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Chapter 6

The Genetics of Mental Retardation

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Additional information is available at the end of the chapter

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1. Introduction

Mental retardation(MR) was defined by the World Health Organisation as an intelligent quotient (IQ)<70 that is accompanied by adaptive limitations in two or more key skills areas, before the age of 18. General intellectual functioning is expressed by IQ. Typically, in children younger than 5 years old who present delays in the attainment of developmental milestones at the expected age, the term of "developmental delay" is used. Also, developmental delay is used before the age of 5,when IQ testing is reliable and valid and it takes into consideration learning and adaptive deficits which predict later intellectual disability.

Different classifications have been used to partition people with MR, the most frequent, accepted also by DSM IV (American Psychiatry Association) based on performances on standardised cognitive tests: mild (IQ 50-70), moderate (IQ 35-49), severe (IQ 20-34) and profound (IQ <20). [1]

According to this type of classification the level of difficulties and everyday life needs for the social and psychological support of a person affected by MR, can be established.

The definition and classification tend to accept the diagnosis of non-progressive form identifiable in small babies. In clinical practice, metabolic or neurodegenerative disorders may associate MR, frequently a progressive form, in children prior having normal development. Adrenoleukodystrophy manifests with progressive cognitive regression in boys, after a period of normal development. In addition, a pervasive developmental disorder manifested through cessation and regression of normal development, associating seizures and mycrocephaly in small girls is rather included in mental regression, only after a clear clinical picture in syndromal MR. The clinical association between MR and malformations, neurological disfunctions such as epilepsy or cerebral palsy, sensorial deficits, other maladies or behaviour disturbances are usually earlier directed to evaluation and medical care.

Having such an impact on life, MR is one of the most frequent causes for genetic evaluation in babies in developped countries. Developmental screening addresses those who have developmental delays identifiable in primary care and need referral for furher evaluation.

2. The causes of mental retardation

MR has heterogeneous environmental and genetic causes acting invarious phases of pre, peri and postnatal development.

Prenatal	Environmental factors	-Deficiencies , such as iodine deficiency and folic acid deficiency -Severe malnutrition in pregnancy-Rh incompatibility -Using substances such as alcohol (maternal alcohol syndrome), nicotine, and cocaine during early pregnancy -Exposure to other harmful chemicals such as pollutants, heavy metals, and harmful medications such as thalidomide, phenytoin and warfarin sodium in early pregnancy -Maternal infections such as rubella, syphilis, toxoplasmosis, cytomegalovirus and HIV -Others such as excessive exposure to radiation
	Chromosomal abnormalities(cytogenetic techniques)	Trisomy 21 Partial trisomies (e.g., 4p, 9q) Aneusomies of the X chromosome Partial deletions (eg, 5p-/cri de chat) Translocations
	Cryptic chromosomal abnormalities(complex methods)	-Microdeletions or microduplications of chromosomal segments Wolf-Hirschhorn syndrome Pallister-Killian syndrome 18p deletion -Cryptic subtelomeric rearrangements (eg, deletions, duplications) -Cryptic interstitial rearrangements - microdeletion : ά-thalassemia with mental retardation ,Smith Magenis syndrome (deletie 17p11.2.) , Rubinstein-Taybi syndrome (16p13.3) -Cryptic interstitial rearrangements - duplications: 15q11-13 duplication: Kabuki Makeup syndrome -Contigous gene syndrome
	Mutation of a single gene	X-linked mental retardation Mowat-Wilson syndrome

		Cornelia de Lange syndrome Lissencephaly with cerebellar hypoplasia Walker–Warburg syndrome (also known as HARD syndrome) Muscle–eye–brain disease (MEB) Fukuyama congenital muscular dystrophy (FCMD) with type 2 lissencephaly Neurofibromatosis type 1 (NF1); Cerebral malformations
Perinatal	3rd trimester	Complications of pregnancy Diseases in mother such as heart and kidney disease and diabetes Placental dysfunction
	During delivery	Severe prematurity, very low birth weight, birth asphyxia Difficult and/or complicated delivery Birth trauma, vascular accidents
	Neonatal	Septicemia, severe jaundice, hypoglycemia
Postnatal (in infancy and childhood)	Traumatic, accidental, infectious	Brain infections such as tuberculosis, encephalitis, and bacterial meningitis Head injury Chronic lead exposure Severe and prolonged malnutrition Gross under stimulation
	MR that develops after a period of normal development	Lysosomal storage diseases Peroxizomal disorders Exposure to heavy metals, pesticide, malnutrition
	Multifactorial or complex inheritance MR	

Table 1. Causes of mental retardation in regards to development stage.

Current research has been directed to clarify the genetic base of what was accepted as 'idiopathic MR'. The initial reports about the implication of telomeric rearrangements in MR etiology created the necessity of a screening method. The prevalence of this type of modification was established at 5%, being higher in severe mental retardation group, nearly half of all being *de novo* mutations. The tendency to find a phenotype associated remained unfulfilled partly because of the reduced number of cases and partly because of the heterogeneity of the rearrangements. Deletion of the majority of end chromosomes were implicated in MR, some causing clinical recognizable syndromes such as Wolf-Hirchorn or Miller-Dieker syndromes.

By contrast, interstitial rearrangements are always clinically expressed by MR and cause recognizable phenotypic features. Submicroscopic deletions are responsible for the learning disabilities, velo-cardio-facial malformations from DiGorges syndrome (22q11 deletion), recognisable asymmetric cognition profile in Williams–Beuren syndrome (7q11.2 deletion) or cognitive and growth retardation from Smith–Magenis syndrome (17p11.2 deletion). The

use of genomewide microarray-CGH has implicated interstitial chromosomal deletions or duplications in a significant part of unexplained MR so far.

MR can be part of a complex cognitive impairment in disorders caused by deregulations in imprinted genes. As examples, there are the Angelman syndrome and Prader Willi syndrome, both associated with microdeletions of the same region corresponding to 15q11.2–15q13, the paternally derived chromosome 15 causing PWS, and the maternally derived chromosome 15 causing AS.

A mutation in a single gene, should intervene in the biological mechanism of MR. A dysfunctional protein coded by this gene can deregulate functional cellular pathways or processes, influencing cellular connectivity, synaptic structure or function. As the result of this common genetic and physiopathological mechanism cerebral complex functions are impaired, the clinical expression being a limited ability to process information. Abnormalities of genes function may be implicated in almost any biological process that the cell conducts: DNA replication repair and recombination, translation, control of gene expression, membrane structure, membrane transport, energy conservation, cell communication, the cytoskeleton, cell life and division cycle. In an attempt of classify MR genes, two categories were taken into consideration: one including genes implicated in brain development, neurogenesis and neuronal migration, for which MR may be considered to be a secondary symptom due to brain malformation, and another one having those genes responsible for MR conditions without apparent brain abnormalities.

The list of indentified genes associated with MR is constantly growing. Using OMIM database entries and recent epidemiological studies the relative distribution of MR genes has been analysed. From the approximately 282 human MR genes, 16% reside on chromosome X, whereas its content represents only 3.37–4% of all known and predicted genes. The majority of known mutations in X-linked genes are loss-of-function mutations. Citation

X-linked forms of mental retardation are estimated to cause 10-20% of all inherited cases of mental retardation. The first gene to be identified was *FMR1* that causes fragile X syndrome and still remains the commonest single gene abnormality to be identified. The prevalence of many mutations isvery rare, many X-linked mental retardation disorders being present only in a limited number of patients. The future of microarray technology will enhance the diagnostic possibilities of cases suspected of X-linked mental retardation. Screening candidates are CGG repeat expansion in the fragile X-syndrome, the A140V and the mutation in the MECP2 gene.

2.1. Chromosomal abnormalities

Autosomal chromosom aneuploidies

Aberrations in autosomal chromosome number in live born babies are restricted to

aneuploidies: trisomy 13 (Patau's syndrome), 18 (Edward's syndrome) and trisomy 21 (Down syndrome), monosomy of any autosomal chromosome being lethal in the earliest stages of embryonic life. Malformations' severity can be lethal in the first week of life for

newborns with Patau or Edward's syndrome; otherwise the level of functioning and cognitive development is severely affected.

Down syndrome(DS)

Down syndrome is the most frequent genetic cause of mental retardation. Results of standardized intelligence test IQ scores, in Down syndrome, may vary from low normal to severely retarded 85-20, dependent on the degree of cognitive deficits. Children with mosaicism may obtain scores with 10-30 point higher on IQ measurement that those with trisomy 21. [4,5] Longitudinal observation findings regarding cognitive development sustained that learning in children with Down syndrome may continue through late childhood and adolescence.

Early identified difficulties in achieving developmental milestones and learning disabilities, especially with language, create the opportunity of adequate education thus promoting a better social adaptation. Children with Down syndrome may present developmental stages similar to other children in the domain of sensoriomotor, adaptive and social interaction skills but with a slower rate.[2] Examination of developmental scores of young children with DS aresimilar with those of normal children, in Personal, Social and Adaptive Domains. Developmental scores are less similar in Communication and Cognitive Domains of the Battelle Developmental Inventory this being more evident as they approached 36thmonth. [3]

Neuropathological studies in Down syndrome showed that persistent hypocellularity to be one cause of intellectual disability. In DS individuals, cell density revealed reduced neuron number in late gestation (after weeks 19–23) by comparison with early gestation [6,7,8]. The same cellular reduction is maintained from the fetal age, through newborn period in the hippocampus, parahippocampalgyrus, cerebellum and neocortex. [6,7,9] Reduced volumes of the hippocampus, entorhinal, frontal, prefrontal, and temporal cortices, amygdala, cerebellum, brain stem nuclei, and mammillary bodies of the hypothalamus have been found in children and adults with DS. [10,11]

Autosomal structural anomalies

Wolf-Hirschhorn syndrome

Wolf-Hirschhorn syndrome(WHS) deletion of genetic material near the end of the short (p) arm of chromosome 4(4p-) the critical region- 4p16.3. The size of the deletion varies among affected individuals, larger deletions associate more severe intellectual disability and physical abnormalities than smaller deletions. A combination of Chromosomal microarray (CMA), FISH, and/or G-banded cytogenetic studies may be necessary for complete characterization of the chromosomerearrangement. [12]

The phenotype is dominated by prenatal and postnatal growth delay, a facial appearance of "Greek warrior helmet " with microcephaly, high forehead, broad bridge of the nose continuing to the forehead, hypertelorism, epicanthus, highly arched eyebrows, short philtrum, downturned mouth, micrognathia, and poorly formed ears, congenital heart and urinary defect and skeletal anomalies. [13] Central nervous system defects, sensorial defects (hearing and seeing), hypotonia and seizures complete the panel of intellectual disability. One third

of the individuals with WHS have mild to moderate mental retardation. Battaglia et al [2008] found mild mental retardation in 10% of the patients, moderate in 25%, and severe/profound in 65%. [14]

Phenotypic expression of WHS is related to the loss of multiple genes on the short arm of chromosome 4. From these, the lost of WHSC1, LETM1, and MSX1 is correlated with typical signs and symptoms of this disorder.

Cri du Chat syndrome

Cri du Chat syndrome (CdCS) is caused by a deletion of variable size occurring on the short arm of chromosome 5 (5p-). Localization of the deletion can be terminal, 5p terminal, in the majority of cases, but also we can find interstitial deletion, *de novo* translocation and familial translocation.

Imagistic findings in CdCS, especially MRI, were atrophy of the brainstem mainly involving the pons, cerebellum, median cerebellar peduncles and cerebellar white matter. [15]

Recent studies attempted to correlate genetic substrate with cognitive develop and behavioural pattern. The first assumption that any break point on chromosome 5 produces a typical phenotype of CdCS was modified by the newest studies results. In this way two distinct regions were implicated: one for the cat-like cry in 5p15.3 (between loci D5S13 and D5S760) and the other for dysmorphism, microcephaly, and mental retardation in 5p15.2 (between loci D5S23 and D5S791).

In 5p15.2 region, two separate subregions were also mapped: one for childhood facial dysmorphism and moderate mental retardation and the other for adult facial dysmorphism and severe mental retardation. The involvement in brain development and function, suggested by the presence of mental retardation may be sustained by the mapping of different genes (*SEMAF*,*CTNND2*) in this region.

CTNND2 gene codes a protein called delta-catenin involved in cell adhesion and movement. For example in a developing brain it is involved in neuronal migration, serving as a guide for nerve cell proper positions. In mature nerve cells delta-catenin has a role in synapses functioning. The disruption of these processes may be the fundament of the severe intellectual disability in individual who have CdCS and loss of CTNND2. [16]

SEMAF gene code a protein called Semaphorine F, in axonal guidance during neural development. The importance for axonal guidance and neuronal precursors migration during cortical development had been prooven in mice, suggesting that *SEMAF* may be responsible for some of the features of CdCS. [17]

Deletion of 5p15.3 was identified in individuals with speech delay but with no major intellectual impairment, also with subjects milder degree of cognitive impairment and fewer behavioural problems than those with deletion breakpoints in p15.2.[18] This region was implicated by abnormal gene expression in anomalous cerebral lateralisation which support the hypothesis of a separate region for the speech delay distal of p15.3 In general, individuals have delayed speech and language development, some never develop spoken language. Their receptive language is better than their expressive language, although both are delayed.

Subjects with deletion breakpoints in 5p15.3 had a milder degree of cognitive impairment and fewer behavioural problems than those with deletion breakpoints in p15.2. [19]

Pallister-Killian Syndrome

In people with Pallister-Killian mosaic syndrome (PKS) some cells have 2 extra copies of the short, p, arm of chromosome 12 fusionated as isochromosome 12p or i(12p). The genetic material from the isochromosome disrupts the normal course of development, causing the characteristic features of this disorder. The phenotypic expression is variable and also all affected children have mosaic tetrasomy 12p, onlythose who have a complete phenotype can be said to have PKS.

PKS is considered a neurodevelopmental disorder.PKS children experience learning disabilities some of them only mild but the majority severe to profound. Speech tends to be late, is often limited and sometimes absent. The learning processes may be influenced by the sensorial deficits (hearing and vision) and by the reduced interest for communication and the lack of eye contact reported by parents in the early years.

They have the ability to communicate their needs and preferences using gestures and vocal noises, since preschool and later they can attend special schools with dedicated support worker.

18p deletion

18p deletion or "18p-" means that part or the entire short arm of chromosome 18 is missing, or deleted, the individuals having only one of two copies of chromosome 18short arm. In some patients, this deletion is the only chromosomal change, in others can be the result of a more complex modification, for example an unbalanced translocation. People with an unbalanced translocation may have features of 18p- as well as features of the chromosome duplication. Atypical phenotype in a child with 18p- may is an argument to analyze the subtelomeric regions of all the chromosomes. [20]

Clinical phenotype at birth presents low weight, microcephaly, rectangular face, ptosis, epicanthal folds, low nasal bridge, hypertelorism, high-arched palate, prominent philtrum and large protruding ears. They may have low muscle tone – hypotonia and other neurological manifestation: a higher risk to associate holoprosencephaly, seizures and dystonia.

Holoprosencepahly may be severe in some newborn influencing survival, in others individuals milder forms causing brain minor changes, such as a missing corpus callosum, hydrocephalus or a change in the structure of the pituitary gland. Cerebral changes may be recognised in facial features such cleft lip and palate or hypotelorism or single incisor at the midline of the mouth.

Children may show delay in achieving milestones, mostly in the motor and verbal field. They may take longer to roll over, to sit, crawl and walk, and also language skills may develop later.

People with 18p- may manifest a variable degree of cognitive disabilities, tested IQ scores range from average to severe mental retardation.

Sex chromosomal aneuploidies

Turner syndrome(45X0)

Typically, genetic diagnosis of Turner syndrome had been done in adolescence, when puberty had fails to install. Although initially disregarded, many years after diagnosis the patients were considered to have mental retardation. Numerous researches showed lower Performance IQ than Verbal IQ and deficiency in nonverbal, visuo-spatial areas.

Psychosocial aspects of TS girls life seem to be impaired by low self-esteem, social isolation and peer relationships. Differences in appearance, short stature and the delay in the onset of puberty affect their self –esteem. They also may exhibit adjustment problems, anxiety and social immaturity.

A particular phenotype may be present to a significant number of patients with Turner syndrome called X ring Turner syndrome, having a X0 cell line, a ring X and almost every time a 46XX cell line. A study of Kuntsi et al., concluded that the presence of X ring chromsome leads to a reduction in cognitive performance, most of patients meeting criteria for mental retardation and special education. [21]

XXY Klinefelter syndrome(KS)

In boys with KS, the diagnosis may be established at birth or may be delayed to late childhood or adolescence since many of clinical features (delayed puberty, diminished or absent secondary sex characteristics, diminished testes) manifest in this period accompanied bycontinuousbehavioural problems and externalizing symptoms. Adults may be diagnosed during evaluation for infertilityor gynecomastia. [22] When present, mental retardation is usually mild. Verbal IQ scores measured in KS children are below average, while Performance IQ is normal.

Knowledgeabout increasing risk for specific developmental reading and having impaired verbal ability, in females with an extra X chromosome, the same hypothesis was raised about men. An exhaustive literature review of Rovert et al. concluded that KS children manifest deficit in verbal abilities and language processing. They presented a pattern of underachievement in school and a higher risk for dyslexia. [23]

IQ was found to be only 10-15 lower than the average peers in a control group of 13 years old boys. The level of intellectual deficit increases with the number of X chromosome, mental retardation being identified to individuals with more than four X

Other extra sex chromosome phenotypes

Clinical and developmental impact of a supernumerary sex chromosome led to the studies focused on establishing and recognising the physical and cognitive profiles of these disorders. Supernumerary X chromosome was proved to influence the cognitive development, with direct impact on language. Each extra X chromosome reduces the overall IQ by 15–16 points. [24] In this way, individuals affected by sex chromosome aneuploidy have a higher risk to develop mental retardation and significant psychopathology with every extra X chromosome. Since additional Y chromosomes are often accompanied by additional X chromo-

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somes (48,XXYY, 49,XXXYY), it was difficult to pinpoint specific features in these phenotypes that are unique to either the X or Y chromosome. [23] Some differences have been observed althout:48, XXYY have higher scores in adaptive scales in daily living skills, socialization, and communication. The groups with 48,XXXY and 49,XXXXY have lower functioning cognitively compared to 48,XXYY, secondary to extra X. Every day living skills are impaired in this group, but also socialization, and communication.

	Clinical phenotype	IQs range	Behavioral phenotype
48,XXYY	tall, with long legs underdeveloped genitalia , hypergonadotropichypogonadism , gynecomastia	60 to 80	higher risk for internalizing and externalizing symptoms; anxiety and withdrawal aggressive and delinquent behaviors
48,XXXY	average to tall stature, facial dysmorphism: hypertelorism, flat nasal bridge, underdeveloped genitalia , hypergonadotropichypogonadism , gynecomastia	40 and 60	immaturity, passivity, with occasional irritability, temper tantrums, and outbursts
49,XXXXY	microcephaly coarse face, ocular hypertelorism, flat nasal bridge, and upslanting palpebral fissures underdeveloped genitalia , hypergonadotropichypogonadism ,	20 to 60	

Table 2. Clinical and behavioral phenotype in supernumerary sex chromosome disorders .

Volumetric studies demonstrated significantly reduced brain volumes in subjects with XXX and XXY, but not in XYY subjects, indicates that the presence of a extra X chromosome has a demonstrable effect on brain development. In the same direction the research on the presence of an extra Y chromosome couldn't be associated with significant volumetric brain differences relative to normal male controls. [25]

2.2. Contigous gene syndromes associated with cognitive deficits

In contiguous gene syndromes, the disorder is due to microdeletions or microduplications of chromosomal segments associated with clusters of single gene disorders. These disorders were recognized clinically prior to their cytogenetic localization. Usually the cytogenetic abnormalities are detected by high-resolution chromosome analysis like FISH, but there may be patients having submicroscopic molecular deletion. [26]

A particularity of contiguous gene syndromes is that loci that are physically contiguous with the deleted zone have an phenotypic impact. The clinical expression of the phenotype may vary from one individual to another depending on the extent of the deletion.

Since most of the patients of these contiguous syndromes many present a degree of mental retardation recommendation have been made for chromosome analyses to the patient with mental retardation and mendelian traits that are not usually associated with mental retardation.

PraderWilli syndrome(PWS)

PWS is caused by a chromosomal deletion on chromosome 15. Most cases of PWS (about 70 %) occur when the paternal region 15q11-q13is deleted in each cell. In another 25 % of cases, a person with PWS has two copies of chromosome 15 inherited from the mother – isodisomy (UDP). Rarely, PWS can also be caused by a chromosomal translocation, or by a mutation or other defect, that inactivates genes on the paternal chromosome 15. Approximately 1-5% of patients have neither deletion nor UDP, but a small deletion inthe centre controlling the imprinting process within 15q11-13.[27]Each of these genetic changes results in a loss of gene function in a critical region of chromosome 15. Due to imprinting, the maternally inherited copies of these genes are virtually silent, only the paternal copies of the genes are expressed. PWS results from the loss of paternal copies of this region.

On average people with PWS shows mild level of mental retardation, although individually their IQ scores may range from average to profoundly mentally retarded. Repeated studies since PWS had been discovered tried to establish a correlation between body mass index with IQ[28]. No significant relation has been found.

Specifically, the syndrome includes a particular eating behaviour (a compulsive search for food, non-selective non-discriminatory ingestion of large quantities of food and also, stealing food), irritability, reduced tolerance to frustration, stubbornness, anger, pinching skin, associated, in the vast majority of patients with mild mental retardation. Typically, the behavioural difficulties reach a peak in adolescence or in early adult life. Binge eating is the most severe and debilitating behaviour disorder, leading to obesity, diabetes and severe respiratory difficulties.

Usually, patients are happy and open to interpersonal networking, participating with interest in behavioural training. They can learn to structure their daily routine activities, rewards, breaks, boundaries and firm rules.

An extensive study focused on assessing self-aggressive, stereotyped and obsessive compulsive behaviour in individuals with PWS and showed that skin picking is found in 19.6% of individuals, with low frequencies of nose pinching, kicking and pulling nails and lips hair. From the compulsive behaviour category, the compulsive eating is the most common. Standardized assessments have identified high levels of depressive, anxiety and compulsive symptoms, with functioning impairment, which are not explained by developmental delays, difficulties in nutrition or by obesity in patients with PWS.

Angelman Syndrome (AS)

Is a neurological disorder with a heterogeneous genetic causality.

70% cases of AS occur when a segment of the maternal chromosome 15 containing this gene is deleted. In other cases, AS is caused by a mutation in the maternal copy of the UBE3A

gene. AS results when a person inherits two copies of chromosome 15 from his or her father instead of one copy from each parent- uniparental disomy(UPD). AS may also be caused by a chromosomal rearrangement called a translocation, or by a mutation or other defect in the region of DNA that controls activation of the UBE3A gene. These genetic changes can abnormally turn off UBE3A or other genes on the maternal copy of chromosome 15.

UBE3A gene codes for a protein called ubiquitin protein ligase E3A. Ubiquitin protein ligases is implicated in the process of removing unnecessary protein from cells and maintaining the normal function of cells. In the brain UBE3A is expressed only from maternal allele [29], and it has a higher density in hippocampus and the Purkinje cells from the cerrebellum. Studies suggest that ubiquitin protein ligase E3A plays a critical role in the normal development and function of the nervous system.

The clinical picture comprises of psychomotor development delay, a joyful mood, hyper excitable personality, EEG recording anomalies and severe mental and language retardation. Apparent happiness is brand forthe syndrome, associated with a vague smile, rare specific laughs, exuberant background, hyperactive and stereotyped motor behaviour, and proactively social contact. Autistic symptoms lead to debates in diagnosis. The absence of expressive language, the reduced and inefficient use of nonverbal communication, motor and sensory stereotypes and sleep problems have all been correlated with low development profile and were considered by some authors as "co-morbid autistic disorder". Peters et al (2004) have found an association between AS and autistic spectrum disorders (according to DSM IV) in approximately one half of the evaluated cases. In addition, AS can be associated in various degree with ataxia, epilepsy and microcephaly.[30] Some children can develop severe myoclonic seizures, knowing that myoclonus with cortical origin is another manifestation of AS.

Williams syndrome (WS)

WS is characterized by particular facial appearance, with elfin appearance, cardiac abnormalities/malformations, connective tissue abnormalities, mental retardation or learning disorder, idiopathic infantile hypercalcemia, particular cognitive profile and an unusual personality profile.

The disorder is caused by a deletion of 1.5 megabase the long arm of chromosome 7, including the elastin gene (ELN). 16 genes were identified, so far, in the region 7q11.23. [31] The deleted region includes about 25 genes that probably contribute the manifestations of the syndrome. ELN gene deletion responsible for the synthesis of elastin, is associated with connective and cardiovascular anomalies, which are characteristic for the syndrome (supravalvular aortic stenosis, supravalvular pulmonary stenosis). Deletions of LIMK1, GTF2I, GTF2IRD1 genes are responsible for visual and spatial difficulties in these patients and the CYLN2 gene deletion is associated with particular behaviour, mental retardation and other cognitive deficiencies seen in patients with WS. The STX1A and LIMK1 gens are good candidates in investigating changes in cognitive or behavioural aspects of WS. LIMK1 gene was discussed in causal relationship with visual and spatial characteristics of WS [32], whereas the genes FZD9 and STX1A have been proposed to be involved in alterations of brain devel-

opment. A more severe phenotype with lower cognitive ability is found in individuals with longer deletion (> 2.4 Mb) than typical deletion. Patients with a shorter deletion, that does not involve GTF2I (including those with de novo mutation) do not have intellectual disability, but have the specific WS cognitive phenotype.

Miller-Dieker syndrome

Miller-Dieker syndrome is characterized by lissencephaly and facial dysmorphy.The majority of the children have deletion of chromosome17p13.3.Children may present clinical features of Miller-Dieker syndrome by inheriting an unbalanced translocation.

The size of the deletion varies among affected individuals. The identified genes in this region, implicated in features of Miller-Dieker syndrome are: PAFAH1B1, responsible for the syndrome's characteristic sign of lissencephaly and YWHAE, which increases the severity of the lissencephaly.

Brain malformations cause abnormal muscle tone, spasticity or hypotonia, developmental delay, seizures severe intellectual disability, and feeding difficulties. PAFAH1B1 gene (also known as LIS1) provides instructions for making a protein is thought to be involved in directing the movement of nerve cells (neurokinesis) in the brain. Proper neuronal migration is essential for normal brain development and function. It also promotes neuronal migration by interacting with tubulin in microtubules. [33]

Decreased amount of PAFAH1B1 protein produced by the deletion of one copy of the PAFAH1B1 gene is responsible for many of the features of Miller-Dieker syndrome, including intellectual disability, developmental delay, and recurrent seizures (epilepsy). A decrease in neuronal migration caused by a lack of PAFAH1B1 protein is responsible for the lissencephaly.

YWHAE gene provides instructions for making the 14-3-3 epsilon (ε) protein, which is part of the large of a protein family involved in cell signalling. The 14-3-3ε protein helps to regulate a variety of processes including cell division and sensitivity to insulin in the body, in the brain being involved in neuronal migration by binding to other proteins involved in this process. It is thought that the 14-3-3ε protein is critical for proper neuronal migration and normal brain development. [34]

Di George syndrome

Is also referred as velocardiofacial syndrome and is caused by deletion of one copy of the 22q11.2 region resulting in abnormalities in the development of the third and fourth branchial arches, producing thymic hypoplasia, parathyroid hypoplasia, and conotruncal cardiac defects.

Children have frequently learning disabilities and behavioural problems. Developmental milestones are achieved later the peers of same age. In school age children IQ testing revealed scores that can range from average to mild retardation an a discrepancy between verbal and non-verbal IQ. The school performance may be lower than predicted by IQ testing secondary to weak executive functioning and low verbal abilities. They have also high scores in externalising symptoms secondary to attention deficit disorder, disinhibition and

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impulsivity, but also at internalising symptoms – shyness, anxiety and depression. In one longitudinal study, 20% of VCFS children in mid adolescence had significant prodromal psychotic symptoms. [35]

2.3. Monogenic mental retardation

Studies looking at single genes that may contribute to intellectual disability were started by reports of numerous families in which intellectual disabilities were common and transmitted in Mendelian pattern. In the some of them, the trait was inherited X-linked and was more frequent in males. The detailed analyses of _1000 Online Mendelian Inheritance in Man (OMIM) database entries and of the literature through September 2003 revealed 282 molecularly identified MR genes. [54]

Gene	Locus	Disorder	Protein function
CBP	16p13.3	Rubinstein–Taybi syndrome	CREB binding protein; chromatin-remodelling factor involved in Ras/ERK/MAPK signalling cascade
EP300	22q13.1	Rubinstein–Taybi syndrome	Transcriptional coactivator similar to CBP, with potent histone acetyl transferase: chromatin-remodelling factor
DNMT3B	20q11.2	ICF syndrome: immune deficiency associated with centromeric instability, facial dysmorphy and MR	DNA methyltransferase 3B, involved in chromatin remodelling
GTF2RD1	7q11.23	Williams syndrome	Transcription factors, potential regulator of c-Fos and immediate-early gene expression
CRBN	3p25	Nonsyndromic AR mental retardation	ATP-dependent protease; regulation of mitochondrial energy metabolism
CC2D1A	19p13	Nonsyndromic AR mental retardation	Unknown function, protein contains C2 and DM14 domains
UBE3A	15q11	Angelman syndrome	Ubiquitin–protein ligase E3A; protein degradation (proteasome): CNS development/function
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)

Gene	Locus	Disorder	Protein function
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).
NF1	17q11	Neurofibromatosis type 1 (NF1); MR is present in 50% of NF1 cases	RasGAP function, involved in Ras/ERK/MAPK signalling transcription cascade; postsynaptic protein
Microcephalin	8p22-pter	Microcephaly vera	Cell cycle control and DNA repair
CDK5RAP2	9q33.1	Microchephalyvera	Mitotic spindle function in embryonic neuroblasts
ASPM	1q31.1	Microchephalyvera	Formation of mitotic spindle during mitosis and meiosis
CENPJ	13q12.2	Microchephalyvera	Localization to the spindle poles of mitotic cells

Table 3. Autosomal genes involved in MR disorders [31, 36]

X-linked mental retardation (XLMR)

Since the observations of L. Penrose, in 1983, of existence of a higher number of males than females with mental retardation in the population, several surveys were directed to elucidate the etiology of this report. The results indicated that many genes that determine mental retardation mapped for X chromosome. X-linked mental retardation (XLMR) was defined as a monogenic intellectual disability affecting mostly males, having a higher prevalence of MR relative to females.

The prevalence of XLMR had been estimated in different studied since 1980 the estimation made by Herbst and Miller, of 1.83 affected in 1000 males. [37] Since the X-linked disorders may be transmitted by an unaffected carrier mother, large families with numerous multigenerational individuals with mental retardation facilitated linkage studies and supported the idea of highly heterogeneous pathology.

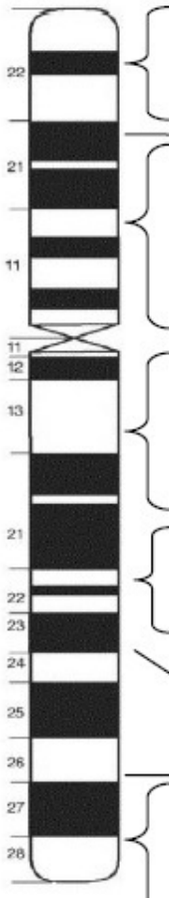
Establishing the distribution of the level of cognitive deficit in the XLMR individuals group was considered a important socio-economic problem giving the extensive impact of MR not only for genetic and medical services but for social system. For mild mental retardation (IQ 70–50), the epidemiological studies found a ratio male- female of 1.9, indicating that 50% of all the cases of mild MR are due to XLMR. For this result it was considered that the excess of cases in males is due to XLMR. The same ratio is lower in moderate to severe MR (IQ<50), of

1.4, and making the same assumption than above we will conclude that 28.5% of all severely retarded males have XLMR. A percent of 10–16% from all severely retarded men is due to XLMR. Finally, in cohorts of mentally retarded males, the prevalence of the Fragile X syndrome was 2–2.5%,[38,39], 25% of all males with severe XLMR have having Fragile X syndrome.

Nonspecific ornonsyndromic XLMR include mental retardation caused by mutations of genes on the X chromosome without accompanying somatic, neurologic, biological, or behavioural manifestations which allows distinction from nonaffected male or from males with identified MR.

In other words, a nonprogressive intellectual disability, segregating in X linked manner that can be distinguished based on the knowledge of their causative gene. The studies of this type of XLMR were directed to establish the relation between X chromosome genes and the cognitive and adaptive functions and processes.

The difficulties in establishing a characteristic pedigree increased the difficulties in establishing the prevalence.



NLGN4	Cell adhesion
RSK2*	Signal transduction, protein serine/threonine kinase
IL1RAPL	Regulator of dense-core-granule exocytosis, signal transduction
TM4SF2	Membrane component, modulation of integrin-mediated signalling, possible role in synapse formation
ZNF41	Transcriptional regulator involved in chromatin remodelling
FTSJ1	Role in tRNA modification and RNA translation, methylation protein synthesis
PQBP1*	Transcription regulation
JARID1C*	Role in chromatin remodelling
FGD1*	Signal transduction, stimulation of neurite outgrowth
DLG3	Postsynaptic scaffolding protein linked to NMDA-type glutamatergic
ARX*	Transcription factor with possible role in the maintenance of specific neuronal subtypes in the cerebral cortex and axonal guidance in the floorplate, neuronal proliferation
ACSL4	Lipid metabolism, long-chain fatty-acid synthase, possible role in membrane synthesis and/or (FACL4) recycling
PAK3	Signal transduction, regulation of actin cytoskeleton, stimulation of neurite outgrowth
AGTR2	Brain-expressed angiotensin receptor 2
ARHGEF6	Integrin-mediated activation of Rac and cdc42, stimulation of neurite outgrowth
MECP2*	Transcriptional silencer of neuronal genes
FMR2	Transcriptional regulator, possibly involved in long-term memory and enhanced long-term potentiation
GDI1	Signal transduction, regulation of Rab4 and Rab5 pools, probably involved in the maturation of synaptic vesicles
SLC6A8*	Creatine transporter, required for maintenance of (phospho) creatine pools in the brain

* are implicated in syndromic XLMR

Figure 1. Gene function in nonsyndromic XLMR(Addapted after Hilger Ropers and Ben C. J, 2005)[40]

The description of an case as a nonsyndromic XLMR entity implies a complex evaluation including: growth, morphological features, neuromuscular development and function, behaviour, brain imaging, and laboratory testing. Affected males were not prove to have morphologic, neuromuscular, or behavioural manifestations that distinguish them from unaffected brothers or from other males with mental retardation. [40]. The degree of mental retardation could vary from mild to severe in the same family but is consistent. Carrier females may experience less severe learning problems. They also lack diagnostic findings on cranial imaging, biochemical studies, or cytogenetic analysis. Head circumferences and heights in affected males were most often in the normal range. Testicular volumes had been documented to be normal or enlarged.

Rett syndrome

Was described as a form of nonsyndromal XLMR. Mutation in gene MECP2 maps on chromosome Xq28.Rett syndrome it is frequently due to the deletion or insertion mutation in MECP2 gene. In 25% from the cases MECP2 large deletion were identified by PCR in girls with typical clinical picture. MECP2 gene is expressed in the brain in the neurons but not in the glia.

Rett syndrome was included in the chromatin modification disorders category because of the role of MECP2 in coding a protein that binds to chromatin and regulates transcription [41].

Clinical onset of the symptoms is early in the childhood, between 6-18 month, with loss of speech, behavioural changes, stereotypical behaviours, loss purposeful use of hands. The little girls affected tend to loss contact and interest for communication, and to occupy their time with repeated hand wringing, washing, or clapping motions. As they grew older microcephaly became evident, motor regression, seizures are added. They may also have an altered pattern of sleep and breathing difficulties.

Syndromic XLMR

Syndromic or specific XLMR implies that beside mental retardation the affected individuals present other manifestations that can include them in one of the categories:

1. syndromes, characterized by multiple congenital anomalies affecting organs and tissues but also including the brain,
2. neuromuscular conditions, with associated neurologic and/or muscular symptoms,
3. metabolic conditions and
4. dominant conditions [42] .

This attempt to classify XLMR has most a theoretical. Thus,because the same genes or even the same mutation can result in either a syndromic or a non-syndromic form of the disease. One example can be *ARX* gene found both in patients with non-syndromic X-linked mental retardation and in the syndromic X-linked West syndrome and Partington syndrome. [43]

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The explanation may be that mutations in these genes in nonsyndromic XLMR families are presumed to cause only a partial loss of function of the encoded proteins, which could explain the absence of syndromic features

The classification from the 2007 XLMR gens update accept three classes to categorize XLMR conditions based on their clinical presentation:

a. syndromes, characterized by multiple congenital anomalies and defects in organs/tissues other than (but also including) the brain;

b. neuromuscular disorders, characterized by neurological or muscular symptoms (epilepsy, dystonia, spasticity, muscle weakness, and so on) but no malformations and

c. nonspecific conditions (MRX), where MR is the only consistent clinical manifestation among the affected individuals. [42]

The conditions associated with MR are recognizable on the basis of a distinctive clinical presentation and they can be considerate separate nosological entities, even if the causative gene or locus is unknown.

This distinction has mostly practical value.

Gene	Disorder	Clinical features	Protein function
FMR1	***Fragile X syndrome***	Facial anomalies, macroorchidism	mRNA processing, mRNA export from nucleus
ABCD1	***X-linked adrenoleukodistrophy***	Cognitive regression, spasticity, seeing loss, dementia, Addison disease	Membrane transporter, peroxisome
MAOA	***MAO-A-deficiency behaviour***	Aggressive and violent MAO	serotonin metabolism
OCRL1	***Lowe syndrome***	Short stature, cataracts, hypotonia, aminoaciduria, progressive renal disease	Signal transduction, lipid metabolism
GK	***Glycerol kinase deficiency***	Short stature, spasticity, osteoporosis	Nuclear translocation of the hyperglycerolaemia glucocorticoid-receptor complex
XNP	***ATR-X, Juberg–Marsidi syndrome, Carpenter syndrome, Holmes–Gang of gene syndrome, Smith–Fineman–Myers syndrome, Chudley–Lowry syndrome Spastic paraplegia***	Microcephaly, hypotonic facies, facial, urogenital and skeletal anomaliesthalassaemia, HbH inclusions, microcephaly, short stature, spastic diplegia	DNA helicase; chromatin remodelling, DNA methylation and regulation expression; regulator of cortical size

Gene	Disorder	Clinical features	Protein function
FGD1	***Aarskog–Scott syndrome***	Facial, digital and genital anomalies, short stature	RhoGEF; possible role in stimulation of actin polymerization
RSK2	***Coffin–Lowry syndrome***	Facial and skeletal anomalies	Serine-threonine protein kinase; CREB phosphorilation; long term memory
OPHN1	***Cerebellar hypoplasia or dysplasia***	Epilepsy, cerebellar anomalies	Negative control of rhoGTPases; and epilepsy stabilization of dendritic arbours
MECP2	***Rett syndrome*** ***Male fatal neonatal encephalopathy*** ***Progressive spasticity Spasticity*** ***NS-XLMR 57*** ***Angelman and Prader–Willi-like phenotypes***	Regression, epilepsy, acquired microcephaly, hand stereotypies, autism Hypotonia, apnea, epilepsy	Transcriptional silencer of neuronal genes
SLC6A8	***Creatine deficiency syndrome***	Epilepsy, facial anomalies	Creatine transporter, maintenance of (phospho) creatine pool in brain
FLNA	***Periventricular heterotopia*** ***Otopalatodigital syndrome I and II***	Epilepsy, brain anomalies, short stature, cleft palate, facial and skeletal anomalies	Actin-binding protein; neuriteoutgrowth;dendritic spine formation
ARX	***West syndrome*** ***Partington syndrome X-linkedlissencephaly, ambiguousgenitalia*** ***Proud syndrome***	Infantile spasms, regression, epilepsy, dystonia Lissencephaly, corpus callosum agenesis, epilepsy, ambiguous genitalia, Microcephaly, corpus callosum agenesis, urogenital anomalies	Transcription factor; neuronal proliferation/ differentiation of GABA-releasing neurons
CDKL5	***Infantile spasms***	Infantile spasms	Serine-threonine kinase; chromatin remodelling
SYN1	***Epilepsy, macrocephaly, aggression***	Epilepsy, macrocephaly, aggression	Synaptic-vesicle associated protein
SMS	***Snyder–Robinson syndrome***	Macrocephaly, palatal anomalies,scoliosis	Spermine synthase
PQBP1	***Renpenning syndrome, Sutherland–Haan syndrome, Hamel cerebro-palatocardiac syndrome, Golabi–Ito–Hall syndrome***	Microcephaly, short stature, slender habitus, long face, congenital heart defect, cleft palate	Polyglutamine-binding; mRNA splicing

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Gene	Disorder	Clinical features	Protein function
PHF6	***Börjeson–Forssman–Lehmann syndrome***	Hypogonadism, obesity, facial anomalies, epilepsy	PHD zinc-finger protein; putative role in transcription
SLC16A2	***Thyroid and neurological abnormalities***	Hypotonia, spasticity, dystonia, abnormal thyroid tests	Monocarboxylate transporter; T3 transport into the cytoplasm
BCOR	***Lenz microphthalmia***	Microphthalmia, skeletal and urogenital anomalies	Transcriptional co-repressor; possible rolein modulation of histone acetylation and chromatin remodelling
PHF8	***Siderius–Hamel cleft lip or palate syndrome***	Cleft lip or palate	PHD zinc-finger protein; putative role in transcription
ATP6AP2	***Epilepsy***	Epilepsy	Renin receptor; activates ERK1 and ERK2
JARIDIC	***Microcephaly, spasticity, epilepsy, short stature, facial anomalies***	Microcephaly, spasticity, epilepsy, facial anomalies short stature,	Transcription factor;chromatin remodelling
IDS	***Hunter disease (MPZII)***	Short stature, skeletal and facial abnormalities, hearing loss	Metabolism, glycosaminoglycan metabolism
PLP1	***Pelizaeus-Merzbacher syndrome***	Nystagmus, truncalhypotonia and progressive spastic paraplegia, ataxia, and dystonia associated with CNS dysmyelination	Membrane component, myelin component
HPRT1	***SyndromeLesch-Nyhan***	Choreoathetosis, self-mutilation, hyperuricemia	Metabolism, purine ribonucleoside salvage
MID1	***Opitz syndrome***	Macrocephaly, facial anomalies, dysgenesis of corpus callosum, cardiac defects, hypotonia	Ubiquitin cycle, microtubule-associated complex
ATP7A	***Menkessyndrome***	Growth deficiency, sparse hair, limited movement, hypertonicity, seizures, arterial tortuosity, childhood death	Membrane transporter, copper-exporting ATPase activity

Table 4. Gene function in syndromic XLMR(Adapted after: Chellyet a.2006, [31]).

Fragile X syndrome

Fragile X syndrome is the most common form of XLMR, affecting approximately 25% of all families suffering from XLMR. It is caused by the loss of function of gene FMR1, which maps on chromosome Xq27.3, a55bp segment of DNA composed by repeats of the nucleotide CGG. CGG repeat is located in the 5◎-untranslated region of FRM1.[44] Normal people have 6-55 copies, carriers have 55-230 copies and to not express the fragile site. In females carriers the FRAX repeats are expanded during meiosis. In affected males 230-1000 repeats are present and they express fragile X mental retardation. Repeat expansion associated with hypermethylation causing reduced or absent expression of FRM protein. The accumulation of untranslated FRM1 mRNA forms inclusion in neurons and glial cells of hippocampus and cerebral cortex causing the neurological manifestations of the syndrome. [45,32]

Clinical features include long narrow face, large and protruding ears, macroorchidism. Patients exhibit also moderate mental retardation, attention deficit, autistic symptoms, seizures and coordination problems.

Autism

First described as a behavioral disorder in children, in 1943 by Leo Kanner, was proven to affect mostly social interactions, the interest for relation, interaction and communication, the ability to decode facial expression and emotional message. It was suggested that autism has an organic basis sustained by the association with mental retardation (75%) and seizures (40%).

Evidence of concordance in twin studies, monozygotic- 60-92%, while in dizygotic twins range 0-10%, and the risk of recurrence higher than the general population in families with one autistic child brought into scientific interest the role of genetic factors in autism. [46]

Autism may occur in patients with monogenic diseases as tuberous sclerosis or Fragile X syndrome. Autistic like symptoms have also described in duplication of chromosome 15q11-13 [47] and deletion on chromosome 2q37.3 [48]

Between 1998 and 2004 an extended effort was carried out in the International Molecular Genetic Study of Autism Consortium. The goal of associating a chromosome with autism was not fulfilled but association studies have found positive association on chromosome 7q, especially with a missense mutation on the LAMB1 gene, and with 17q11.2 [49]

The presence of autistic symptoms in Rett syndrome directed the attention through MECP2 gene. As a result, MECP2 mutation was associated with a low percentage in autism. The same interest was raised by 15q11-13q, secondary to the presence of autistic features in individuals with Prader-Willi syndrome and Angelman syndrome. The result in this cases was a reduced expression of two genes in region 15q11-13q, UBE3A and GABRB3.

If the genomic regions play a role in autism, by genes defect or by common regulatory pathways are the preoccupation of further studies.

2.4. Mental retardation in metabolic disorders

The evolution of metabolic disorders may disrupt development of children with previous normal development. Genetic diseases presenting abnormal use or storage of different nor-

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mal substances (protein, lipids, copper), these disordersmay manifest with a complex perturbation of cognition maturation and motor impairment.

DISORDER	CLINICAL FEATURES
Biotinidase Deficiency	Mental retardation, seizures, skin rash, loss of hair, death
Congenital Hypothyroidism	Mental retardation, other brain damage, growthdelay
Galactosemia	Severe brain damage, developmantal delay, kidney damage, eye abnormalities inneonates, death
ORGANIC ACIDEMIAS A condition in which the body cannot break down and get rid of certain organic acids and the metabolic acids accumulate in blood	
Glutaric Acidemia Type I	Neurological deterioration, muscle weakness or dystonic cerebral palsy, epilesy
Maple Syrup Urine Disease (MSUD)	Neonatal coma, convulsions, mental retardation, death
Malonic Aciduria	Developmental delay, vomiting, seizures, cardiomyopathy, hypoglycemia
Isovaleric Acidemia	Vomiting, lack of appetite, lethargy, neuromuscular irritability, hypothermia
Propionic Acidemia	Mental retardation, seizures, movement disorders, coma, sudden death
Methylmalonic Acidemias	Lethargy, vomiting and dehydration, respiratory distress, muscle weakness, coma, seizures, developmental delay
Multiple Carboxylase Deficiency	Seizures, immune system impairment, skin rashes, hair loss, hearing loss, mental retardation
2-Methyl-3- Hydroxybutyryl CoA Dehydrogenase Deficiency	Developmental delay
3-Methylglutaconyl CoA Hydratase Deficiency	Delayed motor development, short attention span, delayeddevelopment of speech
DISORDERS OF AMINO ACID METABOLISM A condition in which the body cannot break down several amino acids in protein foods and cannot get rid of ammonia, which has a toxic impact	
Arginase Deficiency	Developmental delay, seizures, hyperactivity, ataxia
Argininosuccinate Lyase Deficiency	Mental retardation, potential lethal coma, seizures, anorexia, vomiting, lethargy
Citrullinemia	Mental retardation, potential lethal, coma, seizures, anorexia, vomiting, lethargy
Homocystinuria	Heart disease, stroke, possible mental retardation, psychiatric problems

DISORDER	CLINICAL FEATURES
Phenylketonuria (PKU)	Severe mental retardation, seizures
FATTY ACID OXIDATION DISORDERS (FAOD)	
Problems with enzimes that breakdown of lipids from the food or from fat stored and production of Acetyl Co-A. The proces requires active transport across mitochondrial membrane	
Carnitine disorders Carnitine/Acylcarnitine Translocase deficiency (CAT) Carnitine Palmitoyl Tranferase deficiency Type I (CPT-I) Carnitine Palmitoyl Tranferase deficiency Type II (CPT-2) Carnitine Uptake Defect (CUD)	hypoglycemia, liver disease, sudden infant death(SIDS), encephalopathy, myopathy, cardiomyopathy.
Long chain fatty acid dehydrogenase disorders Long/Very Long Chain Acyl CoA Dehydrogenase deficiency (LCAD/VLCAD) Long Chain Hydroxy Acyl CoA Dehydrogenase deficiency (LCHAD)	hypoglycemia, hepatomegaly, myopathy, SIDS,Reye syndrome, and cardiomyopathy.
Medium chain fatty acid dehydrogenase disorders Medium Chain Acyl CoA Dehydrogenase deficiency (MCAD) Medium Chain 3-Ketoacyl CoA Thiolase deficiency (MCKAT) Multiple Acyl CoA Dehydrogenase deficiency (GA-II)	Children with MCAD are typically normal at birth and develop episodes of hypoketotic hypoglycemia, vomiting, lethargy, seizures associated with fasting.
Short chain fatty acid dehydrogenase disorders Short Chain Acyl CoA Dehydrogenase deficiency (SCAD) Short Chain Hydroxy Acyl CoA Dehydrogenase deficiency (SCHAD)	SCAD deficiency presents in the neonatal period with failure-to-thrive, hypotonia, and metabolis acidosis; hyperammonemia and lactic acidosis have been reported.
Glutaric acidemia (aciduria) types 1 and 2	Liver and muscle fat Macrocephaly, brain atrophy (type 1) Cortical dysplasias and heterotopias, polycystic kidneys (type 2)
MITHOCONDRIAL DISORDERS	
The illness result from deficiency of any mitochondria-located protein which is involved in energy metabolism. Variability in part due to variable numbers of affected mitochondria, and to the affected tissue, the most damaged cells of the brain, heart, liver, skeletal muscles, kidney and the endocrine and respiratory systems.	
Acute lactic acidosis Leigh syndrome	Depending on the type of tissues affected, symptoms may include:

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DISORDER	CLINICAL FEATURES
MELAS	loss of motor control
MERF	muscle weakness and pain
MIRAS	respiratory complications
Pyruvate Dehydrogenase Deficiency	gastro-intestinal disorders and swallowing difficulties
	poor growth
	cardiac disease
	liver disease
	diabetes,
	seizures
	visual/hearing problems
	lactic acidosis
	developmental delays
GLYCOGEN STORAGE DISEASES	Hypoglycemia and ketosis (variable)
Abnormal metabolism of glycogen	Deposition of glycogen in tissues
MUCOPOLYSACCHARIDOSES	Because of maternal enzymes, patients normal at birth and then
Defective normal degradation leads to	progress to disfigurement and disability, coarsened facial
glycosaminoglycan accumulation	features
	short stature with disproportionately short trunk and skeletal
	dysplasia
	thickened skin ,organomegaly , hernias, excessive body hair,
	progressive joint stiffness
	Developmental delay
	Severe behavioral problems
	Hearing loss
	Communicating hydrocephalus
PEROXISOMAL DISORDERS	
This results in the over-accumulation of and branched chain fatty acids, such as	
Zellweger spectrum disorders	Destruction of the myelin (demyelination) leads to loss of white
Zellweger Syndrome	matter (leukodystrophy). Children may develop life-threatening
Neonatal Adrenoleukodystrophy	problems in other organs and tissues, such as the liver, heart,
Infantile Refsum Disease	and kidneys, adrenal glands
Chondrodysplasia Punctua spectrum	abnormal cartilage and bone development, chondrodysplasia
	punctata especially in the hands and feet, hearing loss and short
	stature, cardiac defects, and seizure disorders
LEUKODYSTROPHIES	
Genetically determined progressive disorders that affect the brain, spinal cord and peripheral nerves. The injury affect the white matter of the nervous system and is progressive, tends to get worse as the child gets older.	
Adrenoleukodystrophy	
Alexander's disease	
Canavan disease	

DISORDER	CLINICAL FEATURES
Cerebrotendinous Xanthomatosis Krabbe's disease	
Pelizaeus-Merzbacher disease	
LIPID STORAGE DISORDERS	
Various disorders have characteristic patterns of organ involvement, depending on particular substrate that is stored.	
Mutation causes abnormal enzyme function. Leads to glycosphingolipid accumulation in lysosomes	
Fabry disease	Progressive clinical manifestations neurodegenerative disease, organomegaly, skeletal abnormalities, pulmonary infiltrates
GM1 gangliosidosis	
Tay–Sachs disease	
Niemann-Pick disease	
GM2 gangliosidosis	
Gaucher disease	
Wolman disesse	
Fucosidosis	
Alpha-manosidosis	
Metacromatic leukodystropy	
Galactosialidosis	
MENKES SYNDROME	Alteration of copper metabolism. Children develop hypotonia, seisures, hypotermia, developmental and grow delay.
OCCIPITAL HORN SYNDROME	

Table 5. Metabolic diseases associated with MR or DD.

Researches led to the understanding of mental retardation in these diseases and to identification and implementation of the therapies, which prevent the consequences associated to the genetic defect. The positive results of therapies instituted in a timely manner put the basis of extensive screening programs for newborns designed to avoid irreversible changes in development processes.

2.5. Multifactorial inheritance and mental retardation

A clinical phenotype is frequently the result of a complexity of interaction between different pathways including many genes, proteins and environmental factors. Such diseases are of defective cellular migration (such as lissencephaly, heterotopias), neural tube defects, congenital hydrocephalus, myoclonic epilepsy, and narcolepsy. The experiences showed that these do not respect the Mendelian patterns of inheritance, althought genetic factors are implicated since a higher reccurence had been observed in some families.

The neural tube defect include spina bifida, anencephalyand any other defect that is a failure of closure of the neural tube and, in some cases, hydrocephalus associated to thedisturbance of the circulation of the cerebrospinal fluid.

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Empirical data show that couples who have one child with a neural tube defect are at greater risk of having a second child with a neural tube defect thanother couples in the general population. Randomized controled data sustainned that maternal folic acid supplements lower the the number of children born with spina bifida. [50]. Later studies sustained mothernal folic acid supplement for many months, even years, before conception for women of having a child with a neural tube defect (a previous child with neural tube defect, mother taking antiepileptic medication).

Polymorphic DNA sequence variation could not sustain a single polymorphism in genes encoding enzymes involved in folate metabolism as a risk factor factor in all populations for neural tube defect. [51,52]

Genetic counselling for this families is important to take into consideration the neural tube defect isolated and those in which it forms part of asyndrome.

3. Establishing the diagnosis of mental retardation

Developmental disabilities may affect children in a single domain or in several arias of their life: global developmental delay, motor impairment, isolated speech and language delay, severe primary sensorial deficits and pervasive disabilities.

The earliest elucidation of the etiology of developmental delay may improve the quality of child life. In inborn errors of amino acids or organic acids, a correct diagnosis improves the evolution. Following an accurate clinical, biochemical, and sometimes molecular, a treatment could be initiated in this cases.

Even in the cases in which the diagnosis is not going to change the evolution for the child, a positive impact may have on the family. A team approach may empower parents to deal with disabilities and to search and choose proper medical, educational and social facilities.

The physician must be directed to evaluate child developmental level at every evaluation. A suspicion of mental retardation in any child may be raised in any child based on some clues: delayed speech, dysmorphic features (minor anomalies), difficult to manage temperament, hypotonia generally or of the extremities, clumsiness, general inability to do things for self and, not least, expressed concern by the parents.

1.Personal clinical history	length of pregnancy, premature onset of labour or rupture of the membranes, duration and course of labour, type of delivery and any complications, Apgar scores at one and (especially) five minutes should be reviewed, and birth weight length and head circumference measurements obtained and plotted on appropriate growth charts illnesses, feeding or sleeping difficulties in the newborn period and problems with sucking or swallowing, temperament

	atypical course in child development seizures
Documented medical situations from prior evaluations may offer an objective perspective for the professionals.	
2. Family history	existing cases of DD/MR history of infertility or fetal loss maternal health during gestation: use of drugs, tobacco, alcohol, sign of infections, hospitalisation, risk for sexually transmitted diseases
3. Dysmorphologic examination	unusualcranio-facial, skeletal, palmar crease patterns. macrocephaly; microcephaly genital anormalities
Minor abnormalities, involving the face, ears, hands or feet may provide clues to developmental problems of possible prenatal origin. Most minor abnormalities are readily recognized even on cursory examination.(53)	
4. Developmental evaluation	formal developmental screening behaviour problems ADHD autism/autistic- like behaviours
The formal test that address developmental delay have more domains: gross motor/fine, speech-language, cognition, social. For the physician it will be important to ask specific questions about the child's current developmental abilities at each visit.	
5. Neurologic examination	-hypotonia, spasticity, ataxia - seizures - cerebral palsy
An EEG can be obtained when a child with global developmental delay has a history or examination features suggesting the presence of epilepsy or a specific epileptic syndrome: Lennox-Gastaut syndrome, myoclonic epilepsy, Rett syndrome. If available, MRI should be obtained in the presence of physical findings (e.g., microcephaly, focal motor findings).(53)	
6. Endocrinologic examination	-growth delay -obesity -genital abnormalities - clinical signs for hypotiroidy
7. Other clinical examination (cardiologist, orthopedicsurgeon, gynecologist, ophthalmologist, audiologist).	- heart malformations -skeletal
Children with global developmental delay may undergo appropriate vision and audiometric assessment at the time of their diagnosis. Vision assessment can include vision screening and a full ophthalmologic examination (visual acuity, extra-oculo-movements, funduscopic). Audiometric assessment can include behavioural audiometry or brainstem auditory evoked response testing when feasible. Transient evoked otoacoustic emissions are used as screening studies in newborns.	

8. Karyotype	common cytogenetic abnormalities found included Down syndrome, sex chromosome aneuploidies (47, XXY), fragile X syndrome, and unbalanced translocations/deletion syndromes
9. FISH	microdeletion/microduplication abnormalities
10. Metabolic testing	testing amino and organic acids thyroid function IGF

Table 6. Clinical genetics evaluation of the child with suspicion of MR.

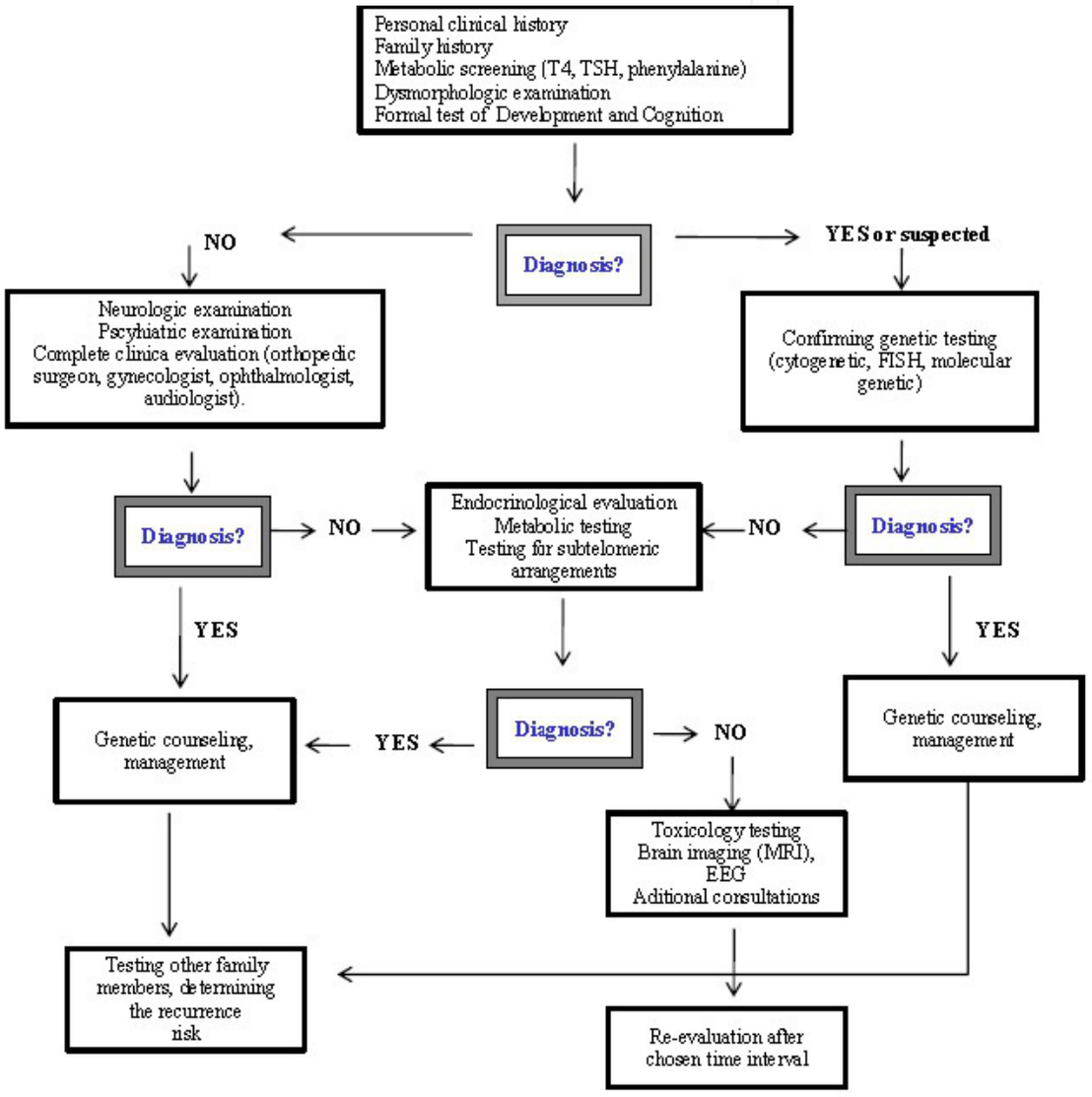

Figure 2. Algorithm of evaluation in DD/MR

Specific protocols for evaluation of children with DD/MR may be developed by every medical service based on the implication of a complex team and having as one of the objectives to keep the parents informed and facilitate the acquisition of the abilities and medical information that will make them able to manage their child at home.

4. Conclusion

Genetic factors have a major role in the etiology of mental retardation. In this chapter, we made a review of the genetic causes in mental retardation disorders, from chromosomal abnormalities, to contiguous gene syndromes, to monogenic mental retardation, to metabolic disorders that present with mental retardation and multifactorial inheritance.

Tremendous research strains were made to determine the genetic substrate along with the structural and functional impact of mental retardation. Firstly, efforts were targeted at understanding the cause and the natural history of the mental retardation disorders. Secondly, research aimed to precociously detect disorders (that can be treated), trough neonatal screening. Positive economic and social impact was shown by the extensive experience in screening, diagnosis and management of inborn errors of metabolism (PKU, hypothiroidism, organic acidemias). Unfortunately, most mental retardation syndromes do not have a treatment, and in these cases, the management is very difficult, expensive and lifelong. Thus, tailored professional support is needed for a family with a child with a mental retardation disease, in order to avoid social isolation and even isolation from the family. Access to interventions, based on developing skills and methods of coping, emotional management, support groups have reduced the negative impact on family functioning and established the base for development of resources in the community.

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