X LINKED MENTAL RETARDATION

Imen Rejeb*, Lamia Ben Jemaa(*, **), Habiba Chaabouni(*,**)

** Laboratoire de Génétique Humaine, Faculté de Médecine de Tunis –Tunisie-*
*** Service des Maladies Congénitales et Héréditaires, Hôpital Charles Nicolle de Tunis –Tunisie-*

I. Rejeb, L. Ben Jemaa, H. Chaabouni
GENETIQUE DU RETARD MENTAL LIE AU CHROMOSOME X
LA TUNISIE MEDICALE - 2009 ; Vol 87 (n°05) : 311 - 318

I. Rejeb, L. Ben Jemaa, H. Chaabouni
X LINKED MENTAL RETARDATION
LA TUNISIE MEDICALE - 2009 ; Vol 87 (n°05) : 311 - 318

RÉSUMÉ

Prérequis : Le retard mental est une entité très hétérogène. Il y a plus de 900 anomalies génétiques associées au retard mental, il affecte environ 3% de la population générale. La majorité des retards mentaux sont syndromiques et le syndrome de l' X fragile est le syndrome le plus fréquemment rencontré. Le retard mental lié au chromosome X (XLMR) est subdivisé en deux catégories : le retard mental syndromique (MRXS) quand le retard mental est associé à des signes cliniques et le retard mental non-syndromique (MRX) quand le retard mental est isolé.

But : Le but de cette revue systématique de la littérature était de réunir les résultats de plusieurs études sur le retard mental lié au chromosome X et de présenter les différents gènes impliqués dans cette maladie. Nous passons en revue les différents gènes impliqués dans le retard mental lié au chromosome X, les signes cliniques associés ainsi que les corrélations phénotype-génotype.

Méthodes : Une recherche exhaustive de la littérature récente a été effectuée sur les sites web « Science Direct » et « Interscience Wiley». Les mots clefs utilisés étaient « retard mental », « chromosome X», « gène », « retard mental syndromique », « retard mental non-syndromique ».

Résultats : Dans cette revue un certain nombre de gènes de retard mental lié au chromosome X ainsi que les signes cliniques associés sont discutés. Nous avons classé ces gènes par ordre de leur première implication dans le retard mental lié au chromosome X. Un tableau présenté sur le site « XLMR Update Web site » énumère les 82 gènes connus ainsi que leurs protéines correspondantes.

MOTS-CLÉS
Chromosome X - retard mental

SUMMARY

Background : Mental retardation (MR) is a group of heterogeneous clinical conditions. There are more than 900 genetic disorders associated with MR and it affects around 3% of the general population. Many MR conditions described are syndromic, fragile X syndrome being the most common clinical entity among them. X-linked mental retardation (XLMR) is subdivided in two categories: syndromic XLMR (MRXS) when MR is associated with clinical features and non-syndromic XLMR (MRX) when MR is isolated.

Aim: The aim of this systematic review of the literature was to join together the results of several studies related to X linked mental retardation and to present various genes implicated in this disease. In this review, focus has been given on genes implicated in mental retardation, the clinical data and on phenotype-genotype correlations.

Methods: An exhaustive electronic and library research of the recent literature was carried out on the Web sites "Science Direct" and "Interscience Wiley". The key words used were "mental retardation", "X chromosome", "gene", "syndromic mental retardation", "non-syndromic mental retardation".

Results: In this review a number of X linked genes, the clinical features associated with the gene abnormality, and the prevalence of the disease gene are discussed. We classified these genes by order of their first implication in MR. A table presented on the XLMR Update Web site who list the 82 known XLMR genes is available as XLMR Genes and corresponding proteins.

KEY-WORDS
X-linked - mental retardation

التخلف الذهني الجيني المرتبط بالصبغي

الباحثون : رجب . إ - بن جمع . ل - شعبوني . ح.

الهدف من هذه الدراسة هو تجميع نتائج البحوث المتعددة المتعلقة بالتخلف الذهني المرتبط بالصبغي وآستعراض مختلف الجينات المتسببة لهذه الإصابة كما تعرضنا في هذه الدراسة إلى العلامات السريرية المصاحبة . قمنا بترتيب الجينات حسب مسؤوليتها في هذا التخلف وأنجزنا جدولا يحتوي على 82 جينا معروفا إلى جانب البروتينات.

The American Association on Mental Retardation (1) defines mental retardation (MR) as follows: MR is a disability characterized by significant limitations both in intellectual functioning and in adaptive behaviour as expressed in conceptual, social, and practical adaptive skills. This disability originates before the age of 18 years. Although not perfect, the intellectual criterion for the diagnosis of MR is often represented by a Full Scale Intelligence Quotient of 70 or less. Mental retardation can be regarded as a symptom, therefore the underlying causes of MR are extremely heterogeneous, and in the majority of cases the cause of MR is unknown (Hamel BCJ. PhD Thesis) (2, 3). It is assumed that genes influencing cognitive function are ubiquitous in the human genome.

To date, more such genes have been found on the X-chromosome than on any other comparable segment of the autosomes. This might be a reflection of the greater ease in identifying genes on the hemizygous X-chromosome compared with the autosomes. Another, explanation lies in the heritability of a X-chromosomal gene defect, which usually does not manifest a phenotype in female carriers. Therefore, X-linked defects might be considered one of the most frequent genetic causes of MR. The importance of genes on the X-chromosome in the cause of MR has been recognized for decades. Two factors contributed to this recognition. Males outnumber females in nearly all surveys of MR with an excess of about 30% (4-5). In addition, numerous families have been reported in which MR segregated in an X-linked inheritance pattern. Historically, X-linked MR (XLMR) is divided into syndromic XLMR (MRXS), when the MR is associated with clinical, radiologic, or metabolic features or in non-syndromic (or non-specific) XLMR (MRX) when MR is isolated. On the basis of the IQ value, mental retardation may be classified in four categories of severity: mild (IQ 50–70), moderate (IQ 35–50), severe (IQ 20–35), and profound (IQ<20). At present, about 140 syndromic XLMR conditions have been reported; in almost half of these, causative mutations in genes have been identified, of which some were allelic. In contrast, in 24 of the presently known 82 MRX families (reported families with lodscore ? 2) mutations have been found. Mutations have also been identified in genes implicated in both syndromic and non-syndromic XLMR (OPHN1, MECP2, SLC6A8, ARX, PQBP1, JARIDIC…), which suggests that there is often no molecular basis for strictly dividing syndromic and non-syndromic entities (6).

Prevalence of XLMR:

The fragile X syndrome is the most frequent cause in XLMR, with an estimated prevalence of one in 4000 males (7, 8). It accounts for 15–25% of all patients with XLMR (9). The prevalence of XLMR has been estimated in one in 600 males (10), but there is a considerable variation in estimated prevalences of MR caused by monogenic XLMR. Although it was thought that 20–25% of male MR was caused by X-linked factors (4, 10), recent studies reported lower percentages of 10 to 12% (11, 12). The number of identified genes mutated in syndromic or non-syndromic forms of XLMR has increased considerably in the past years, but the number of mutations found in cohorts of sporadic male patients with MR appeared to be very low (12,13).A search for mutations of MECP2, ARX, and SLC6A8 was systematically carried out on panels consisting of linked families and small, unlinked families (14, 15). Additionally, mutation analysis of ARX, MECP2, and SLC6A8 in “sporadic” patients with an unexplained MR has been performed (13, 16, 17). All three genes were found to be mutated in 2–6.8% (2) of families linked to the regions of the respective gene localizations or small “unlinked” families compatible with X-linked inheritance. It appeared that the frequency of mutations in unrelated “sporadic” mentally retarded males is much lower (0.13– 0.43%) (2).

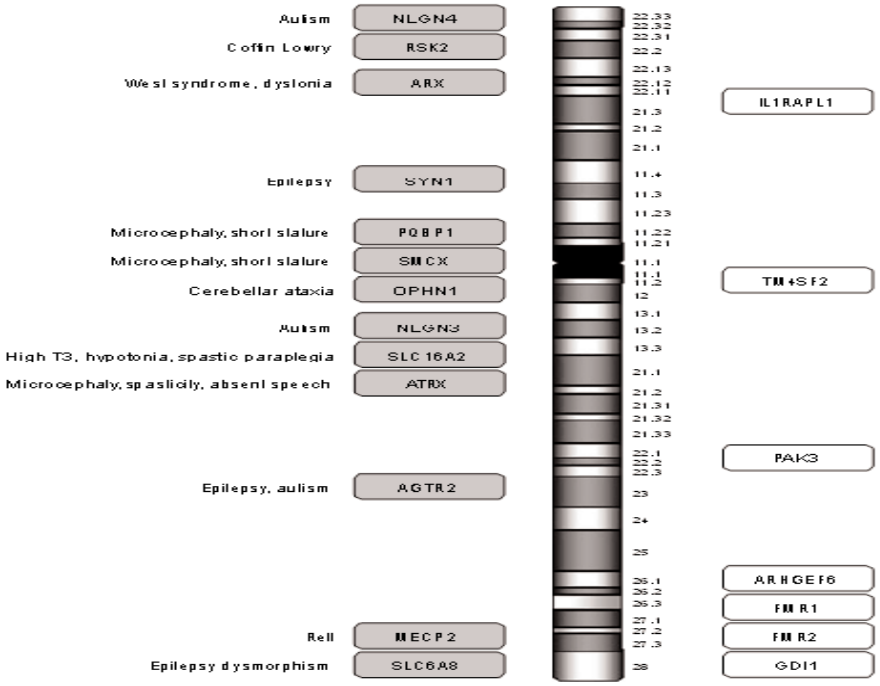
Diagnosis of XLMR:

The clinical diagnosis of XLMR is usually a diagnosis of exclusion of other causes of developmental delay in a male (table 1)(18) .All patients where XLMR is suspected should have the benefit of constitutional 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 (19, 20). Mutation analysis for Fragile X syndrome is also essential. Having excluded a karyotype abnormality and Fragile X syndrome by seeking an expansion in FMR1, X linked genes must be screened , where mutations have been described that result in either syndromic or non-syndromic mental retardation (figure 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 and the relative prevalence of the gene abnormality in the study population.

Table 1 : Investigation of a male child with possible XLMR based on Shevell et al (18)

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 T3 thyroid function tests if spastic paraplegin is present.

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. (6)



The aim of this systematic review of the literature was to join together the results of several studies related to X linked mental retardation and to present various genes implicated in this disease. In this review, focus has been given on genes implicated in mental retardation, the clinical data and on phenotype-genotype correlations.

METHODS

Search strategy:

The search strategy was based on a website entitled the XLMR Update Web site (http://xlmr.interfree.it/home.htm), in this site tables and maps are available. We can find tables listing XLMR syndromes, neuromuscular conditions, nonspecific MRX cases, XLMR genes and corresponding proteins. We can also find maps of all cloned XLMR genes. In this site we find links to the related articles available on “science direct” and “interscience wiley”.

Selection criteria

The selection criteria were applied to the titles and abstracts of publications. After a pilot study, more strict criteria were formulated and were applied during a second phase to articles fulfilling the first-phase criteria: articles must be published in peer-reviewed medical journals, articles must be written in English or French. Articles reporting genes that are associated only with a syndrome are not discussed, for example FMR1, L1CAM, PLP1, and DCX.

RESULTS

In this review we report 23 genes (FMR1 has been excluded) of the 82 MRX families where mutations have been found, the clinical features associated with the gene abnormality and the prevalence of the disease gene are discussed. We classified these genes by order of their first implication in MR. A table presented on the XLMR Update Web site who list the 82 known XLMR cloned genes is available as XLMR Genes and corresponding proteins.

GENES INVOLVED IN MENTAL RETARDATION

FMR2

The gene FMR2 was identified in 1992 (21, 22, 23) with an estimated incidence of 1 in 50,000/100,000 males (23). The FMR2 gene is located in Xq28 and it is associated with FRAXE, a folate-sensitive fragile site. The molecular basis is due to an unstable GCC repeat that silences gene expression when it is methylated and over 200 copies, although its function remains unknown. The phenotype associated can be mild or borderline mental retardation.

ATRX: XH2

Stayton et al. (24) described the cloning and characterization of a gene, provisionally called X-linked helicase-2 (XH2), located on chromosome Xq13. In patients with the ATR-X syndrome, an X-linked disorder comprising severe psychomotor retardation, characteristic facial features, genital abnormalities, and alpha-thalassemia, Gibbons et al. (1995)(25) identified mutations in the XH2 gene.

GDI1

GDI1 discovered in 1996 (26) codes for a Rab GDP-

dissociation inhibitor, ·GDI1, it is located on Xq28, and it is also predominantly expressed in brain (27). As an example of a candidate gene approach, three point mutations were found on GDI1 in MRX patients, one causing loss of function, and two missense mutations causing a dramatic decrease in the affinity between ·GDI1 and one of its binding proteins. After identification of two MRX genes coding for proteins that regulate members of the Ras superfamily of small GTP-binding proteins, a hypothesis was raised suggesting that RhoGAP and RabGDI and its effectors could have a major impact on the regulation of neuronal development and synaptic function (28). Moderate to severe mental retardation was found in 7 males and milder intellectual impairment in 2 females, without any specific clinical, radiologic, or biologic features.

PAK3

PAK3 discovered in 1996(29) is a member of the large family of p21- activating protein kinases (PAKs). The PAK3 gene is predominantly expressed in foetal and adult brain, and it has been implicated as a critical downstream effector that links RhoGTPases to the actin cytoskeleton and to MAP kinase cascades, including the c-Jun amino-terminal kinase (JNK) and p38. We have reported the first PAK3 gene splice mutation that activates a cryptic donor splice site identified in a family with X-linked MR (31).Affected males had borderline to mild mental retardation and most were able to function independently and hold menial jobs. Several patients had psychiatric disorders. All carrier women had normal intelligence (31).

ARHGEF6:

ARHGEF6 discovered in 1998 (32)(also known as aPIX or Cool-2) is encoding a protein that interacts with Rho-GTPases (33). It is located on Xq26 and it was identified after molecular characterization of a balanced X;21 translocation in a male with mental retardation, mild dysmorphic features, and sensorineural hearing loss. Additionally, a point mutation was identified in one MRX family causing a preferential exon skipping (33).

OPHN1

The Oligophrenin 1 gene (OPHN1) was identified in 1998 by cloning the breakpoint of a t(X; 12) in a mentally retarded female (34). Subsequently, a frameshift mutation was identified in MRX60. Oligophrenin 1 gene is located on Xq12 and encodes a Rho-GTPase activating protein. Inactivation of OPHN1 increases the activity of small RhoGTPases, RhoA, Rac, and Cdc42, which link cell-surface receptors to the organization of the actin cytoskeleton. Other MRX genes known to mediate through the same pathway are RhoGEF(35) and PAK3(36).

Mutation analysis seems warranted for familial as well as sporadic MR males with cerebellar vermis hypoplasia, associated with ventriculomegaly/ hydrocephaly, epilepsy, hypogenitalism (cryptorchidism, hypoplastic scrotum, and microphallus), and strabismus.

PQBP1

The polyglutamine-binding protein 1 (PQBP1) located on Xp11.23 was identified in 1999 and is supposed to interact with expanded polyglutamine tracts of huntingtin, ataxin, and androgen receptor (37, 38, 39). PQBP1 should be tested for males showing a distinct syndromic phenotype comprising MR, short stature with lean body habitus, microcephaly, small testes, and spasticity. In children, the facial characteristics might be absent, and in those cases, familial X-linked microcephaly may be the only feature that warrants PQBP1 testing (6).

ARX

Mutations in the ARX gene located on Xp22.11 identified in 1999 cause several different MR syndromes (40, 41). Mutations of ARX are associated with striking pleiotropy and consistent genotype-phenotype correlation, although intrafamilial variability does occur (42). For example, Turner et al. (43) described a family with four affected males, one with West syndrome, another Partington syndrome, and two others non-syndromic MR. Moreover, in a study of 46 males with the 428–451dup (24 bp), it was shown that the degree of MR ranged from mild to severe and infantile spasms occurred in 12.5% and other less severe forms of seizures in 37.5%. Characteristic dystonic movements of the hands were observed in 63% and dysarthria in 54% (44). A point mutation in ARX gene L33P was found in a Tunisian family linked to Xp21.3 (MRX54) in which males present only mental retardation (45).

RSK2: RPS6KA3

Merienne et al. (46) studied a family in which multiple males had been diagnosed with non-specific mental retardation. They re-examined 2 of the affected individuals, then 38 and 29 years old, and found that they exhibited none of the facial, digital, or skeletal features or the abnormal posture or gait typical of Coffin-Lowry syndrome. Furthermore, both presented with very mild mental retardation, compatible with social autonomy. The XLMR locus in this family (MRX19) was mapped to a 42-cM region in Xp22. Localization of the RPS6KA3 (ribosomal protein S6 kinase polypeptide 3) gene within this interval prompted Merienne et al. to analyze genomic DNA from 1 male patient for the presence of mutations in the RPS6KA3 gene.

MECP2

Rett syndrome is a progressive neurological disease that primarily affects females (incidence 1/10,000) (47). After a normal developmental period of 6–18 months, affected children lose acquired skills such as purposeful hand use and speech and show deceleration of head circumference. Social behaviour becomes impaired, many girls develop seizures and anxiety, and the vast majority displays a continual, stereotypic hand-wringing movement (47). Mutations in the methyl-CpG-binding protein 2 (MECP2) gene have been identified in up to 80% of Rett syndrome cases (48,49).MECP2 is located on Xq28, this gene is a member of methyl-CpG-binding protein family and acts as a non-global transcriptional repressor. In boys with MECP2 mutations, the clinical picture can vary considerably, depending on the nature of the mutation. There are two categories of sporadic MR male patients in which MECP2 mutation analysis may be considered: males born with congenital encephalopathy, in particular, when there is a sister (or close maternal female relative) with Rett syndrome and males with classic Rett syndrome. In familial cases, MECP2 analysis might be considered in families compatible with X-linked inheritance, where affected males have MR spasticity, movement disorder, or resting tremors, and the Xq28 region can not be excluded by linkage analysis.

IL1RAPL
IL1RAPL was isolated in 1999 by positional cloning in the Xp22.1–p21.3 region defined by overlapping microdeletions in two MRX families, found to be expressed at a low level in foetal and adult brain and mutated in two independent MRX families (34). IL1RAPL (interleukin-1 receptor accessory protein like) is a member of the IL-1 receptor family. . Families with IL1RAPL1 deletions show mental retardation, adrenal hypoplasia, Duchenne muscular dystrophy and glycerol kinase deficiency (34).

TM4SF2:
TM4SF2 was identified in 2000 by positional cloning after characterizing an X;2 balanced translocation in a female patient with mild mental retardation and it is located on Xp11.4(35). The TM4SF2 gene is expressed in a range of human tissues, including foetal and adult brain. Different mutations in TM4SF2 were found in two MRX families with mild to moderate mental retardation. Its encoded protein is a member of the tetraspanin family, members of which are known to participate in molecular complexes such as ,-integrins. Such complexes are accepted to be involved in the regulation of actin cytoskeleton organization, suggesting that the primary defect resulting from mutations in the TM4SF2 gene would be an impaired ability of the actin cytoskeleton to drive neurite outgrowth leading to an abnormal neuronal function.

JARID1C
JARID1C was identified in 2000 (51). Mutations in the gene JARID1C/SMCX (Xp11.22) were recently found to cause XLMR (52). All JARID genes show strong homology to the transcription factor RBBP2, which is assumed to play a role in chromatin remodelling (53). As the gene was identified only very recently, clinical data of patients with JARIDIC mutations are very scarce. Some are non-syndromic while in others, a syndromic phenotype is present. Features observed in several patients are short stature, microcephaly, strabismus, hypermetropia, diastema of teeth, cryptorchism (progressive) spasticity, epilepsy, and behavioral or mood problems. A combination of these features seems indicative for screening for JARID1C mutations.

FACL4:
Raynaud et al. reported a 4-generation family with non-specific X-linked mental retardation mapped between DXS990 and DXS1227 (Xq21.33-q27.1) with a maximum lod at theta = 0.0 of 2.14 at DXS1001 (54). Affected males showed non-specific, non-progressive mental retardation ranging from severe to moderate, without seizures, whereas carrier females showed highly variable cognitive capacities, ranging from moderate mental retardation to normal intelligence. In the proband of the family reported by Raynaud et al. as MRX63, Meloni et al. identified a mutation in the FACL4(Fatty Acid CoA Ligase, Long Chain 4 gene localised in Xq22.3(55).

SLC6A8
Mutations in the creatine transporter gene SLC6A8 located on Xq28 identified in 2001(56), lead to severe MR in males, whereas in about half of the population of female carriers, mild learning disabilities appeared to be common (57). Complete absence of creatine and phosphocreatine in the brain, as revealed by brain proton magnetic–resonance spectroscopy (H-MRS), increased creatine-creatinine ratios in plasma and urine, but normal guanidinoacetate levels are pathognomonic for this disorder, and at physiological concentrations, the uptake of creatine into fibroblasts from male patients is markedly impaired. Features in “young” sporadic and familial cases indicating creatine deficiency are short stature, low weight gain and poor muscle build, hypotonia, movement disorder (extrapyramidal/spasticity), seizures, behavior and expressive language problems, and “in older males” progression of intestinal, neurological, and psychiatric features could be added. Mutation analysis should be preceded by a urine analysis of the creatine:creatinine ratios. Only in patients with abnormal ratios or absence of creatine on brain H-MRS, DNA analysis of the SLC6A8 gene should be performed.

AGTR2:
Vervoort et al. (58) screened affected males from 33 families with possible X-linked MR but no definitive linkage data, and a large cohort of 552 unrelated male patients with MR of unknown cause but negative for the FMR1 expansion. Eight of the 590 unrelated male patients with MR were found to have sequence changes in the AGTR2 (Angiotensin II Receptor, Type 2) gene localised in Xq22-q23 , including 1 frameshift and 3 missense mutations. Five of 9 patients with AGTR2 mutations had seizures and, with the exception of 1 patient, they were not hypertensive. The mental retardation ranged from moderate to severe. Two patients also showed autistic behavior. Vervoort et al. concluded that there is a role for AGTR2 in brain development and cognitive function.

ZNF41:
In a patient with X-linked mental retardation, Shoichet et al. (59) found a 738C-T transition in the ZNF41 (Zinc Finger protein 41) gene, predicted to result in a pro111-to-leu (P111L) amino acid change. The abnormality was also found in his affected brother. The index patient had delayed early milestones and at the age of 5 years was functioning at an intellectual level of age 3 years. He exhibited language retardation, avoided social contact, and was hyperactive. He had no dysmorphic features or additional neurologic abnormalities. Both of the mother's brothers were affected but further clinical data were not available. The mother was shown to carry the mutation.

FTSJ1:
Freude et al. found that FTSJ1 (Fts J homolog E.coli) is localised in Xp11.23 (60). In a family reported by Hamel et al. (61), and designated MRX44 (309549), Freude et al. found a mutation in the FTSJ1 gene. Other mutations in this gene were found in 2 other families. In a large Belgian family with nonsyndromic X-linked mental retardation designated MRX9. The findings indicated that the FTSJ1 protein, which may be associated with ribosomal stability, is associated with X-linked mental retardation.

DLG3

Tarpey et al. identified truncating mutations in the human DLG3 gene localised in Xq13.1 in 4 of 329 families with moderate to severe X-linked mental retardation (62). All the affected males in the families had moderate to severe mental retardation while female carriers were usually of normal intellect. DLG3 (discs large homolog3) encodes synapse-associated protein 102 (SAP102), a member of the membrane-associated guanylate kinase protein family. Neuronal SAP102 is expressed during early brain development and is localized to the postsynaptic density of excitatory synapses.

NLGN4:

Neuroligins constitute a family of proteins thought to mediate cell-to-cell interactions between neurons. Neuroligins function as ligands for the neurexin family of cell surface receptors. NLGN4 localised in Xp22.3 is a member of this family. In all affected members of a large French family with X-linked mental retardation, with or without autism or pervasive developmental disorder, Laumonnier et al. identified a 2-bp deletion, in the fifth exon of the NLGN4 gene (63). Healthy males in the family did not have the deletion, and obligate carrier females were heterozygous for the mutation. Laumonnier et al. (63) noted that mutations in the NLGN4 gene are involved in a wide spectrum of phenotypes.

NLGN3

During the sequencing of an Xq13 locus associated with mental retardation, Philibert et al. independently identified NLGN3 which they recognized as a human homolog of rat neuroligin-3 (NL3)(64). In 2 brothers, one with X-linked autism and the other with X-linked Asperger syndrome, Jamain et al. (65) identified a mutation in the NLGN3 gene.

SYN1:

Garcia et al. (66) reported a novel X-linked recessive syndrome in 4-generation kindred in which some males of normal intelligence had epilepsy and others had various combinations of epilepsy, learning difficulties, macrocephaly, and aggressive behavior. The natural history of seizures was variable, occurring only during childhood in some, developing at age 27 in 1, and appearing only in association with specific stimuli in others. Genetic linkage analysis mapped the disorder in this family to Xp11.3-q12, between the MAOB gene and marker DXS1275. A maximum 2-point lod score of 4.06 at theta = 0.0 was found with DXS1039. By direct sequencing of the SYN1 (Synapsin I) gene, Garcia et al. (66) identified a 356trp-to-ter mutation in all 10 affected males and in obligate carrier females.

SLC16A2:

Mutations in SLC16A2 (solute carrier family 16 (mono-carboxylic acid transporter), member 2 localised in Xq13.2, also known as MCT8, a thyroid hormone transporter gene, were first reported in five unrelated boys with severe mental retardation and high triiodothyronine T3 (67) . For patients with abnormal triiodothyronine (T3) levels, global developmental delay, central hypotonia, spastic paraplegia, dystonic movements, rotary nystagmus, and impaired hearing and gaze SLC16A2 should be screened.

DISCUSSION

At present 24 MRX genes have been resolved (we have excluded the FMR1 gene listed as Fragile X syndrome FRAXA), which together explain 24 of the 82 linked MRX families with a lodscore > 2(6). The identification of 24 MRX genes allowed us to explore their functional roles in neuronal development and cognitive processes .Valuable neurobiological information will be provided by animal studies, as shown by recent research in the fmr1 knockout mice (68, 69). Elucidating the MRX genes and their functions will reveal crucial pathways for normal function of the brain and will contribute to broaden the knowledge on pathophysiology of XLMR. This will form the basis for further neurobiological research in obtaining more insight in mental and motor development. In addition, this knowledge will also guide the selection of novel candidate genes not only on the X-chromosome but also elsewhere on the genome.

Historically, XLMR is classified in syndromal and non-syndromal forms. Designating an XLMR entity as non-syndromic implies that no other clinical features but MR are consistently present among affected individuals. Patients initially diagnosed with non-syndromic MR should, therefore be thoroughly re-examined when mutations in MRX(S) genes are identified. The classical example of the fragile X syndrome illustrates this well. The family originally described in 1943 as being non-syndromic was restudied in 1981 by Richards et al. (70), who noted that the affected males showed prognathism, large ears and macroorchidism and could therefore be classified as syndromic.

In clinical practice, karyotyping and molecular studies of the FMR1 gene are commonly performed in male patients with MR of unknown cause. In larger families, linkage mapping may focus mutation screening on one or more of the known XLMR genes present in the linkage interval. Therefore careful clinical examination of males with MR is important because this will lead to a pre-selection for molecular testing in a given family.

CONCLUSION

For the majority of patients, clinical features will not be specific enough to guide mutation analysis for a specific XLMR gene. Therefore, it is obvious that mutation analysis in unexplained MR needs to be more robust and cheaper before it is ready to be used in clinical practice.

Although the understanding of molecular mechanisms of XLMR genes and of neural function of the proteins they encode are progressing, therapeutic strategies for MR are far away. The pathophysiological processes of MR in the human brain are very complex and, have most probably started already in early pregnancy. Despite these difficulties, the first attempt at treatment with group 1 mGluR antagonists or AMPA receptor enhancers, is currently being performed in a cohort of fragile X patients (68) (see also http:// www.fraxa.org/ra_berry-kravis.aspx.). Future studies might reveal whether these

neuropharmacological approaches are effective as hypothesized, but it might be clear that it will take decades for therapeutic interventions to come. In addition to pharmaceutical intervention, one should not forget the positive effects that can be obtained by conventional 'treatment', offering MR individuals a stimulating and activating environment.

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 and genes are listed at (http://xlmr.interfree.it/home.htm).

RÉFÉRENCES

1. American Association on Mental Retardation. Mental Retardation: Definition, Classification, and Systems of Supports, 10th edn. Washington, 2002.
2. Hamel BCJ. X-linked mental retardation; a clinical and molecular study. PhD Thesis. Nijmegen (webdoc.ubn.-kun.nl/mono/h/hamel_b/xlinmere.pdf)1999.
3. Leonard H, Wen X. The epidemiology of mental retardation: challenges and opportunities in the new millennium. Ment Retard Dev Disabil Res Rev 2002; 8: 117–134.
4. Turner G, Turner B. X-linked mental retardation. J Med Genet 1974; 11: 109–113.
5. Croen LA, Grether JK, Selvin S. The epidemiology of mental retardation of unknown cause. Pediatrics 2001; 107: E86.
6. Kleefstra T, Hamel BCJ. X-linked mental retardation: further lumping, splitting and emerging phenotypes. Clin Genet 2005; 67: 451–467
7. Crawford DC, Acuna JM, Sherman SL. FMR1 and the fragile X syndrome: human genome epidemiology review. Genet Med 2001; 3: 359–371.
8. Turner G, Webb T, Wake S, Robinson H. Prevalence of fragile X syndrome. Am J Med Genet 1996: 64; 196–197.
9. 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: 713–724.
10. Herbst DS, Miller JR. Nonspecific X-linked mental retardation II. the frequency in British Columbia. Am J Med Genet 1980; 7: 461–469.
11. Ropers HH, Hamel BCJ. X-linked mental retardation. Nat Rev Genet 2005; 6: 46–57.
12. 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: 689–693.
13. Gronskov K, Hjalgrim H, Nielsen IM, Brondum-Nielsen K. Screening of the ARX gene in 682 retarded males. Eur J Hum Genet 2004 ; 12: 701–705.
14. Bienvenu T, Poirier K, Friocourt G et al. ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation. Hum Mol Genet 2002; 11: 981–991.
15. Rosenberg EH, Almeida LS, Kleefstra T et al. High prevalence of SLC6A8 deficiency in X-linked mental retardation. Am J Hum Genet 2004; 75: 97–105.
16. Yntema HG, Kleefstra T, Oudakker AR et al. Low frequency of MECP2 mutations in mentally retarded males. Eur J Hum Genet 2002; 10: 487–490.
17. Wood T, Rosenberg EH, Clark AJ et al. Molecular and biochemical testing of creatine deficiency in an MR population suggests a 1% prevalence. American Society of Human Genetics, 54th annual meeting, Toronto 2004.
18. Shevell M, Ashwal S, Donley D et al. 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 :367–80.
19. Knight SJ, Regan R, Nicod A et al. Subtle chromosomal rearrangements in children with unexplained mental retardation. Lancet 1999; 354:1676–81.
20. Flint J, Knight S. The use of telomere probes to investigate submicroscopic rearrangements associated with mental retardation. Curr Opin Genet Dev 2003; 13:310–16.
21. Sutherland, G. R.; Baker, E. Characterisation of a new rare fragile site easily confused with the fragile X. Hum Molec Genet 1992; 1: 111-113.
22. Gecz J, Gedeon AK, Sutherland GR, Mulley JC. Identification of the gene FMR2, associated with FRAXE mental retardation. Nature Genet 1996 ; 13:105–108.
23. Gu Y, Shen Y, Gibbs RA, Nelson DA. Identification of FMR2, a novel gene associated with the FRAXE CCG repeat and CpG island. Nature Genet 1996; 13:109–113.
24. Stayton C L, Dabovic B., Gulisano M et al. Cloning and characterization of a new human Xq13 gene, encoding a putative helicase. Hum Molec Genet 1994; 3: 1957-1964.
25. Gibbons R J, Picketts D J, Villard L, Higgs DR. Mutations in a putative global transcriptional regulator cause X-linked mental retardation with alpha-thalassemia (ATR-X syndrome). Cell 1995; 80: 837-845.
26. Hamel B C J, Kremer H, Wesby-van Swaay E et al. A gene for nonspecific X-linked mental retardation (MRX41) is located in the distal segment of Xq28. Am J Med Genet. 1996; 64: 131-133.
27. D'Adamo P, Menegon A, Lo Nigro C, et al. Mutations in GDI1 are responsible for X-linked non-specific mental retardation. Nat Genet 1998; 19:134–139.
28. Antonarakis SE, Van Aelst L. Mind the GAP, Rho, Rab and GDI. Nat Genet 1998; 19:106–108.
29. Donnelly A J, Partington M W, Ryan A K, Mulley J C. Regional localisation of two non-specific X-linked mental retardation genes (MRX30 and MRX31). Am J Med Genet 1996; 64: 113-120.
30. Allen KM, Gleeson JG, Bagrodia S, et al. PAK3 mutation in nonspecific X-linked mental retardation. Nat Genet 1998 ; 20:25–30.
31. Rejeb I, Saillour Y, Castelnau L, et al. A novel splice mutation in PAK3 gene underlying mental retardation with neuropsychiatric features. Eur J Hum Genet 2008; 16:1358-63.
32. Yntema H G, Hamel B C, Smits A P et al. Localisation of a gene for non-specific X linked mental retardation (MRX46) to Xq25-q26. J Med Genet 1998; 35: 801-805.
33. Kutsche K, Yntema H, Brandt A, et al. Mutations in ARHGEF6,

encoding a guanine nucleotide exchange factor for Rho GTPases, in patients with X-linked mental retardation. Nat Genet 2000 ; 26:247–250.
34. Carrié A, Jun L, Bienvenu T, et al. A new member of the IL-1 receptor family highly expressed in hippocampus and involved in X-linked mental retardation. Nat Genet 1999 ; 23:25–31.
35. Zemni R, Bienvenu T, Vinet MC, et al. A new gene involved in X-linked mental retardation identified by analysis of an X;2 balanced translocation. Nat Genet 2000; 24:167–170.
36. Allen KM, Gleeson JG, Bagrodia S et al. PAK3 mutation in nonsyndromic X-linked mental retardation. Nat Genet 1998 ; 20: 25–30.
37. Billuart P, Bienvenu T, Ronce N et al. Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation. Nature 1998; 392: 923–926.
38. Okazawa H, Rich T, Chang A et al. Interaction between mutant ataxin-1 and PQBP-1 affects transcription and cell death. Neuron 2002; 34: 701–713.
39. Kalscheuer VM, Freude K, Musante L et al. Mutations in the polyglutamine binding protein 1 gene cause X-linked mental retardation. Nat Genet 2003; 35: 313–115.
40. Stromme P, Sundet K, Mork C, Cassiman J-J, Fryns J-P, Claes S. X linked mental retardation and infantile spasms in a family: new clinical data and linkage to Xp11.4-Xp22.11. J Med Genet 1999; 36: 374-378.
41. Stromme P, Mangelsdorf ME, Shaw MA et al. Mutations in the human ortholog of Aristaless cause X-linked mental retardation and epilepsy. Nat Genet 2002; 30:441-5.
42. Kato M, Das S, Petras K et al. Mutations of ARX are associated with striking pleiotropy and consistent genotypephenotype correlation. Hum Mutat 2004; 23: 147–159.
43. Partington MW, Mulley JC, Sutherland GR, Hockey A, Thode A, Turner G. X-linked mental retardation with dystonic movements of the hands. Am J Med Genet 1988; 30: 251–262.
44. Frints SG, Froyen G, Marynen P, Willekens D, Legius E, Fryns JP. Re-evaluation of MRX36 family after discovery of an ARX gene mutation reveals mild neurological features of Partington syndrome. Am J Med Genet 2002; 112: 427–428.
45. Bienvenu T, Poirier K. ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation.Hum Mol Genet 2002; 11:981-991.
46. Merienne K, Jacquot S, Pannetier S et al. A missense mutation in RPS6KA3 (RSK2) responsible for non-specific mental retardation. (Letter) Nat Genet 1999; 22; 13-14.
47. Hagberg B, Hanefeld F, Percy A, Skjeldal O. An update on clinically applicable diagnostic criteria in Rett syndrome. Euro J Paediatr Neurol 2002; 6: 293–297.
48. Mnatzakanian GN, Lohi H, Munteanu I et al. A previously unidentified MECP2 open reading frame defines a new protein isoform relevant to Rett syndrome. Nat Genet 2004; 36: 339–341.
49. Amir RE, Van den Veyver IB, WanM, Tran CQ, FranckeU, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet 1999; 23: 185–188.
50. Kutsche K, Yntema H, Brandt A et al. Mutations in ARHGEF6, encoding a guanine nucleotide exhange factor for Rho GTPases, in patients with X-linked mental retardation. Nat Genet 2000; 26: 247–250.
51. Claes S, Devriendt K ,Van Goethem G et al. Novel syndromic form of X-linked complicated spastic paraplegia. Am J Med Genet 2000; 94: 1-4.
52. Jensen LR, Amende M, Gurok U et al. Mutations in the JARID1C Gene, Which Is Involved in Transcriptional Regulation and Chromatin Remodeling, Cause X-Linked Mental Retardation. Am J Hum Genet 2004; 76: 227–236.
53. Clissold PM, Ponting CP. JmjC: cupin metalloenzyme-like domains in jumonji, hairless and phospholipase A2beta. Trends Biochem Sci 2001; 26: 7–9.
54. Raynaud, M.; Moizard, M.-P.; Dessay, B.et al. Systematic analysis of X-inactivation in 19 XLMR families: extremely skewed profiles in carriers in three families. Euro J Hum Genet 2000; 8: 253-258.
55. Meloni I, Muscettola M, Raynaud Met al. FACL4, encoding fatty acid-CoA ligase 4, is mutated in nonspecific X-linked mental retardation. Nat Genet 2002; 30: 436-440.
56. Salomons GS, van Dooren S. J. M., Verhoeven, N. M.et al. X-linked creatine-transporter gene (SLC6A8) defect: a new creatine-deficiency syndrome. Am J Hum Genet 2001; 68: 1497-1500.
57. Salomons GS, van Dooren SJ, Verhoeven NM et al. X-linked creatine transporter defect: an overview. J Inherit Metab Dis 2003; 26: 309–318.
58. Vervoort V S, Beachem M A, Edwards P S et al. AGTR2 mutations in X-linked mental retardation. Science 2002; 296: 2401-2403.
59. Shoichet S A, Hoffmann K, Menzel C et al. 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: 1341-1354.
60. Freude K, Hoffmann K, Jensen L-R et al. 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: 305-309.
61. Hamel B C J, Smits A P T, van den Helm B et al. Four families (MRX43, MRX44, MRX45, MRX52) with nonspecific X-linked mental retardation: clinical and psychometric data and results of linkage analysis. Am J Med Genet 1999; 85: 290-304.
62. Tarpey P, Parnau J, Blow M et al. Mutations in the DLG3 gene cause non-syndromic X-linked mental retardation. Am J Hum Genet 2004; 75: 318-324.
63. Laumonnier F, Bonnet-Brilhault F, Gomot M et al. 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: 552-557.
64. Philibert R A, Winfield S L, Sandhu H K, Martin B M, Ginns E I. The structure and expression of the human neuroligin-3 gene. Gene 2000; 246: 303-310.
65. Jamain S, Quach H, Betancur C et al. 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: 27-29.
66. Garcia C C, Blair H J, Seager M et al. Identification of a mutation in synapsin I, a synaptic vesicle protein, in a family with epilepsy. J Med Genet 2004; 41: 183-187.
67. Friesema E C H, Grueters A, Biebermann H et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. Lancet 2004; 364: 1435-1437.
68. Chiurazzi P, Neri G, Oostra BA. Understanding the biological underpinnings of fragile X syndrome. Curr Opin Pediatr 2003; 15: 559–566.
69. Willemsen R, Oostra BA, Bassell GJ, Dictenberg J. The fragile X syndrome: from molecular genetics to neurobiology. Ment Retard Dev Disabil Res Rev 2004; 10: 60–67.
70. Richards BW, Sylvester PE, Brooker C. Fragile X-linked mental retardation: the Martin–Bell syndrome. J Ment Defic Res 1981; 25 (Pt 4): 253–256.