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REVIEW

Genetics and pathophysiology of mental retardation

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Mental retardation (MR) is defined as an overall intelligence quotient lower than 70, associated with functional deficit in adaptive behavior, such as daily-living skills, social skills and communication. Affecting 1–3% of the population and resulting from extraordinary heterogeneous environmental, chromosomal and monogenic causes, MR represents one of the most difficult challenges faced today by clinician and geneticists. Detailed analysis of the Online Mendelian Inheritance in Man database and literature searches revealed more than a thousand entries for MR, and more than 290 genes involved in clinical phenotypes or syndromes, metabolic or neurological disorders characterized by MR. We estimate that many more MR genes remain to be identified. The purpose of this review is to provide an overview on the remarkable progress achieved over the last decade in delineating genetic causes of MR, and to highlight the emerging biological and cellular processes and pathways underlying pathogeneses of human cognitive disorders.
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Definition

Although controversies and debates over the definition and classification of mental retardation (MR) are still topical subjects, MR is defined as a disability characterized by significant limitations in intellectual functioning and in adaptive behavior, as expressed in conceptual, social and practical adaptive skills, that onset before the age of 18 years.[1] Intellectual functioning and its severity is commonly based on the evaluation of Full Scale Intelligence Quotient (FSIQ), and MR, which could be regarded in many disorders as a symptom, is represented by an intelligence quotient (IQ) of 70 or less. On the basis of the IQ, the most commonly used classification distinguishes two main categories: mild MR with an IQ between 50 and 70, and severe MR with an IQ below 50. Narrow definitions of MR restrict it to cases of non-progressive cognitive impairment detectable early after birth. Nonetheless, numerous hereditary neurodegenerative and metabolic disorders characterized by progressive cognitive deterioration beginning some time after a period of normal development are often included among the disorders with MR. Rett's syndrome, a neurodevelopmental disorder characterized by cessation and regression of cognitive development that affect almost exclusively young females, is one of the examples that is difficult to reconcile with the conventional definition of MR, athough it is systematically classified as syndromic MR. In this review, we chose a broader, albeit less precise, definition that includes progressive disorders with onset of cognitive impairment in childhood.

Conventionally, genetic forms of MR are subdivided into two major categories — syndromic MR characterized by associated clinical, radiological, metabolic or biological features, and non-syndromic (or non-specific) MR forms in which cognitive impairment represents the only manifestation of the disease. Although this distinction remains very useful for clinical purposes, recent phenotype–genotype studies and detailed clinical follow-up of patients are indicating that the boundaries between syndromic and non-syndromic MR forms are vanishing, and some of the latter forms could be recognized as syndromic forms.[2–6]

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Prevalence and diagnosis

In developed countries, MR represents the most frequent cause of severe handicap in children and one of the main reasons for referral in clinical genetic practices. Reported estimates are of 0.3–0.5% for moderate and severe MR (IQ < 50) and of 1–3% when mild MR (IQ ranging from 50 to 70) is included (see review by Stevenson *et al*[7]), and genetic causes may account for 25–50% of severe MR cases.[8] Causes of MR are extremely heterogeneous and can be environmental (malnutrition over pregnancy, environmental neurotoxicity, premature birth, perinatal brain ischemia, fetal alcohol syndrome, pre- or post-natal infections), chromosomal (aneuploidies, microdeletion syndrome), or monogenic (one finds 1177 Mendelian traits or genes in OMIM when searching for MR), but a precise cause is found only in about 50% of cases with moderate to severe MR, and in an even lower proportion for individuals with mild MR. In addition to conventional chromosomal aneuploidies, such as trisomy 21, that account for about 1.2/1000 live births, compelling evidence are suggesting that subtelomeric rearrangements, as a group, may account for 5–7% of syndromic forms of MR.[9] For monogenic causes, genes have mainly been found on the X chromosome than on any other comparable segment of the autosomes. This is partially related to the greater ease in pointing out X-linked genetic disorders (including those characterized by MR) and in identifying the corresponding genes and mutations involved. Epidemiological studies repeatedly showed a sex bias, with 30–50% excess of males over females, and led to the assumption that much of the excess of male MR may be due to X-linked genes.[7,10,11] If monogenic XLMR was to account for an excess of 30% of mentally retarded males over females, one would expect that 20–25% of genetically based MR in males, including sporadic MR cases, are caused by XLMR genes (see also Supplementary information S2 in Ropers and Hamel[5]). However, recent molecular studies,[12,13] in combination with clinical follow-up of a large cohort of patients,[7] are suggesting that the proportion of monogenic XLMR in sporadic MR males would account at best for 8–10% of the genetic causes of MR. More generally, this new revision of estimates downwards and the recent progress in genetic counseling and prenatal diagnosis of specific MR conditions such as fragile X syndrome, as well as the lack of data concerning the prevalence of autosomal causes justify achievement of further epidemiological studies on MR. Moreover, as the frequency of premature birth has increased and control over pregnancy and perinatal periods of predisposing environmental and nutritional factors for brain damage have been improved, frequencies related to genetic versus nongenetic causes have perhaps evolved over the last decay. Such new epidemiological studies should allow better evaluation of genetic causes involved in cognitive impairment and recurrence risks in undiagnosed mental retardation.

Genetic causes and hypotheses for physiopathology

On the basis of our current knowledge, MR resulting from constitutive or somatic mosaic deregulation of genetic information and programs might occur through (i) chromosomal rearrangements that result mainly into deleterious gene dosage effect, (ii) deregulation of the imprinting of specific genes or genome regions and (iii) dysfunction of single genes (monogenic causes of MR), which are individually required for development of cognitive functions (Table 1). MR resulting from these monogenic causes is either the only clinical manifestation of the disorders or a symptom of a clinical syndrome with or without detectable brain abnormalities. The section below should be regarded as an attempt to provide an updated view (but not an exhaustive list) of the genetic causes of MR, according to their involvement in the emerging molecular pathways and cellular processes thought to contribute to the physiopathological mechanisms underlying cognitive impairment.

Chromosomal abnormalities, subtelomeric and interstitial rearrangements

MR disorders resulting from aneuploidies such as trisomy 21, trisomy 13, trisomy 18 and partial chromosomal aneusomies such as 5p− have been the subject of regular extensive reviews, and will not be considered further in this review. However, in recent years, cryptic chromosomal

Table 1 Etiological classification of mental retardation

Acquired and environmental causes
(Pre-, peri- and postnatal causes)
Maternal intoxication (eg, alcohol, drugs)
Prematurity
Fetal infection (eg, CMV, toxoplasmosis)
Peri- and postnatal trauma, vascular accidents, asphyxia
Postnatal infections
Chromosomal abnormalities
(Detectable by conventional cytogenetic techniques)
Trisomy 21,
Aneusomies of the X chromosome
Partial trisomies (eg, 4p, 9q)
Partial deletions (eg, 5p−/cri de chat
Translocations
Cryptic chromosomal abnormalities
(Too small to be detected by conventional cytogenetic methods)
Cryptic subtelomeric rearrangements (eg, deletions, duplications)
Cryptic interstitial rearrangements (eg, deletions, duplications)
Contiguous gene syndromes
Deregulation of imprinted genes (e.g., UPD, deletion, imprinting defect)
Prader—Willi
Angelman syndrome
Monogenic disorders (see Table 2).

anomalies, particularly subtelomeric and interstitial rearrangements, for example, chromosomal deletions or duplications, too small (<3–5 Mb) to be detected by conventional cytogenetic analysis have emerged as a significant cause of 'idiopathic MR'.[9,14,15] They usually involve several genes and cause contiguous gene syndromes. It is widely accepted that subtelomeric rearrangements, as a group, are responsible for 5–7% of all cases of MR, intermediate in frequency between trisomy 21 and the fragile X syndrome. This high frequency stresses the need for the development of fast, efficient and reliable screening methods for subtelomeric rearrangements that can be used on a routine basis. A variety of methods have been successfully adapted for subtelomeric rearrangement screening, and at least seven different methods have been applied (reviewed in Rooms *et al*[16]). Multiprobe FISH and MLPA are the most widely used. Deletions of most, but not all, individual chromosome ends have been reported in patients with MR.[9,17] Loss of specific chromosome ends may cause recognizable syndromes: Wolf–Hirschorn syndrome, caused by the deletion of the tip of chromosome 4p; ATR-16 syndrome, caused by deletion of the tip of chromosome 16; or Miller–Dieker syndrome, caused by deletion of the tip of chromosome 17p. However, in many cases and because of the low number of patients with deletions, the definition of a specific phenotype associated with deletions of a particular chromosome end is sometimes not possible. Therefore, as the clinical phenotype of the patients provides few clues to orient the search for subtelomeric deletions, 'who to screen' within the population of MR patients remains a difficult issue. Guidelines have been proposed to facilitate pre-selection of patients among moderately–severely MR patients.[18] However, in view of recent reports that showed significant rates of subtelomeric rearrangements among more mildly affected patients,[19–21] screening of mild MR patients should not be excluded, athough further studies are required to confirm these initial observations. In addition to subtelomeric rearrangements, interstitial rearrangements have been implicated in a number of MR syndromes, including DiGorges (22q11 deletion), Williams–Beuren (7q11.2 deletion) and Smith–Magenis (17p11.2 deletion), and are diagnosed mainly by molecular cytogenetic approaches. Moreover, recent diagnostic studies using chromosome-specific,[22] or genomewide microarray-CGH (about 3500 clones at 1 Mb resolution),[23] have shown that interstitial chromosomal deletions or duplications may account for a significant proportion of unexplained MR. For instance, Van Esch *et al*[22] showed that small duplications encompassing MECP2 region is a frequent cause of severe MR and progressive neurological symptoms in males. Alhough detection rate of these subtelomeric and interstitial abnormalities is largely dependent on the clinical inclusion criteria employed and the applied techniques, genomewide screening is likely to become a routine diagnostic approach in the field of MR. Another potential interesting consequence related to the detection of interstitial rearrangements is the definition of critical regions containing candidate genes involved in dominant autosomal MR. For instance, it has been shown that mutations in a new member of the chromodomain gene family cause CHARGE syndrome,[24] and mutations of RAI1 (retinoic acid-induced[1] gene), a PHD-containing protein, cause Smith–Maganis syndrome.[25]

Deregulation of imprinted genes

Genomic imprinting describes the preferential or exclusive expression of a gene from only one of the two parental alleles. The allele-specific expression of imprinted genes is based on allele-specific epigenetic modifications, such as DNA-cytosine methylation and histone acetylation and methylation. In the germ cells, these epigenetic modifications are erased, subsequently established newly in a parent-specific manner and maintained after fertilization. Imprinted genes are usually clustered in the genome, and clearly established imprinting effect has been reported for regions of chromosomes 7, 11, 14 and 15. Approximately, 80 transcriptional units have been identified as imprinted in human and mouse genomes[26] (http://www.mgu.har.mrc.ac.uk/research/imprinting/). Deregulation of imprinted genes has been observed in numerous human diseases, including syndromes characterized by brain dysfunction and cognitive impairment.[27,28] The most known of such diseases are probably the Angelman's syndrome (AS) and the Prader–Willi syndrome (PWS). AS is a worldwide disorder that occurs with a prevalence of about 1/12 000.[29,30] AS patients suffer from severe speech deficit, severe MR and behavioral problems. The phenotype of PWS is characterized by neonatal hypotonia, hyperphagia, obesity, short stature, hypogonadism and MR of variable severity.[27] Over the past 10 years, complementary studies demonstrated that AS and PWS are associated, in many cases, with microdeletions of the same genomic region corresponding to 15 15q11.2–15q13. Then it became evident that deletions of the paternally derived chromosome 15 caused PWS, and ones on the maternally derived chromosome 15 caused AS. The two syndromes are, however, caused by different genes, but they lie in an imprinted genomic region in close proximity to one another. Further studies showed that multiple molecular genetic mechanisms can lead to PWS and AS, but in PWS each mechanism results in a loss of expression of paternally imprinted genes, and in AS each mechanism leads to a loss of expression of maternally imprinted genes (reviewed in Nicholls and Knepper[31]).

Monogenic causes involved in mental retardation disorders

Because of the recent progress, genetics and classification of XLMR genes are the subject of regular reviews[4–6] and

updated lists can be found through the online resources: http://xlmr.interfree.it/home.htm and http://www.ggc.org/xlmr_update.htm. In a recent review, Inlow and Restifo[32] presented a status report on autosomal and X-linked monogenic causes of MR through careful search for 'mental retardation' entries in the literature and in the Online Mendelian Inheritance in Man (OMIM) database (http://www.ncbi.nlm.nih.gov/entrez/). They identified more than 1237 entries for MR and recorded 282 MR genes. A complete and accurate count of genes involved in MR disorders is perhaps beyond the scope of this review; however, given the number of OMIM entries for MR and the fact that *in silico* search for known genes is dependent of criteria such as clinical descriptions of disorders, definitions and terminology to design MR (learning disability, cognitive impairment, developmental delay…), it is reasonable to speculate that 282 genes represent a substantial underestimation of the correct number of MR-related genes. Regardless of the scheme and rational used, it is difficult on the basis of our current poor understanding of molecular and biological functions of MR genes, as well as limited diagnostic possibilities, to propose a straightforward clinical or molecular classification of MR conditions. In this review, we propose to discuss first the apparent over-representation of MR genes on the X chromosome with respect to the autosomes, and attempt to provide a comprehensive overview of the monogenic causes that integrates clinical, genetic and functional considerations.

Chromosomal distribution of genes involved in mental retardation disorders Over the past few years, it is mainly the search for genes mutated in syndromic and nonsyndromic forms of X-linked MR that has been productive in recent years. No fewer than 60 X-linked genes involved in MR disorders have been identified.[5,6] At first sight, the apparent excess of X-linked genes involved in MR disorders supports the hypothesis suggesting that the human X chromosome contains a disproportionately high density of genes influencing cognitive abilities.[33–36] Using the human genome sequencing data and annotations, Skuse[36] found that the X chromosome contains about 931 genes (ensembl version 26.31.1) that represent 3.37% of all genes, whereas 'X-linked mental retardation entries' corresponding to known genes and candidate loci represent 27% (333) of the 1237 entries for 'mental retardation' recorded in OMIM database. The relative chromosomal distribution of MR genes has also been thoroughly analyzed by Inlow and Restifo.[32] Approximately, out of 282 human MR genes, 16% reside on the X chromosome, whereas its content represent only 3.37–4% of all known and predicted genes (a four-fold over-representation). In line with these estimates is another OMIM-based analysis study reported by Zechner *et al.*[37] The authors reported a 7.2-fold X-chromosome bias for MR genes, whereas genes causing common morphological phenotypes (polydactyly, cleft palate, facial dysplasia, skeletal dysplasia and growth retardation) have, on average, only a 2.4-fold X-chromosome bias. However, in view of some recent epidemiological and molecular data, this apparent biased distribution will probably not resist prospective studies that integrate recent estimates downwards of XLMR prevalence[12,13] and contribution of submicroscopic rearrangements in MR conditions, as well as evaluation of the potential number of autosomal dominant and recessive MR genes, which are much more difficult to delineate because of the scarcity of affected families.

Molecular and biological functions of genes involved in mental retardation Before summarizing our knowledge concerning potential molecular and cellular processes underlying genetically based MR, a simplified classification that distinguishes MR with detectable cortical brain developmental abnormalities and MR with an apparent normal brain organization should be kept in mind. Indeed, in many cases, MR is part of a complex syndrome comprising developmental brain abnormalities such as microcephaly, lissencephaly, neuronal heterotopia, agenesis, polymicrogyria and schizencephaly, which result in a cerebral cortex that lacks the normal pattern of organization. MR in these cases is most likely to be a secondary symptom, and genes involved can be considered as factors required for normal development of the CNS. In contrast, MR conditions in which MR is associated with an apparent normal brain structure and architecture, subtle neuronal and/or glial cell functional, morphological or cell–cell interaction and connection abnormalities are likely to be the bases for MR. Accordingly, two major groups of genes could be distinguished: (i) genes involved in MR disorders with brain developmental abnormalities; (ii) genes involved in MR disorders with no specific brain abnormality, with an update concerning recessive autosomal MR genes. Alhough it has many weaknesses, this subdivision allows to highlight genes implicated in potential common genetic and functional pathways and provides bases and frameworks for understanding physiopathological mechanisms underlying MR (Table 2).

As we have recently discussed in a separate review monogenic causes and potential physiopathological mechanisms underlying MR disorders associated with brain malformation[38] (see also Table 2), here we focused on MR with no apparent developmental brain malformation and reviewed our current understanding of some of the primary defects involved, with insights from recent molecular biology advances and the study of mouse models. For the subgroup of MR disorders with no apparent brain malformation (irrespective of other potential distinguishing features), most of the known genes are X-linked, although the number of autosomal loci and genes involved in autosomal recessive nonsyndromic mental retardation

Table 2 Monogenic causes of mental retardation

Gene	*Locus*	*Disorder/phenotype*	*Function of encoded protein; subcellular localization**
Genes required for neurogenesis			
Microcephalin	MCPH1/8p22-pter	Microcephaly vera	Cell cycle control and DNA repair
CDK5RAP2	MCPH3/q34	Microchephaly vera	Mitotic spindle function in embryonic neuroblasts
ASPM	MCPH5/1q31	Microchephaly vera	Formation of mitotic spindle during mitosis and meiosis
CENPJ	13q12.2	Microchephaly vera	Localization to the spindle poles of mitotic cells
Genes required for neuronal migration			
LIS1	17p13.3	Miller Dieker syndrome: type 1 lissencephaly, pachygyria, subcortical band heterotopia (double cortex)	Interacts with dynein and plays a role in several function, including nuclear migration and differentiation
DCX/Dbcn	Xq22.3	Type 1 lissencephaly, pachygyria, subcortical band heterotopia (double cortex)	Microtubule-associated protein (MAP)
RELN	7q22	Lissencephaly with cerebellar hypoplasia	Extracellular matrix (ECM) molecule, reelin pathway
VLDLR	9p24	Lissencephaly with cerebellar hypoplasia	Low-density lipoprotein receptor, reelin pathway
POMT1	9q34	Walker–Warburg syndrome (also known as HARD syndrome**)	Protein *o*-mannosyltransferase 1 (glycosylation of alpha-dystroglycan)
POMT2	14q24.3	Walker–Warburg syndrome	Protein *o*-mannosyltransferase 2 (glycosylation of alpha-dystroglycan)
POMGnT1	1p34	Muscle–eye–brain disease (MEB)	Protein *o*-mannose beta-1,2-n-acetylglucosaminyltransferase
Fukutin	9q31	Fukuyama congenital muscular dystrophy (FCMD) with type 2 lissencephaly	Homology with glycoprotein-modifying enzymes (no biochemical activity has been reported).
FLNA	Xq28	Bilateral periventricular nodular heterotopia (BPNH)	Filamin-1 (actin crosslinking phosphoprotein)
Genes required for cellular processes involved in neuronal and synaptic functions			
FMR1	Xq27	Fragile X syndrome (Facial anomalies with macro-orchidism)	mRNA-binding protein, role in mRNA translation; potential regulation by RhoGTPase pathways; postsynaptic localization
FGD1	Xp11.2	Aarskog-Scott syndrome (Facial, digital and genital anomalies)	RhoGEF protein (GTP exchange factor), activate Rac1 and Cdc42
PAK3	Xq21.3	Nonsyndromic XLMR	P21-activated kinase 3; effector of Rac1 and Cdc42
ARHGEF6	Xq26	Nonsyndromic XLMR	RhoGEF protein, integrin-mediated activation of Rac1 and Cdc42
OPHN1	Xq12	MR with cerebella and vermis hypoplasia	RhoGAP protein (negative control of RhoGTPases; stimulates GTPase activity of RhoA, Rac1 and Cdc42; pre- and post synaptic localization
TM4SF2	Xq11	Nonsyndromic XLMR	Member of the tetraspanin family, integrin-mediated RhoGTPase pathway regulation
NLGN4	Xp22.3	Nonsyndromic XLMR, autism, Asperger syndrome	Member of the neuroligin family, role in synapse formation and activity; post synaptic localization
DLG3	Xq13.1	Nonsyndromic XLMR	Protein involved in postsynaptic density structures; postsynaptic localization
GDI1	Xq28	Nonsyndromic XLMR	Regulation of Rab4 and Rab5 activity, and of synaptic vesicle recycling; pre- and post synaptic localization
IL1RAPL	Xp22.1	Nonsyndromic XLMR	Potential involvement in exocytosis and ion channel activity
Transcription signaling cascade, remodeling and transcription factors			
NF1	17q11	Neurofibromatosis type 1 (NF1); MR is present in 50% of NF1 cases	RasGAP function, involved in Ras/ERK/MAPK signaling transcription cascade; postsynaptic protein

Table 2 (*Continued*)

Gene	*Locus*	*Disorder/phenotype*	*Function of encoded protein; subcellular localization**
RSK2	Xp22.2	Coffin-Lowry syndrome (facial and skeletal anomalies)	Serine-threonine protein kinase, phosphorylates CREB, involved in Ras/ERK/MAPK signaling cascade, present in the postsynaptic compartment
CDKL5	Xp22.2	Rett-like syndrome with infantile spasms	Serine-threonine kinase (STK9), interacts with MECP2, potential implication in chromatin remodeling
CBP	16p13.3	Rubinstein–Taybi syndrome (mental retardation, broad thumbs and toes, dysmorphic face)	CREB (cAMP response element-binding protein 1) binding protein; chromatin-remodeling factor involved in Ras/ERK/MAPK signaling cascade
EP300	22q13.1	Rubinstein–Taybi syndrome	Transcriptional coactivator similar to CBP, with potent histone acetyl transferase: chromatin-remodeling factor
XNP	Xq13	Large spectrum of phenotypes including ATRX syndrome (microcephaly, facial dysmorphic face, skeletal anomalies and alpha-thalessemia)	Homology with DNA helicases of the SNF2/SWI2 family, chromatin-remodeling factor, regulation of gene expression
MECP2	Xq28	Rett syndrome (female-specific syndrome) and other phenotypes including nonsyndromic MR	Methy-CpG-binding protein 2; chromatin-remodeling factor, involved in a transcriptional silencer complex
DNMT3B	20q11.2	ICF syndrome: immune deficiency associated with centromeric instability, facial dysmorphy and MR	DNA methyltransferase 3B, involved in chromatin remodeling
ARX	Xp22.1	Large spectrum of MR phenotypes: XLAG (X-linked lissencephaly and abnormal genitalia); West syndrome, Partington syndrome; nonsyndromic MR	Transcription factor of the aristaless homeoprotein-related proteins family
JARID1C	Xp11.2	Spectrum of phenotypes: MR with microcephaly, short stature, epilepsy, facial anomalies and nonsyndromic MR	Transcription factor and chromatin remodeling
FMR2	Xq28	Nonsyndromic MR	Potential transcription factor
SOX3	Xq27	Isolated GH deficiency, short stature and MR	SRY-BOX 3: transcription factor
PHF8	Xp11.2	MR with cleft lip or palate	PHD zinc-finger protein, potential role in transcription
ZNF41	Xp11.2	Nonsyndromic MR	Potential transcription factor
GTF2I/GTF2RD1	7q11.23	Williams syndrome	Transcription factors, potential regulator of c-Fos and immediate-early gene expression
PHF6	Xq26	Börjeson–Forssman–Lehmann syndrome (hypogonadism, obesity, facial anomalies, epilepsy)	Homeodomain-like transcription factor
Other genes involved in MR			
RPSS12	4q24	Nonsyndromic ARMR	Member of the trypsin-like serine protease family, enriched in the presynaptic compartment
CRBN	3p25	Nonsyndromic ARMR	ATP-dependent protease; regulation of mitochondrial energy metabolism
CC2D1A	19p13	Nonsyndromic ARMR	Unknown function, protein contains C2 and DM14 domains
FTSJ1	Xq11.2	Nonsyndromic XLMR	Role in tRNA modification and mRNA translation
PQBP1	Xq11.2	Large spectrum of MR phenotypes including nonsyndromic MR	Polyglutanime-binding protein, potentially involved in pre-mRNA splicing
FACL4	Xq22.3	Nonsyndromic XLMR	Fatty-acid synthase-CoA ligase 4; possible role in membrane synthesis and/or recycling
SLC6A8	Xq28	Creatine deficiency syndrome (MR with epilepsy and dysmorphic features) and nonsyndromic MR	Creatine transporter, role in homeostasis of creatine in the brain
OCRL1	Xq25	Lowe syndrome (MR, bilateral cataract and renal Fanconi syndrome)	Inositolpolyphosphate 5-phosphatase (central domain) and RHoGAP-like C-terminal domain
AGTR2	Xq24	Nonsyndromic XLMR	Angiotensin II receptor type 2, signaling pathway

Table 2 (*Continued*)

Gene	*Locus*	*Disorder/phenotype*	*Function of encoded protein; subcellular localization**
SLC16A2	Xq13.2	Severe syndromic form MR with abnormal levels of thyroid hormones	Monocarbohydrate transporter, T3 transporter
SMS	Xp22.1	Snyder–Robinson syndrome (macrocephaly, scoliosis, dysmorphic features)	Sperimin synthase, CNS development/ function (neuron excitability)
UBE3A	15q11	Angelman syndrome	Ubiquitin–protein ligase E3A; protein degradation (proteasome): CNS development/function (neuron differentiation)

The table does not represent an exhaustive list of genes involved in MR disorders. For additional genes, see the review by Inlow and Restifo,[32] and online resources: http://xlmr.interfree.it/home.htm and http://www.ggc.org/xlmr_update.htm. *Subcellular localization is indicated mainly for protein shown to be present in the pre- and/or post-synaptic compartments; **HARD syndrome includes hydrocephalus (H), agyria (A), retinal dysplasia (RD), with or without encephalocele, often associated with congenital muscular dystrophies.

(NSMR) is progressively increasing (Table 2). Characterized MR-related genes encode diverse proteins that fall into distinct functional subclasses such as transcription and chromatin-remodeling factors, transmembrane proteins, microtubule- and actin-associated proteins, regulators and/or effectors of RhoGTPase pathways. However, despite this apparent diversity, unifying biological networks and pathways underlying potential physiopathological mechanisms for MR are emerging and we propose to discuss in this review MR-related genes shown to be involved in neuronal connectivity and synapse structure and activity. We also propose to discuss the increasing evidence that link deregulation of transcription control and chromatin remodeling to cognitive impairment.

Synaptic structure and function and mental retardation The recent remarkable progress in the field of MR is suggesting that defects in synaptogenesis and synaptic activities as well as their plasticity, especially in postnatal stage during learning and acquisition of intellectual performances and emotional behavior, are perhaps crucial cellular processes that underlie cognitive impairment resulting from mutations in some MR-related genes. In accordance with this emerging hypothesis is the subcellular localization at the pre- and/or postsynaptic compartments of functional pools of proteins encoded by MR genes. With the exception of transcription factors and chromatin-remodeling proteins (see Discussion), this subcellular localization may hold true for most of the known MR-related proteins (Table 2), including FMRP, OPHN1, NLGN4, DLG3, RabGDI, Neurotrypsin and probably PAK3. For ILRAPL, the synaptic localization was suggested by its potential implication in regulation of exocytosis.[39]

A well-advanced research focus that illustrates the importance of the 'synapse' in the physiopathology of MR is FMRP protein, whose absence causes fragile X syndrome: the most common known monogenic cause of MR with no major apparent specific developmental brain anomaly. FMRP is an RNA-binding protein that could be detected in the nucleus, the soma as well as in the dendritic spines, where FMRP associates with polyribosomes and is upregulated in response to stimulation by metabotropic glutamate receptors (mGluRs). Morphological and/or functional abnormalities of synapses in the cerebral cortex, cerebellum and hippocampus have been shown and proposed to contribute in the cognitive deficit of fragile X patients (see review by Bagni *et al*[40]). More recently, Koekkoek *et al*[41] showed that both global and Purkinje cell-specific knockout Fmr1 exhibit abnormal morphology of dendritic spines of Purkinje cells, correlating with synaptic dysfunction and cerebellar deficit at both the cellular and behavioral levels. These consequences on synapse morphology and activity are coherent with a local (at the synapse) function of FMRP as a regulator of activity-dependent translation of mRNA-encoding proteins involved in actin/microtubule-dependent synapse growth, remodeling and function.[40] Interestingly, using *Drosophila* model, Schenck *et al*[42] showed that FMRP function is perhaps regulated through Rac1-, a member of the RhoGTPase subfamily, dependent signaling pathway.[42,43]

The importance of synaptic structure and function and their control through RhoGTPase signaling pathways in the physiopathology of MR is also supported by the compelling evidence including identification of MR genes such as OPHN1, PAK3, ARHGEF6 and FGD1, that encode regulators and/or effectors of RhoGTPases (Figure 1), and the recently demonstrated implication of OPHN1 and PAK3 in the regulation of dendritic spine morphology and/or synaptic activity.[44–46] It is worth noticing that OPHN1 was also found to interact with the postsynaptic adaptor protein Homer that links glutamate receptors (GluR-1) to multiple intracellular targets and influences spine morphogenesis and synaptic transmission.[46]

For PAK3 (p21-activated kinase), a member of PAK protein family that are activated by the two small RhoGTPases Rac and Cdc42 (cell division cycle[42]), the contribution in synapse formation and plasticity was clearly demonstrated by two groups.[44,45] Using transient

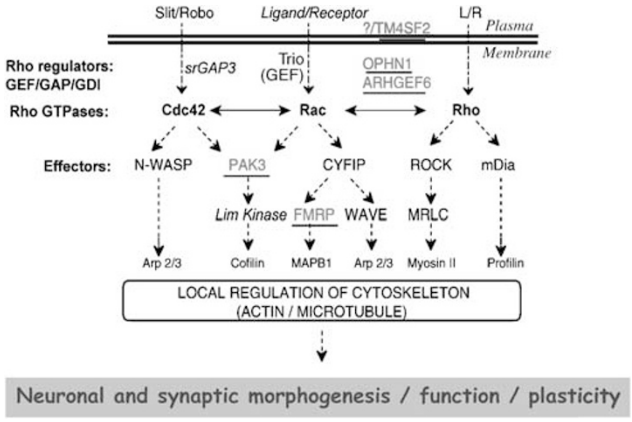

Figure 1 Simplified RhoGTPase signal transduction pathways and MR. Extracellular guidance cues (ligands) interact with growth cone, synaptic and membrane receptors and activate signaling cascades that involve RhoGTPases. Activated RhoGTPase pathways control actin/microtubule cytoskeleton dynamics, which in turn regulate changes of growth cone, neuronal and synapse morphogenesis and activity. Interestingly, the dysfunction of these pathways through loss of function of PAK3 (p21-activating kinase), OPHN1 (RhoGAP), TM4SF2 (teraspanin), ARHGEF (RhoGEF) and FMRP (fragile X mental retardation protein) (underlined proteins) leads to MR.

overexpression in hippocampal organotypic slice cultures, Boda *et al*[45] showed that PAK3 is localized at dendritic spines, and that PAK3 inactivation results in formation of abnormal dendritic spines and a reduced spontaneous synaptic activity and defective long-term potentiation (LTP). Meng *et al*[44] generated a knockout mice model deficient for PAK3 and showed that this model exhibits significant abnormalities in synaptic plasticity, especially hippocampal late-phase LTP, and deficiencies in learning and memory. Surprisingly, in this knockout model, neither *ex vivo* cultures of hippocampal neuronal cells nor Golgi staining of fixed brain sections showed significant alteration in spine morphology, density or length. Although the mechanisms by which PAK3, an effector of Rac1 and Cdc42, produces these effects remain an intriguing question, it is well established that in response to both positive and negative external guidance cues, RhoGTPases are the key components of signaling pathways controlling the organization of the actin cytoskeleton, and in neuronal cells are known to regulate neurite outgrowth, growth cone morphology as well as growth cone guidance, synaptogenesis and neuronal networks connectivity. Establishment of these networks and their adaptation occur not only during brain development, but also in postnatal stages. Indeed, neuronal and synaptic remodeling and plasticity, including morphological changes of dendritic spines (structure localized at the postsynaptic sites of excitatory synapses), occur throughout life and are essential for the functioning of mature synapses as well as establishment of new ones. Although there is no demonstration that links defects of neuronal connectivity and MR, abnormalities of dendritic spines morphology and density have been observed, by Golgi studies on post-mortem brains, in several forms of MR disorders, including trisomy 21, fragile X and Rett's syndromes (reviewed in[47]).

Potential roles in the regulation of synaptic activity have also been proposed for another subgroup of genes involved in MR conditions that encode for transmembrane proteins such as NLGN4,[48,49] DLG3[50] and IL1RAPL[51] and for the soluble protein GDI1.[52,53] At first sight, predicted primary functions of these proteins are diverse and different from those highlighted in the previous paragraph. However, it is interesting to mention, at least for the proteins that have been thoroughly analyzed, that these proteins have in common the subcellular localization at the pre- and/or postsynaptic compartments. NLGN4 gene has been found mutated in a wide spectrum of phenotype, ranging from mild MR without communication deficits to Asperger's syndrome with normal or supranormal intelligence.[48,49] NLGN4 protein is a member of the neuroligin family of postsynaptic adhesion neuronal cell-surface molecules. It is particularly abundant in the postsynaptic membrane of exitatory and inhibitory synapses and can trigger postsynaptic differentiation as well as formation of functional presynaptic terminals in axons through interaction with its receptor β-neurexin.[54,55] The importance of the regulation of synaptic activity in the pathogeny of MR is also reinforced by the implication in XLMR of another synaptic protein encoded by the DLG3 gene.[50] DLG3 encodes the synapse-associated protein 102 (SAP102), a member of the membrane-associated guanylate kinase protein family. Mutations identified in DLG3 shown to be associated with MR are predicted to impair the ability of SAP102 to interact with NMDA receptors and/or other proteins involved in downstream NMDA receptor signaling pathways.[50] For the two other XLMR-related genes, GDI1[52,53] and IL1RAPL,[51] literature data are also suggesting their participation in the regulation of synaptic activity. In the mammalian brain, GDIα encoded by the *GDI1* gene is the most abundant form of GDI in the CNS and was thought to be involved in the regulation of Rab proteins, which participate in synaptic vesicle recycling and fusion.[56] RabGDIα-deficient mice revealed a role for this protein in neurotransmitter release and synaptic activity in the hippocampus.[57] More recently, D'Adamo *et al*[58] have produced a mouse model deficient for Gdi1 and showed that the lack of Gdi1 has an effect on the distribution of Rab4 and Rab5 pools, which are Rab proteins involved in synaptic vesicle exocytosis and that GDI deficiency is associated with a defect in short-term memory. Implication in the regulation of synaptic activity was also proposed for IL1RAP, another X-linked gene involved in MR. Recent studies showed that IL1RAP interacts with NCS-1 (neuronal calcium sensor-1), and the functional relevance of this interaction was further strengthened by the regulatory effect of IL1RAPL on exocytosis known to be induced by NCS-1.[39]

Altogether, these genetic data in combination with functional studies suggest that deregulation of subtle mechanisms orchestrating synaptic activity and plasticity could be regarded as one of the cellular bases that contributes to the pathogeny of a variety of autosomal and X-linked MR. In view of this emerging hypothesis, we are attempted to bring out the parallel between synaptic dysfunction thought to underlie cognitive impairment and synaptic biochemical variations, reported by Kandel *et al*,[59] associated with short- and long-term changes that reflect simple forms of memory storage. In their 'model', Kandel and colleagues described the process of memory storage and learning as a 'dialogue between genes and synapses' and proposed that short-term memory results from immediate synaptic biochemical changes (such as activation of CaMKII and increase in AMPA glutamate receptor activity), whereas long-term memory storage generally requires transcription and translation of new proteins that enhance the strength or number of active synapses. To bring further this hypothetical parallel, we can speculate that in MR conditions, inappropriate synaptic responses that follow sensory–motor stimuli could be relayed by a long-term synaptic defect through deregulation of signaling transcription cascades involved in the expression of factors that are crucial for synaptic morphogenesis, activity and plasticity. In favor of this view, which combines short- and long-term effects on synaptic activities, are the implication in MR, as primary defects, of transcription and remodeling factors (see below), and the fact that RhoGTPase-dependent MR genes may also be involved in the regulation of transcription signaling cascades regulated by RhoGTPase pathways. This transcriptional regulatory role in synaptic activity and plasticity also seems to be effective for PAK3, as knockout mice deficient for PAK3 exhibit a dramatic reduction of the phosphorylated active form of the transcription factor cAMP-response element-binding protein.

Transcription control, chromatin remodeling and mental retardation MR disorders resulting from mutations in genes encoding transcription factors and cofactors, partners of signal transduction cascades, as well as chromatin-remodeling proteins, represent a major group of monogenic causes of MR (Table 2). One of the most studied transcription-signaling cascades involved in cognitive disorders is the Ras–MAPK pathway (Figure 2). Among the Ras–MAPK pathway members shown to be involved in MR disorders are the proteins encoded by NF1, RSK2 and CBP genes (Figure 2). The product of NF1 has the capacity to regulate several intracellular processes, including the ERK–MAP kinase cascade, adenylyl cyclase and microtubule-binding activity.[60] In addition to neurofibromatosis, NF1 mutations result in MR in about 50% of patients. In an elegant study, Costa *et al*[61] inactivated in mice different isoforms of NF1 resulting from alternative splicing events,

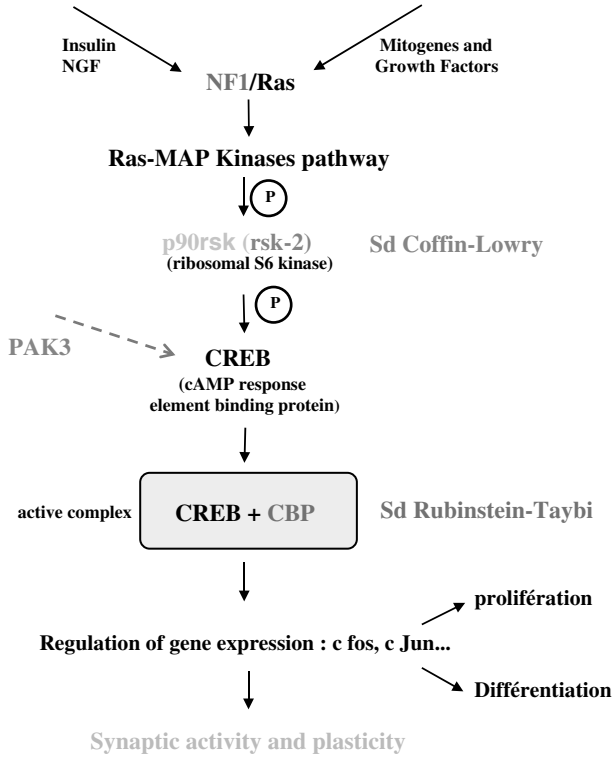

Figure 2 A schematic of the Ras/MAPK transcription-signaling cascade showing known genes/proteins (NF1, RKS2, CBP, PAK3) involved in MR disorders (NF1 and PAK3-related MR, Coffin–Lowry and Rubinstein–Taybi MR syndromes). This pathway was also shown in model organisms to be involved in learning and memory processes. These cognitive functions require gene transcription and translation of proteins. Newly synthesized proteins cause long-term changes of synapses, including dendritic spines development, morphogenesis and activity. NF1, neurofibromatosis type 1 oncogene; RAS, low molecular weight GTP-binding protein (G protein); MAPK, mitogen-activated protein kinase; CBP-, CREB-binding protein.

and identified the specific coding exon that contributes to the regulation of NF1-GAP domain and in the interaction with the NF1 target Ras as being critical for learning in mice and therefore may be involved in the pathogeny of cognitive deficit in humans. Downstream to NF1, Ras/MAPK pathway activation requires CREB phosphorylation through kinases such as RSK2 (ribosomal protein S6 serine/threonine kinase). Interestingly, RSK2 is the gene disrupted in Coffin–Lowry MR syndrome (CLS)[62] and CREB phosphorylation was shown to be perturbed in fibroblasts from CLS patients.[63,64] Moreover, another MR disorder associated with disruptions of the ERK/CREB pathway (Figure 2) is Rubinstein–Taybi syndrome (RTS). The gene involved in RTS was identified as CREB-binding protein (CBP),[65] known to have intrinsic histone acetyltransferase activity.[66] So, CBP seems to be important for chromatin-remodeling events and gene regulation. Unlike CREB, which binds directly to a specific DNA sequence, CBP is a transcriptional coactivator that interacts with proteins

such as phospho-CREB to regulate basal transcriptional complex activity.

An additional interesting example of MR-related gene encoding a protein implicated in chromatin remodeling is MECP2 (methyl-CpG-binding protein 2) gene. Mutations in MECP2 were found in the vast majority of Rett's syndrome patients. This is a female-specific syndrome characterized mainly by cessation and regression of development in early childhood that strikes many months after birth (about 12–18 months), following a period of apparently normal growth and development. Subsequent studies showed that both mutation type and patterns of X-chromosome inactivation (XCI) are the bases for a surprisingly wide range of phenotypes, not only in females but also in males.[67–70] Moreover, recent data showed that mutations in the cyclin-dependent protein kinase-like 5 (*CDKL5/STK9*) are responsible for neurodevelopmental disorder with clinical features that are reminiscent of Rett's syndrome.[71,72] Given the clinical overlap resulting from mutation in MECP2 and CDKL5 genes, their involvement in a common genetic and pathogenic pathways has been suspected and further studies showed that spatio-temporal expression of Cdkl5 overlaps with that of Mecp2 and that Mecp2 and Cdkl5 interact *in vivo* and *in vitro*.[73]

MeCP2 was first identified as a member of the methyl-CpG-binding domain (MBD) protein family. It binds to methylated CpG dimer pairs in DNA, and subsequent recruitment of transcriptional co-repressors such as Sin3A and histone deacetylases (HDAC) is thought to lead to chromatin condensation and repression of the expression of target genes. Comparative expression studies using knockout models allowed us to identify a limited number of differentially expressed genes, such as the brain-derived neurotrophic factor (BDNF).[74–76] Interestingly, brain-specific inactivation of Mecp2 in postmitotic neurons of developing brain gave rise to a postnatal neurological Rett-like phenotype that is virtually indistinguishable from the mice in which constitutive inactivation of MeCP2 occurred in all tissues.[77,78] These data indicate that brain function, rather than brain development *per se*, is sensitive to the absence of MeCP2. This finding is coherent with the growing body of evidence indicating that MeCP2 is important for maturation and maintenance of postmitotic neurons in rodent brains.[79,80] Identification of target genes regulated by signaling transcription partners (NF1, RSK2 and CDKL5), chromatin-remodeling factors (MeCP2 and CBP) and transcription factors such as FMR2, SOX3 and ARX (Table 2) remains among the prerequisites to understand the biological and cellular processes underlying MR. However, despite this logical gap, much of the current advanced knowledge linking transcription regulators and development of cognition functions is the result of experimental work achieved over several decades that demonstrated a clear relation between some specific signaling transcription cascades – activity-dependent synaptic changes and learning and memory processes.[59,81] Although definitions of neurobiological processes underlying MR are at an early stage, altogether these recent data indicate that specific transcription-signaling cascades and their downstream effects on the expression of target genes, some of which encode for synaptic proteins, are involved in the regulation of biological and cellular processes underlying in human MR physiopathological mechanisms and in animal models learning and memory processes.

Conclusion

The genetic heterogeneity that underlies cognitive impairment is unprecedented; however, in view of the current knowledge, a 'synapse-based' hypothesis for the pathogeny of several forms of MR could be proposed. Dysfunction of proteins encoded by genes involved in a large spectrum of cognitive deficits extending from mild MR with or without autistic and behavioral features to severe MR might lead, via deregulation of specific pathways and cellular processes, to defects in synaptic structure and/or function, and neuronal connectivity, thereby hampering the ability of the brain to process information. The resulting limited ability of the brain to process information would result in MR. In view of this hypothesis, it is tempting to speculate that in some forms of MR, deficient proteins are required in postnatal stages (during active learning periods) and the resulting deficits are likely to be subtle and to a certain extent may be prevented and/or improved if early postnatal diagnosis and appropriate therapeutic approaches are implemented. This assumption is based on the fact that behavioral and cognitive therapies can help mentally retarded patients reach their maximum potential.[82,83] Also, MR owing to congenital hypothyroidism is now largely preventable through screening and hormone replacement.[84] Other examples of efficient therapeutic approaches are dietary restrictions and supplements for inborn errors of metabolism such as phenylketonuria.[85,86] Another example suggesting that cognitive deficits could, to a certain extent, be partially reversible is provided through the autosomal form of inborn errors of creatine biosynthesis that corresponds to guanidinoacetate methyltransferase (GAMT) deficiency.[87] In this metabolic disorder with MR, cognitive impairment could be improved by arginine restriction and ornithine/creatine supplementation.[88] Interestingly, the possibility of ameliorating learning capabilities by inhibiting histone deacetyltransferase was reported in animal models deficient for the *Cbp* chromatin remodeling factor.[89] Moreover, McBride *et al*[90] showed that a pharmacological approach using mGluR antagonists can rescue synaptic plasticity, courtship behavior and mushroom body defects in a *Drosophila* model of fragile X syndrome. Although therapeutic possibilities in human remain very rare, these examples emphasize,

however, the necessity of establishing accurate diagnosis that could lead to preventive and therapeutic actions.

Finally, it should be stressed that genetic counseling and prenatal diagnosis related to mental handicap raise sensitive ethical issues, especially for the milder forms of MR, or for carrier females who manifest subtle cognitive deficits. Assessing cognitive function is complex, and performances can be subject to profound social and environmental factors in the family and in schools. The level of expectation with respect to intellectual performances also depends on the family, and on the type of society to which an individual belongs. Great care should thus be exercised in the diagnostic and genetic counseling applications in this fascinating research domain.

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