# Clinical Approaches to Genetic Mental Retardation

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The questions that most parents ask clinical geneticists following the birth of a mentally retarded child usually include "Is mental retardation genetic? What are the risks that we may have more mentally retarded children in the future? How can this be prevented?" The ability to make a specific genetic diagnosis in a family enables reproductive counseling that includes carrier screening and prenatal diagnosis. Individuals with easily recognizable MR-causing conditions are diagnosed by pediatricians or family physicians; other patients are referred to a tertiary care center for the diagnostic workup. This workup is usually very expensive and complex due to the large number of genes and chromosomal rearrangements involved in the etiology of MR. Only a few relatively common genetic MR syndromes exist, the most frequent of which are Down syndrome and fragile X syndrome [1].

## Epidemiology

MR affects approximately 1–3% of the general population [1]. Defining features of MR include intellectual functioning level (IQ) below 70, significant limitations in two or more adaptive skill areas, and the condition present from childhood (defined as age 18 or less) [2]. The ratio of mentally retarded males to females is as high as 1.4–1.6:1, mainly because of a large number of X-linked MR genes, but other factors are involved as well [3,4].

## Etiology and classification of MR

The etiologies of MR are diverse and include teratogenic and environmental factors, perinatal asphyxia and genetic causes. Environmental and teratogenic causes are found in 5–13% of cases and causes related to prematurity in 2–10% of cases [4]. Genetic etiologies are found in approximately two-thirds of cases [4]. Culturo-familial MR is believed to be caused by a combination of genetic and environmental factors. In one study, the frequency of this form of MR was found to be 6% [5]. MR can be subdivided into syndromic forms, which are characterized by MR accompanied by malformations, dysmorphic features, or neurological abnormalities, and non-syndromic forms, which are characterized by MR without any additional features. For several genes, different mutations in the same gene can result in both syndromic and non-syndromic MR [6]. An etiological diagnosis can be made in approximately half the patients [4,7]. Both syndromic and non-syndromic forms of MR can be caused by chromosomal abnormalities, mutations in a single gene (Mendelian inheritance), or mutations in a number of genes combined with environmental factors (multifactorial inheritance) [Figure 1]. Mendelian disorders include MR syndromes caused by single gene mutations, which can be transmitted by X-linked, autosomal dominant or autosomal recessive inheritance.

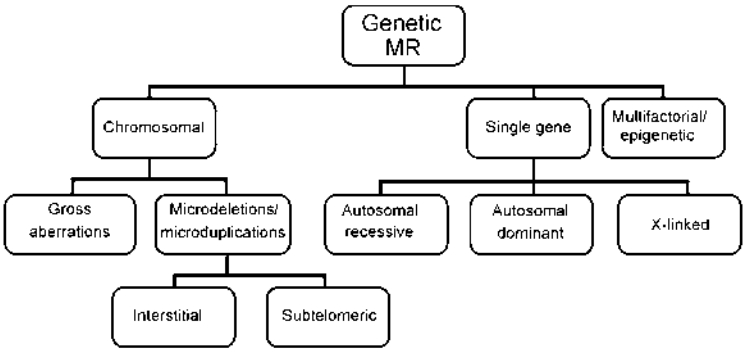


**Figure 1.** Main genetic etiologies of mental retardation

*In non-syndromic MR, no clinical diagnostic clues are available to link the clinical phenotype to a specific molecular defect; achieving a molecular diagnosis in these patients is successful in only a minority of cases*

### Syndromic MR

Specific clinically recognizable features accompanying the MR can increase the success rate of detecting the cause. Many of these syndromes are characterized by MR combined with specific dysmorphic features and unique behavioral characteristics. The diagnostic approach is quite straightforward in patients with syndromic MR: if a specific syndrome is recognized, testing for

MR = mental retardation

specific chromosomal abnormalities or mutations in the specific gene can be performed. Syndromic MR is more frequently caused by chromosomal abnormalities (gross chromosomal aberrations or microdeletions/microduplications) than is non-syndromic. Gross chromosomal abnormalities represent the most frequent cause of syndromic MR, causing retardation that can range from mild to profound [7]. In 5–7% of patients with dysmorphic features and congenital anomalies, subtelomeric microdeletions or microduplications can be identified [8]. In syndromic patients, the use of comparative genomic hybridization arrays enables detection of genomic copy number changes in as many as 16% of patients [9].

*Neuroradiological and extensive metabolic testing are no longer considered obligatory in the clinical assessment of individuals with MR; the decision on metabolic workup should be guided by clinical symptoms and inheritance pattern*

Metabolic and endocrine conditions comprise an important subgroup of syndromic MR, accounting for 1–5% of cases [4]. Screening newborns for metabolic and endocrine conditions (such as phenylketonuria and hypothyroidism) is important for prevention of MR caused by these treatable conditions. In some countries, expanded newborn screening for inborn errors of metabolism by tandem mass spectrometry is performed. Metabolic diseases are usually characterized by a progressive course and neurological symptoms, such as hypotonia, spasticity, seizures, coarse facial features, hepatosplenomegaly, eye abnormalities, and abnormal vision or hearing. It is important to consider the possibility of a metabolic or endocrine condition, since some of these are treatable. However, mutations in many genes do not show the "classical" phenotype of metabolic disease characterized by developmental regression. Mutations in these genes can be assumed due to the existence of specific metabolic or endocrine clues, such as abnormally high free triiodothyronine levels in SLC16A2 gene mutations and abnormal urine and plasma creatine/creatinine levels in SLC6A8 mutations [10]. Glycosylation defects were recently found to be relatively frequent in children with MR as compared to disorders of abnormal amino acid or organic acid metabolism [7].

#### Non-syndromic MR

In non-syndromic MR, no clinical diagnostic clues are available to link the clinical phenotype to a specific molecular defect. The frequency of gross chromosomal aberrations in patients with non-syndromic MR is unknown. No studies evaluating the diagnostic yield of microdeletion/microduplication detection in non-syndromic patients with MR using genome-wide CGH array have been reported. Therefore, at present, no conclusions can be reached regarding the frequency of cryptic chromosomal aberrations in non-syndromic MR. The relative frequency of non-syndromic MR caused by monogenic autosomal or X-linked conditions is also currently unknown.

#### Autism

Autism can be divided into "idiopathic," which comprises the majority of cases, and "secondary," in which an environmental agent, chromosome abnormality, or single-gene disorder can be identified. Approximately 90–95% of autistic individuals have idiopathic autism; 5–10% can be diagnosed with secondary autism. Between 50 and 70% of autistic children are mentally retarded. Approximately 3% of individuals with autism have a maternally inherited chromosomal duplication in the Prader-Willi syndrome/Angelman syndrome region of 15q11-q13. An additional 3–5% of individuals with autism have other chromosome abnormalities, including apparently balanced and unbalanced translocations, inversions, rings, interstitial deletions and duplications, and marker chromosomes [11]. Recently reported were a recurrent microdeletion and a reciprocal microduplication at 16p11.2 that carry substantial susceptibility to autism and account for approximately 1% of cases [12].

## Chromosomal aberrations

#### Gross chromosomal aberrations

Every individual chromosomal band contains a large number of different genes. Therefore, even a tiny chromosomal aberration can be responsible for the altered functioning of many genes and, consequently, for severe clinical features. Routine cytogenetic testing should be performed on every patient with mental retardation in whom no clinical or genetic diagnosis of a specific syndrome caused by a single gene has been made. Regular karyotype analysis detects imbalances of about 5–10 megabases, while high resolution karyotype detects imbalances of about 3 Mb. For comparison, the size of the human genome is almost 3000 Mb. The recurrence risk of additional affected offspring to a couple with a mentally retarded child due to a gross chromosomal aberration depends on the exact type of abnormality, but in most cases it is very low, apart from those families where one of the parents carries a balanced chromosomal rearrangement.

#### Microdeletions and microduplications

Karyotyping is often unable to detect subtle gains or losses smaller than 3 Mb. Improved resolution became available with the introduction of the fluorescent in situ hybridization technique. This technique is based on hybridization of a specific genomic probe to the chromosomal spread; if a particular genomic region is absent, no fluorescent signal will be observed. The FISH technique is used to identify microdeletion and microduplica-

CGH = comparative genomic hybridization
Mb = megabase
FISH = fluorescent in situ hybridization

tion syndromes when a specific diagnosis is suspected, such as DiGeorge syndrome or William's syndrome. Deletions or duplications can occur either at the ends of the chromosomes, called subtelomeric regions, or in the interstitial regions. The FISH technique has been extended to develop a strategy of screening for subtelomeric aberrations in individuals with MR. Subtelomeric rearrangements can be associated with a familial recurrence risk of up to 50% in cases where one of the parents has a balanced rearrangement, while aberrations in the interstitial regions are usually sporadic. Identification of interstitial or subtelomeric genomic copy number changes in mentally retarded patients can be achieved by using high density whole-genome CGH arrays. CGH array is a recent technology based on the general principle of gene chips for exploring genomic imbalances and chromosomal aberrations [13]. This technique involves hybridization of two DNA samples, one from the patient and one from a control, labeled with different fluorescent colors, to a microarray chip of mapped DNA fragments immobilized on glass slides. Recently, many new microdeletion or microduplication syndromes have been identified and characterized using CGH arrays. Currently used whole-genome CGH arrays allow detection of copy number changes of 100–200 kb, and a new generation of oligonucleotide CGH arrays offers resolution as high as 30 kb. Among patients with syndromic moderate to severe MR, the frequency of microdeletions and microduplications can be twice as high as in patients with mild or borderline MR [14].

Recently, the use of CGH arrays has shed some light on the pathogenesis of autism – copy number changes were found in 10% of patients, especially in sporadic cases [15]. However, these copy number changes might be associated with a predisposition to autism but may not be fully causative of the autistic phenotype.

**Table 1.** Recurrence risks for MR caused by single gene mutations according to the mode of inheritance

| Mode of inheritance | RR in the offspring of a couple with an affected child | RR in the offspring of healthy siblings of an individual with MR (males)* | RR in the offspring of healthy siblings of an individual with MR (females)* |
|---|---|---|---|
| Autosomal recessive | 25% | < 1% | < 1% |
| Autosomal dominant** | 50% | As in general population | As in general population |
| Autosomal dominant (new mutation in the proband) | < 1% | As in general population | As in general population |
| X-linked recessive | 50% for male offspring; milder clinical features possible in up to 50% of female offspring | As in general population | 25% for male offspring; milder clinical features possible in up to 25% of female offspring |
| X-linked recessive (new mutation in the proband) | < 1% | As in general population | As in general population |

RR = recurrence risk

* Assuming no consanguinity with the spouse

** Assuming no incomplete penetrance

## MR caused by single gene mutations

Why are we concerned about the mode of inheritance and exact genetic basis of MR? The mode of inheritance determines the recurrence risks for family members [Table 1]. For example, in the autosomal recessive mode of inheritance, both parents are healthy but each carries a mutation in one of the two copies of the same gene causing MR. Such a couple has a 25% risk for affected offspring in each pregnancy, while the recurrence risk for pregnancies of unaffected siblings is very low – less than 1% [Table 1]. However, in X-linked MR, the recurrence risk for MR in the pregnancies of the unaffected females in the family can be up to 25% [Table 1]. Therefore, the ability to distinguish between different modes of inheritance enables precise estimation of the reproductive risks for unaffected family members. It is important to remember that several syndromes are caused by mutations in several genes with different inheritance patterns: after we have counseled the family regarding a specific type of inheritance, new information on possible inheritance patterns might become available, thereby changing the recurrence risk figures. For example, Cornelia de Lange syndrome was thought to be transmitted by autosomal dominant inheritance and to be sporadic due to a new mutation; however, a gene causing an X-linked form has recently been discovered. The question of recontacting families who were counseled in the past in order to advise them of this important new information regarding a possible higher recurrence risk is of the utmost importance.

### X-linked MR

Research in the field of X-linked MR has been very successful in the past few years. It is thought that about 10% of MR in males is caused by mutations in X-linked genes [16]. The majority of identified single genes that give rise to MR are on the X chromosome; at least one new gene is discovered every few months. The first gene to be identified was the *FMR1* gene that causes fragile X syndrome, and this still remains the commonest single gene abnormality detected [17,18].

Linkage studies to identify the causative gene in a family with XLMR can be performed in families when a few affected patients with the same phenotype are diagnosed, using only the markers on the X chromosome, which significantly reduces the amount of work involved. Currently, more than 50 genes associated with syndromic and more than 25 associated with non-syndromic X-linked MR have been identified [19]. These account for MR in approximately 40% of the families with XLMR [19].

The variability of the phenotypic consequences of mutations in a single gene is demonstrated by the identification of mutations in the same genes in syndromic and non-syndromic patients. For example, mutations in the *ARX* gene have been identified in patients with X-linked West syndrome, Partington syndrome, X-linked lissencephaly with ambiguous genitalia, X-linked myoclonic epilepsy with generalized spasticity, and non-syndromic XLMR

XLMR = X-linked MR

[20-22]. Mutations in the *OPHN1* gene cause non-syndromic XLMR, but also MR associated with cerebellar hypoplasia [23]. Mutations in the *POBP1* gene can cause non-syndromic XLMR [24], but also Renpenning syndrome, characterized by MR, microcephaly and microorchidism [25]. Mutations in two X-linked genes encoding neuroligins NLGN3 and NLGN4 have been shown to be associated with autism [26], although these mutations only account for a minority of cases. It is emerging that the proteins encoded by different MR-causing genes have different biological functions and are important for neuronal differentiation and synaptic plasticity, synaptic vesicle cycling, regulation of the actin cytoskeleton, chromatin remodeling, gene expression regulation and other functions [27]. Identification of specific mutations in an affected family is important due to the high recurrence risk [Table 1].

#### Autosomal MR

In contrast to the significant progress in XLMR research, there is still a large gap in our knowledge regarding the genetic basis of autosomal non-syndromic MR. Identification of autosomal dominant genes causing MR is very difficult due to the lack of large families, since the affected individuals rarely reproduce. No genes causing autosomal dominant familial non-syndromic MR have been reported to date, although several genes assumed to be involved in autosomal dominant non-syndromic MR have been identified by mapping of the chromosomal breakpoints in patients with balanced chromosomal aberrations [28].

So far only five genes causing autosomal recessive non-syndromic MR have been identified: *PRSS12* on chromosome 4q26, *CRBN* on 3p26, *CC2D1A* on chromosome 19p13, *GRIK2* on chromosome 6q16 and *TUSC3* on chromosome 8p22 [29-33]. In addition, 10 new loci have recently been mapped, indicating extreme genetic heterogeneity of this condition. There is increasing evidence that mutations in the currently known genes are responsible for only a small percentage of the total number of cases of autosomal recessive non-syndromic MR [34], although large studies evaluating the contribution of these genes to the causation of autosomal recessive non-syndromic MR are still lacking. While mutations in the *PRSS12*, *CRBN* and *CC2D1A* genes cause a similar degree of severity of MR in all the affected members of the same family, mutations in other genes can cause MR varying from mild to severe among different members of the same family. Interestingly, all the mutations in the genes causing autosomal recessive non-syndromic MR identified to date are protein-truncating mutations. It can be speculated that milder missense mutations or sequence variants in these and other genes might cause an additive effect in the pathogenesis of mild cognitive impairment.

## Diagnostic tools for mental retardation

Careful clinical evaluation including neurological and dysmorphological examination should be performed in all cases of MR in order to detect specific clinical features that can guide a clinician to investigate a particular chromosomal abnormality or gene. In a systematic review of the usefulness of diagnostic investigations in patients with MR [35], a very high diagnostic yield was found for dysmorphological examination (39–81%). It was estimated that the mean yield of chromosome abnormalities detected on karyotyping was 9.5% and the median yield from subtelomeric studies was 4.4%. For fragile X screening, the yield was 2.0%. For metabolic investigations, the mean yield was only 1.0%. The yield for reaching a diagnosis based on neuroradiological studies only was 1.3% [35]. In other studies, children with developmental delay or retardation were diagnosed with metabolic disorders in 0–5% of the cases [4]. Therefore, the decision regarding metabolic studies should be guided by the clinical symptoms.

*Diagnostic workup of patients with MR ideally should include all or some of the following tests: karyotyping, fragile X analysis, X-inactivation studies, CGH array, and sequencing of the known MR-causing genes*

#### Non-syndromic mental retardation

Achieving a molecular diagnosis in patients with non-syndromic MR is successful in only a minority of cases. Regarding molecular evaluation of these patients, the most important question is how many genes (autosomal and X-linked) are involved in non-syndromic MR, and which diagnostic techniques should be applied. In contrast to patients with syndromic MR, even a thorough clinical examination of patients with non-syndromic MR is not helpful in establishing an underlying molecular defect. In all MR patients, even without dysmorphic features, initial diagnostic evaluation should include conventional karyotyping and exclusion of fragile X syndrome [35]. An additional step in searching for molecular defects might include detection of genomic copy number alterations by high resolution whole-genome CGH array. CGH array would ideally be combined with sequencing of the MR-causing genes. However, most of these tests are currently not available in Israel as a clinical service. Following identification of additional genes causing non-syndromic MR, high throughput features of resequencing microarrays should enable efficient identification of molecular defects in the known genes in affected individuals using a single microarray platform. Resequencing microarrays have recently been designed for various diseases showing high genetic heterogeneity [36].

## Diagnostic workup in a single male patient with MR

#### Clinical evaluation

The diagnostic workup of a single male patient with MR should begin with a thorough clinical evaluation. A *family pedigree* should be constructed in order to establish the possible mode of inheritance, which, if there are no other cases of MR in the family,

could be compatible with various inheritance patterns such as XLMR, autosomal recessive or autosomal dominant, polygenic, submicroscopic aberrations or mitochondrial inheritance.

A*namnesis* should be inclusive of information regarding the onset of the condition, whether or not the disease is progressive, the presence of any neurological abnormalities, whether the patient has seizures, and the presence of any other relevant features. P*hysical examination* should include measurements of height, weight and head circumference and dysmorphological and neurological examination. If the head circumference is abnormal, the parents' head circumferences should be measured. Vision and hearing should be assessed.

#### Laboratory examinations

M*etabolic testing* is no longer considered part of the routine obligatory diagnostic evaluation in individuals with MR [35]. However, specific metabolic or endocrine clues, such as abnormally high free T3 levels in *SLC16A2* gene mutations and abnormal urine and plasma creatine/creatinine levels in *SLC6A8* mutations, might be of help in the ascertainment of a specific diagnosis and should be considered according to the clinical features (for example, the presence of hypotonia or seizures in patients with *SLC6A8* mutations). In addition, even mild neurological abnormalities should prompt *neuroimaging* in mentally retarded patients, since this can aid in establishing the diagnosis in specific MR syndromes such as those caused by mutations in *OPHN1* and *ARX*.

#### Genetic examinations

Since chromosomal abnormalities comprise the most frequent cause of genetic MR, *karyotyping* should be the first step in the genetic evaluation of individuals with MR of any severity. This should be followed by molecular testing for *fragile* X *syndrome*. Additional steps in searching for molecular defects might include analysis of pathogenic genomic copy number aberrations by whole-genome or X chromosome *CGH array* according to the suspected pattern of inheritance [37].

In addition, in families with no clear X-linked inheritance (no affected males in two consecutive generations), X *inactivation studies* might be considered. X inactivation in females carrying XLMR-causing genes has been shown to be non-random for at least some of the genes [38]. X inactivation studies can aid in the clarification of the mode of inheritance and investigation of carrier status in other females in XLMR families; this is applicable only in cases where obligate female carriers show non-random X inactivation.

Resequencing of the known X-linked and autosomal MR-causing genes should ideally follow; a resequencing microarray for XLMR genes is currently available on a research basis only. Molecular diagnosis by resequencing the currently known XLMR-causing genes in the male proband can be achieved in 42% of the XLMR families [19].

T3 = triiodothyronine

#### Genetic counseling

In a family with a single mentally retarded male, the recurrence risk is low, since only about 10% of males with MR are thought to carry a mutated X-linked gene [19]. Therefore the empiric recurrence risk for MR in an additional male in such a family is about 5%. If X inactivation in the mother of a mentally retarded male is non-random, there is a higher probability of XLMR and hence the recurrence risk is higher – up to 50% in males. It is possible to offer prenatal diagnosis to at-risk family members only after identification of a specific MR-causing molecular defect in the affected individual. Once a cytogenetic or molecular diagnosis has been established, prenatal diagnosis can be performed using a specific diagnostic test on chorionic villus sampling or amniocentesis. Pre-implantation genetic diagnosis is based on in vitro fertilization and examination of the embryos for disease status. Only unaffected embryos are implanted in the uterus, thus eliminating the need to terminate a pregnancy.

If the molecular defect in the male proband still remains unknown, fetal sexing can be carried out in order to prevent births of affected males; however, this approach should be undertaken only after giving appropriate genetic counseling to the at-risk couples.

Additional possibilities for a couple with MR in the family include adoption and donation of sperm or ovum, depending on the mode of inheritance (donation of ovum in case of XLMR or mitochondrial inheritance; donation of ovum or sperm in case of autosomal recessive inheritance). These options should be discussed during the genetic counseling session.

#### Prevention of non-syndromic MR in the general population

At the population level, a large-scale program for the prevention of non-syndromic MR based on carrier screening was initiated and successfully implemented in an isolated population with a high carrier frequency [39], but this approach is applicable only rarely and in very specific situations when a founder mutation is responsible for a large proportion of the MR cases in a specific community. For most of the MR-causing genes, population-based screening is not recommended due to the low carrier frequency. Recently there have been some attempts to introduce a population-based fragile X carrier screening program, and in Israel this is offered as a private service [40].

In summary, the identification of new genes causing MR, together with the development of new high throughput technologies, will hopefully provide families with an accurate molecular diagnosis, genetic counseling that is based on a more accurate assessment of the recurrence risk, and the possibility of prenatal testing.

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