 1C	Nucleus	Transcriptionregulation, histone H3-k4 demethylase	
SMC1A/ SMC1L1	53.41–53.47	Xp11.22	*300040	SMC1 structural maintenance of chromosomes 1-like 1 (yeast)	Nucleus	Cell cycle, mitotic spindle organization and biogenesis, chromosome segregation	
+HADH2	53.47	Xp11.22	*300256	Hydroxyacyl-coenzyme A dehydrogenase, type II	Mitochondrion	Metabolism, lipid metabolism	Yes
HUWE1	53.74–53.56	Xp11.22	—	E3 ubiquitin-protein ligase HUWE1 (UREB1, ARFBP1)	Cytoplasm	Ubiquitin-protein ligase, mRNA transport	
PHF8	53.98–54.09	Xp11.22	*300560	PHD finger protein 8	Nucleus?	Transcription regulation	
FGD1	54.48–54.54	Xp11.22	*305400	FYVE, RhoGEF and PH domain-containing protein 1	Cytoplasm	Signal transduction, Rho guanyl-nucleotide exchange factor activity	
+ARHGEF9	62.92–62.77	Xq11.2	*300429	Cdc42 guanine nucleotide exchange factor (GEF) 9	Cytoplasm	Regulation of Rho protein signal transduction	Yes
+OPHN1	67.17–67.57	Xq12	*300127	Oligophrenin 1	Cytoplasm?	Signal transduction, Rho GTPase activator activity	
*DLG3	69.58–69.64	Xq13.1	*300189	Discs, large homolog 3 (neuroendocrine-dlg, *Drosophila*)	Cytoplasm, membrane associated	Signal transduction, guanylate kinase activity	Yes
MED12/ HOPA	70.25–70.27	Xq13.1	*300188	Mediator of RNA polymerase II transcription, subunit 12 homolog	Nucleus	Transcription regulation, RNA polymerase II transcription mediator activity, ligand-dependent nuclear receptor transcription coactivator activity, vitamin D receptor and thyroid hormone receptor binding	
*NLGN3	70.28–70.31	Xq13.1	*300336	Neuroligin 3	Membrane, plasma	Cell adhesion	Yes
+SLC16A2/ MCT8	73.55–73.67	Xq13.2	*300095	Solute carrier family 16, member 2 (monocarboxylic acid transporter 8)	Membrane, plasma	Membrane transport, monocarboxylic acid transporter activity	
KIAA2022	73.87–74.06	Xq13.2	*300524	KIAA2022 protein	Nucleus?	DNA synthesis, DNA polymerase activity, 3′-5′ exonuclease activity	
ATRX	76.64–76.92	Xq21.1	*300032	Alpha thalassemia/mental retardation syndrome X linked / X-linked helicase 2	Nucleus	Transcription regulation, DNA repair, DNA methylation, DNA recombination, DNA helicase	Yes
ATP7A	77.05–77.20	Xq21.1	*300011	ATPase, Cu++ transporting, alpha polypeptide	Cytoplasm, Golgi, endoplasmic reticulum	Membrane transporter, copper-exporting ATPase activity	
+PGK1	77.24–77.27	Xq21.1	*311800	Phosphoglycerate kinase 1	Cytoplasm?	Metabolism, glycolysis, phosphokinase activity	
BRWD3	79.95–79.81	Xq21.1	*300553	Bromodomain and WD repeat domain-containing protein 3	Nucleus?	Transcription factor?	
+SRPX2	99.78–99.81	Xq22.1	*300642	Sushi-repeat-containing protein, X-linked 2	Extracellular, secreted	Signal transduction, growth factor?	
+TIMM8A	100.49	Xq22.1	*300356	Translocase of inner mitochondrial membrane 8 homolog A	Mitochondrion	Membrane transporter, protein transport	
NXF5	100.97–100.99	Xq22.1	*300319	Nuclear RNA export factor 5	Nucleus, cytoplasm	mRNA processing, mRNA export from nucleus	
+PLP	102.91–102.93	Xq22.2	*300401	proteolipid protein 1	Membrane, plasma	Membrane component, myelin component	Yes
+PRPS1	106.76–106.78	Xq22.3	*311850	Phosphoribosyl pyrophosphate synthetase 1	Cytoplasm?	Metabolism, ribonucleoside monophosphate biosynthesis	Yes
*ACSL4	108.77–108.86	Xq23	*300157	Acyl-CoA synthetase long-chain family member 4	Peroxisome membrane	Metabolism, lipid metabolism	
*PAK3	110.23–110.35	Xq23	*300142	P21 (CDKN1A)-activated kinase 3	Cytoplasm?	Signal transduction, protein serine/ threonine kinase	

Table 2 (*Continued*)

Gene name	*Megabases from Xpter*	*Cytoband*	*OMIM*	*Protein name*	*Cellular component*	*Biological function*	*Synaptic localization*
+DCX	110.42–110.54	Xq23	*300121	Doublecortin (doublecortex; lissencephaly, X-linked)	Cytoplasm, cytoskeleton	Cytoskeleton component, microtubule-associated complex	
*AGTR2	115.22	Xq23	*300034	Angiotensin II receptor, type 2	Membrane, plasma	Signal transduction, G-protein-coupled receptor protein signaling pathway	
UBE2A	118.59–118.60	Xq24	*312180	Ubiquitin-conjugating enzyme E2A (RAD6 homolog)	Nucleus	Ubiquitin cycle, ubiquitin-protein ligase	
UPF3B	118.87–118.85	Xq24	*300298	UPF3 regulator of nonsense transcripts homolog B	Nucleus, cytoplasm	mRNA catabolism, nonsense-mediated decay	
+NDUFA1	118.89	Xq24	*300078	NADH dehydrogenase (ubiquinone) 1 α subcomplex	Mitochondrion	Metabolism, energy production, oxidoreductase activity	
+LAMP2	119.44–119.48	Xq24	*309060	Lysosomal-associated membrane protein 2	Lysosome membrane	Membrane, lysosome	
CUL4B	119.59–119.54	Xq24	*300304	Cullin 4B	Nucleus?	Cell cycle, ubiquitin cycle, E3 ubiquitin ligase	
+GRIA3	122.14–122.45	Xq25	*305915	Glutamate receptor ionotropic AMPA 3	Membrane, plasma	Signal transduction, ion transport, glutamate signaling pathway	Yes
OCRL1	128.50–128.55	Xq25	*309000	Phosphatidylinositol polyphosphate 5-phosphatase	Cytoplasm, Golgi	Signal transduction, lipid metabolism	
ZDHHC9	128.80–128.76	Xq25–Xq26.1	*300646	Zinc-finger, DHHC-domain-containing protein 9	Cytoplasm, endoplasmic reticulum	?	
GPC3	132.49–132.95	Xq26.2	*300037	Glypican 3	Extracellular, matrix	Membrane component, integral membrane proteoglycan	
PHF6	133.33–133.39	Xq26.2	*300414	PHD finger protein 6	Nucleus	Transcription regulation	
+HPRT	133.42–133.46	Xq26.2	*308000	Hypoxanthine phosphoribosyltransferase 1	Cytoplasm	Metabolism, purine ribonucleoside salvage	
SLC9A6	134.88–134.95	Xq26.3	*300231	Solute carrier family 9 member 6, sodium/ hydrogen exchanger 6 (NHE6)	Endoplasmic reticulum, mitochondrion	Sodium:hydrogen antiporter activity, lysosome organization and biogenesis, regulation of endosome volume	
*ARHGEF6	135.57–135.69	Xq26.3	*300267	Rac/Cdc42 guanine nucleotide exchange factor (GEF) 6	Cytoplasm	Signal transduction, Rho guanyl-nucleotide exchange factor activity	
SOX3	139.41	Xq27.1	*313430	SRY (sex determining region Y)-box 3 protein	Nucleus	Transcription regulation	
FMR1	146.80–146.84	Xq27.3	*309550	Fragile X mental retardation protein 1 (FMRP)	Nucleus, cytoplasm	mRNA processing, mRNA export from nucleus	
*FMR2	147.39–147.89	Xq28	*309548	AF4/FMR2 family, member 2 protein	Nucleus	Transcription regulation	
IDS	148.36–148.39	Xq28	*309900	Iduronate 2-sulfatase	Lysosome	Metabolism, glycosaminoglycan metabolism	
+MTM1	149.49–149.59	Xq28	*300415	Myotubularin 1	Cytoplasm, membrane associated?	Signal transduction, protein phosphatase, phosphatidylinositol phosphatase activity, protein serine/threonine phosphatase activity, protein tyrosine phosphatase activity	
+SLC6A8	152.43–152.61	Xq28	*300036	Solute carrier family 6 (neurotransmitter transporter, creatine), member 8	Membrane, plasma	Membrane transport, creatine:sodium symporter activity, neurotransmitter:sodium symporter activity	
+ABCD1	152.64–152.66	Xq28	*300371	ATP-binding cassette, subfamily D (ALD), member 1	Peroxisome membrane	Membrane transporter, peroxisome	
+L1CAM	152.78–152.80	Xq28	*308840	L1 cell adhesion molecule	Membrane, plasma	Cell adhesion	Yes
+MECP2	152.94–153.02	Xq28	*300005	Methyl CpG-binding protein 2	Nucleus	Transcription regulation, methylcytosine binding	
FLNA	153.23–153.25	Xq28	*300017	Filamin A, alpha (actin-binding protein 280)	Cytoplasm, cytoskeleton	Signal transduction, actin cytoskeleton, cell motility, positive regulation of I-κB kinase/NF-κB cascade	Yes

Table 2 (*Continued*)

Gene name	*Megabases from Xpter*	*Cytoband*	*OMIM*	*Protein name*	*Cellular component*	*Biological function*	*Synaptic localization*
*RPL10	153.27–153.28	Xq28	*312173	Ribosomal protein L10	Cytoplasm, ribosome	Protein synthesis, ribosomal protein	Yes
*GDI1	153.32	Xq28	*300104	GDP dissociation inhibitor 1	Cytoplasm, membrane associated	Signal transduction, regulation of GTPase activity	Yes
IKBKG	153.42–153.44	Xq28	*300248	Inhibitor of κ light polypeptide gene enhancer in B cells, kinase gamma	Nucleus	Transcription regulation, induction of apoptosis, immune response, I-κB kinase/NF-κB cascade	
DKC1	153.64–153.66	Xq28	*300126	Dyskerin	Nucleus	Cell cycle, rRNA processing, telomere maintenance via telomerase	

Genes whose symbol is preceded by a + sign are involved in neuromuscular disorders (Supplementary Table S2), while those with an asterisk are involved in nonspecific (MRX) conditions (Supplementary Table S3). All other genes are involved in XLMR syndromes (Supplementary Table S1). Cytogenetic localization and the gene's OMIM number are indicated in columns 3 and 4, respectively. The name of the corresponding protein, its subcellular localization, biological function and eventual synaptic localization are reported in columns 5–8. *These genes are involved in nonspecific (MRX) conditions (column 1).

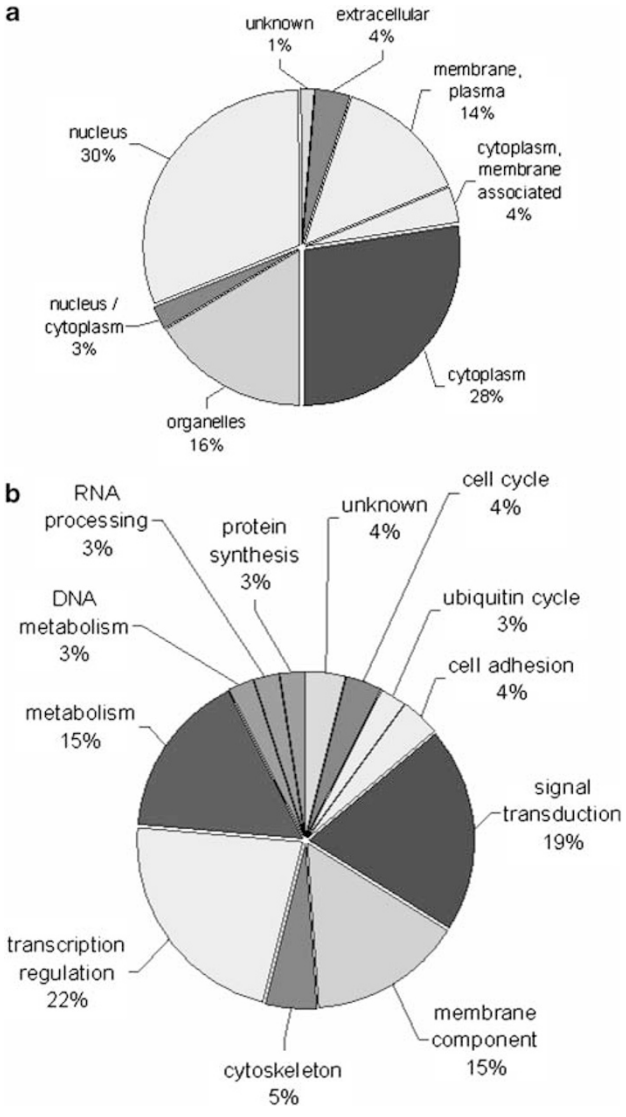


Figure 4 Pie charts illustrating (**a**) subcellular localization and (**b**) the molecular function of proteins encoded by the 82 known XLMR genes, according to the available Gene Ontology annotations (www.geneontology.org).

(http://www. ensembl.org/Homo_sapiens/mapview?chr = X) cause MR when mutated. As argued by Ropers,[42] approximately 40% of these genes are expressed in the brain (although not exclusively), suggesting that the actual number of XLMR genes might be much higher than the 82 presently known, possibly reaching 200. What are the possible strategies for the identification of the remaining XLMR genes?

The most comprehensive approach would be high-throughput genomic DNA resequencing of all genes on the X chromosome. One such international collaborative program has been underway since 2002.[43] The sequencing is based at the Sanger Institute and supported by the Wellcome Trust. A cohort of 250 XLMR families,

contributed by groups at Cambridge University (UK), Greenwood Genetic Center (USA) and Newcastle and Adelaide University (Australia), is utilized as starting material. Since 2004, this international collaboration has identified eight XLMR genes (*DLG3*, *AP1S2*, *CUL4B*, *MED12*, *ZDHHC9*, *BRWD3*, *UPF3B* and *HUWE1*).

A mutational screening of 47 brain-expressed genes from a 7.4 Mb region in Xp11 was undertaken by the EuroMRX consortium[44] and since 2003 it has led to the identification of four genes (*FTSJ1*, *JARID1C*, *PQBP1* and *PHF8*). However, such high-throughput resequencing approaches have their pitfalls and there are no guarantees that all or even the majority of mutations will be identified. The associated high cost, quality of the clinical material as well as the nature (eg duplications) and position (eg outside the coding regions) of the mutation are among the major complications. A candidate gene approach may provide a more focused alternative. Potential candidate genes might belong to at least three categories: (1) genes that are highly expressed in the brain (although many XLMR genes have a fairly 'flat' expression profile, ie they are transcribed at similar levels in several different tissues); (2) paralogues of known XLMR genes, because the corresponding proteins may have similar function (eg NLGN4 and NLGN3); (3) genes encoding proteins that interact with known XLMR proteins, because they cooperate in the same molecular pathways for example, members of the synaptic proteome such as those listed by Laumonnier *et al*.[38] However, the protein encoded by a known XLMR gene may also interact with the mRNA of other target genes, as recently described for FMRP and the PSD95 mRNA.[45] Therefore, the third criterion might be extended to include genes encoding proteins and/or mRNAs that interact with known XLMR proteins. The three above-mentioned criteria might also be used for selecting autosomal genes potentially involved in inherited MR. For example, the gene encoding the PSD95/SAP90 protein is *DLG4*, a paralogue of the XLMR gene *DLG3*. This gene is located on chromosome 17p and represents a potential candidate gene for autosomal MR.

The identification of a chromosome abnormality, such as a reciprocal translocation or a cryptic (submicroscopic) deletion or duplication, may also be extremely helpful in localizing a candidate gene, even in sporadic cases. Subtelomeric translocations have been identified by FISH analysis in up to 5% of patients with a family history of MR and dysmorphic features.[46] More recently, application of array technology to perform comparative genome hybridization (array-CGH) has allowed detection of submicroscopic deletions and duplications that would have been missed by both standard karyotyping and subtelomeric FISH.[47–48] Array-CGH can be performed at different resolution, that is, ~3400 BAC clones may be evenly spaced across the human genome every 1 Mb[48] or more clones (~32000) can be tiled up, providing a resolution of 100 kb.[47]

Lugtenberg *et al*[49] have prepared a specific array with 1460 BAC clones spanning the X chromosome (100 kb resolution) and tested probands from 40 MRX families, finding one family with a 7 Mb duplication in Xp22.2 and two families with a 500 kb duplication in Xq28 encompassing the *MECP2* gene. An even higher resolution is offered by the oligonucleotide arrays such as those employed by Friedman *et al*,[50] who studied 100 children with idiopathic MR. These authors used the Affymetrix GeneChip Human Mapping 100K SNP arrays and found eight cases of *de novo* deletions (as small as 178 kb) and two cases of *de novo* duplications (as small as 1.1 Mb).

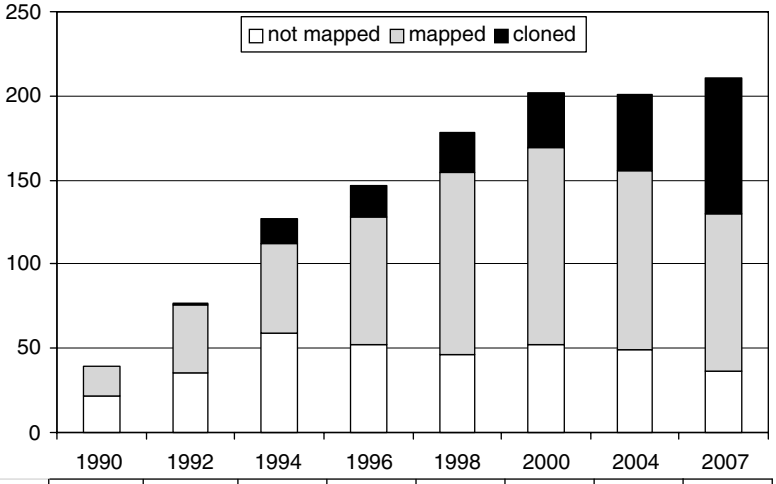
It is important to note that no single technique can substitute for all the others. Balanced translocations that interrupt a given XLMR gene can be identified by standard karyotyping (or subtelomeric FISH), but would go undetected with array-CGH and genomic sequencing. Conversely, submicroscopic duplications may be identified by array-CGH but would be missed with subtelomeric FISH and sequencing. Microdeletions would be readily detected by sequencing in hemizygous males but array-CGH and SNP arrays can identify small deletions also on the autosomes.

Zhang *et al*[51] have developed a cDNA array with ~1700 ESTs corresponding to most protein-coding genes on the X chromosome. Such an array has the potential to detect the presence of mutations in the regulatory region of genes that will result in significantly altered (usually decreased) gene expression levels. These mutations would not be detected by sequencing of the entire open reading frame of the gene. By analyzing the cDNA of 43 probands belonging to independent XLMR families, Zhang *et al*[51] found two patients with a fourfold reduction in the expression of the *PLP2* gene and of the corresponding protein and identified the same point mutation in the promoter, segregating with MR and altering the binding sequence of transcription factor ELK1.

Natural history of the XLMR catalogue

Thirty-nine conditions were listed in the first edition of the catalogue,[18] 17 had been localized by linkage analysis and no XLMR gene had been identified yet. The *FMR1* gene, which is inactivated in the fragile X syndrome and was the first gene responsible for XLMR to be cloned, was discovered just few months later.

Figure 5 illustrates the numbers of XLMR conditions (total, mapped and cloned) at different intervals over the last 17 years (1990–2007). The total number of entries has reached a plateau around 200, but this is not due to the absence of new reports of X-linked families and clinical entities. It rather reflects a balance between the new entries and those that are 'lumped' together because they were shown to have a mutation in the same gene. In contrast,



XLMR update:	1990	1992	1994	1996	1998	2000	2004	2007
Total count	39	77	127	147	178	202	201	215
mapped	17	41	53	76	109	117	107	97
cloned	0	1	15	19	23	33	45	82

Figure 5 Bar chart illustrating the historical progress in the identification of X-linked MR conditions as listed in the various XLMR updates since 1990. The total number of conditions has apparently reached a plateau in 2000, while the number of cloned genes (black) continue to increase at the expense of mapped (gray) and unmapped (white) XLMR conditions. The total number of catalogue entries, of mapped conditions and of cloned XLMR genes is also tabulated.

the number of cloned genes has more than doubled since 2001 and the number of conditions without a gene or at least a locus has decreased to less than 20% of the total number. Some of these latter conditions have been described more than 20 years ago and no sources of DNA might be currently available. Therefore, these 'orphan' entries might never be linked to known XLMR genes unless clinicians contact the families again and establish cell lines to secure a reliable source of DNA and RNA from the index cases. This is obviously true also for every new family identified and reported today.

The natural history of XLMR conditions has thus changed over the last 17 years: while linkage studies on large pedigrees assisted in mapping well-characterized clinical conditions on the X chromosome and candidate gene screening was slowly conducted, nowadays candidate genes abound and large numbers of patients (familial as well as isolated cases) are being screened in search of mutations.

Diagnostic issues

Approximately 50% of children with MR referred to a tertiary care center will receive a causal diagnosis, with clinical history and physical examination being the first and most important steps in the diagnostic process.[52] Consensus recommendations on the evaluation of individuals and children with MR have been prepared by the American College of Medical Genetics[53] and by the Genetics Committee of the American Academy of Pediatrics.[54] Useful flowcharts for diagnostic procedures have also been provided by Battaglia and Carey[55] and van Karnebeek *et al*.[56] This latter review provides an evidence-based information on the usefulness of various diagnostic procedures and is adaptable to the evaluation of potential XLMR patients. Briefly, collection of family history and physical examination (including a dysmorphological and neurological evaluation) are mandatory for every proband. Standard cytogenetic studies should then be performed unless a different cause is already suspected, while FISH analysis for subtelomeric rearrangements may be restricted to a subset of patients with dysmorphic features and/or positive family history. Array-CGH for the identification of cryptic deletions/duplications would represent a further step and may become increasingly common as the price of (micro)arrays decreases. Molecular testing for fragile X syndrome should also be done on all boys and girls lacking another diagnosis, while testing for the *ARX* recurrent mutation (dup24 bp) can be added in the presence of epilepsy and/or dystonia.[57] Search for duplication of the *MECP2* region may be warranted in any male with congenital hypotonia and significant delay.[34] Molecular testing for other XLMR genes might be more cost-effective in the presence of positive family history with convincing evidence of X linkage,[58] unless future technological advances (eg use of DNA resequencing chips for all known XLMR genes) will lower the costs of mutational analysis. Neuroimaging studies (NMR/MRI) to confirm or exclude the presence of brain malformations should be reserved to patients with neurological symptoms, such as epilepsy, micro/macrocephaly and/or associated manifestations for

example, phacomatosis.[59] Finally, simple tests of urine, blood and cerebrospinal fluid may lead to a diagnosis of a metabolic disorder, even in the absence of clear dysmorphic features or neurological symptoms like epilepsy.[60] Metabolic brain imaging (magnetic resonance spectroscopy) has also helped to uncover biochemical abnormalities within the brain, such as a deficit of the creatine transporter encoded by the *SLC6A8* gene. Creatine transporter deficiency has been recently suggested to account for 1% of males with MR of unknown etiology[61] and can be easily suspected in the presence of an increased creatine/creatinine ratio in urine. It goes without saying that in the clinical practice the diagnostic approach will result from a balance between the opinion of the expert clinician, the available means and the affordable costs. Patients and families will have to be involved in a comprehensive genetic counseling leading them to understand the possibilities, but also the limits, of current clinical and molecular genetics.

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