Mental retardation (MR) is among the more significant public health problems because of its prevalence (ca. 2%), the few therapeutic options that are currently available, and the resulting life-long harm to the affected persons, their families, and society as a whole (1). Persons with an intelligence quotient (IQ) below 70 are considered mentally retarded; milder forms of mental retardation, with IQ between 50 and 70 (overall prevalence ca. 1.5%), are more common than moderate and severe forms with IQ below 50 (prevalence 0.4%). Mental retardation is characterized by impaired cognitive, linguistic, and social abilities. It is sometimes already manifest in infancy (with muscular hypotonia, poor visual contact, and diminished motor activity) or early childhood, e.g., with abnormal play and delayed attainment of developmental milestones.

Mental retardation can be caused by genetic or non-genetic factors: for example, infection or intoxication during pregnancy, complications of delivery, or postnatal infection or trauma (table 1). Genetic causes are present in more than 50% of severely mentally retarded MR cases. The elucidation of gene defects in MR improves the diagnosis and management of patients and facilitates genetic counselling of their parents. In the long run, this research will also have therapeutic implications.

### Summary

**Introduction**: Mental retardation (MR) has a prevalence of about 2% and constitutes one of the major unsolved medical problems. MR arises from genetic defects in more than 50% of patients. Methods: Selected literature review. Results: Chromosomal aberrations are a major cause of MR. New molecular genetic and molecular cytogenetic techniques allow even submicroscopic chromosomal aberrations to be detected. The gene defects underlying many syndromic forms of MR have been elucidated in recent years, whereas insight into non-specific (non-syndromic) MR is restricted almost exclusively to the X-chromosome. The Fragile X syndrome is the most frequent monogenic cause of MR in males. A more broadly based search for autosomal gene defects in non-syndromic MR has recently begun. Discussion: The elucidation of gene defects in MR improves the diagnosis and management of patients and facilitates genetic counselling of their parents. In the long run, this research will also have therapeutic implications.

**Key words**: mental retardation, chromosomal aberration, submicroscopic chromosome aberrations, monogenic disorders, X-linked mental retardation

### Table

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Modified from Curry et al. 1997.
persons (2). Most mild forms of MR, however, represent the tail end of the normal distribution of intelligence in the population at large and are due to a complex interaction of genetic predispositions and environmental factors.

For many persons with MR, it is unclear whether a genetic cause or an unknown, exogenous cause is present. This is, however, a question of major importance to parents, if they wish to have more children, as well as to other members of the family: the etiology of MR determines the risk of MR in any subsequently born children, as well as the measures that can be taken to prevent it, if any.

In this article, the authors provide an overview of the known genetic defects and diagnostic possibilities, as well as prospects for further developments in the field. Emphasis is placed on the common non-syndromic types of MR, i.e., those that cannot be classified among the known MR syndromes because of the absence of any accompanying deformities or abnormalities. Syndromic and non-syndromic types of MR are not always clearly distinguishable, and some syndromes can only be diagnosed from a certain age onward (e.g., fragile X syndrome).

Chromosomal aberrations
Some 15% of all mentally retarded persons harbor chromosomal aberrations that can be detected under the light microscope (3). The majority of cases involve trisomy 21 (karyotype 47,XX,+21 or 47,XY,+21; prevalence 1 : 700 to 1 : 1 000), which is clinically expressed as Down syndrome (4). Other chromosomal aberrations are much rarer and are usually associated with further clinical manifestations; among these, for example, are deletions (loss of chromosomal material) in chromosome 5 (cri du chat syndrome) and chromosome 4 (Wolf-Hirschhorn syndrome). With the exception of sex chromosome abnormalities, nearly all unbalanced chromosomal aberrations that can be seen under the light microscope cause mental impairment. Because chromosomal aberrations are so common, all patients with mental retardation of unknown cause should undergo chromosomal analysis.

Submicroscopic chromosomal aberrations
Chromosomal aberrations that are too small to be seen under the light microscope (i.e., smaller than ca. 5 megabases [Mb]) are a further important cause of mental retardation.

Example of a submicroscopic 2.7 Mb deletion on chromosome 14 detected by array CGH (with the kind permission of R. Ullmann). The ca. 32,000 DNA fragments used for hybridization are represented as single points. Deleted BACs are illustrated to the left of the midline.

(Diagram 1)
Microdeletions can be detected with molecular cytogenetic techniques, such as fluorescent in situ hybridization (FISH). FISH is performed when there is concrete clinical suspicion of a particular microdeletion syndrome, e.g., Williams-Beuren syndrome (deletions in 7q11), 22q11 deletion syndrome, 1p36 deletion syndrome, or Smith-Magenis syndrome (deletions in 17p11) (5).

Often, in mentally retarded persons with additional deformities or signs of dysmorphism that cannot be clearly assigned to any known syndrome, a search will also be made for deletions located immediately before the ends of chromosomes (telomeres). Subtelomeric screening reveals abnormalities in 2% to 3% of patients studied (7).

Array CGH (comparative genomic hybridization) is a new technique enabling detection of very small, unbalanced chromosomal aberrations anywhere in the genome (8, 9). It employs arrays of cloned DNA fragments which together incorporate the entire human genome, with a resolution of ca. 100 kilobases (kb) at present. This is a major improvement over conventional chromosomal analysis or CGH (maximal resolution 2 to 3 Mb). An example of a submicroscopic deletion is depicted in diagram 1.

Initial studies have shown that high-resolution CGH can reveal causative chromosomal changes in ca. 7% of patients with non-specific MR and in about 15% to 20% of patients with additional clinical abnormalities (10) (Ullmann, Kirchoff, et al, Max Planck Institute for Molecular Genetics, Berlin: unpublished data). This method enables the detection of almost twice as many unbalanced aberrations as conventional chromosomal analysis. Thus, the demonstration or exclusion of submicroscopic changes ought to be just as important a part of standard diagnostic testing in idiopathic mental retardation as conventional chromosomal analysis. At present, there are only a few laboratories in the world that can perform array CGH testing at the 100 kb resolution level. Soon, however, commercial variants of this technique (oligonucleotide array CGH, single nucleotide polymorphism chips) are likely to be introduced that will reduce the cost to less than 500 euros per analysis. A remaining impediment to the routine diagnostic use of array CGH is the difficulty of distinguishing functionally relevant changes from neutral variations or polymorphisms. The variability of the human genome at the submicroscopic level is unexpectedly high, and the pathological relevance of many of the changes that are seen will only become clear once many patients and many normal controls have been studied.
Balanced chromosomal rearrangements

Not only unbalanced chromosomal aberrations, in which genetic material is lost or added, but also balanced chromosomal rearrangements can lead to mental retardation if they cause genes to be interrupted or less than fully expressed. There are two types of balanced rearrangement, translocation (an exchange of genetic material between different chromosomes) and inversion (a rearrangement within a chromosome). About 6% of all newly arising rearrangements are associated with disease; in half of these cases, the disease is thought to be due to the interruption of a gene (11). The molecular characterization of changes of this type furnishes information about the function of the gene or genes involved and is thus an important way of improving our understanding of the mechanisms leading to mental retardation in humans (diagram 2) (12–14).

X-chromosomal mental retardation

The prevalence of mental retardation is significantly higher in boys than in girls, with a sex ratio of 1.4 : 1 for severe MR and 1.9 : 1 for mild MR (16). The higher prevalence in boys is partly due to X-chromosomal genetic defects, which, according to current estimates, are the cause of mental retardation in about 10% of affected boys (17).

Fragile X syndrome is the most common X-chromosomal type of MR. Patients with this syndrome have a large head circumference, big ears, a prominent chin, and enlarged testicles. The manifestations of the syndrome are variable, however, and do not reach their full extent till puberty. Fragile X syndrome should, therefore, be included in the differential

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**Diagram 3**

Localization of the XLMR genes on the X chromosome. Left side: genes in which mutations lead to syndromic types of XLMR. Right side: genes in which mutations have been found in patients with non-syndromic types of XLMR.
diagnosis of all boys with mental retardation, particularly those with a positive family history. Girls, too, can suffer from fragile X syndrome, though the characteristic features of the syndrome are less commonly observed in girls. The underlying genetic defect (a trinucleotide repeat expansion of the FMR1 gene) has been known since 1991 and can be detected with a simple molecular genetic test (18).

Fragile X syndrome is found in approximately 25% of all families suffering from familial mental retardation with a clearly X-chromosomal inheritance pattern. Recent years have seen the identification of the genetic defects underlying many types of X-chromosomal retardation, both syndromic (e.g., Coffin-Lowry syndrome, ATRX syndrome) and non-syndromic (diagram 3) (19). Many clinically distinguishable syndromic types of X-linked mental retardation (XLMR) are due to a defect in a single gene. Non-syndromic types, in contrast, can be due to defects in many different genes, of which more than 20 are currently known. In practice, however, it is unlikely that a defect will be found in any of these genes, even in patients with familial mental retardation. Therefore, routine diagnostic testing for the exclusion of specific genetic defects can hardly be justified, in view of the high cost of the tests currently in use. Soon, however, newer and cheaper diagnostic techniques will be available. Alternative techniques of (re-)sequencing are now being developed that ought to enable mutation screening at considerably lesser expense. The European Mental Retardation Consortium (EUROMRX; www.euromrx.com) has set itself the goal of detecting at least 90% of all genetic defects causing XLMR by the systematic identification and study of families with X-chromosomal MR. At present, more than 500 families have been studied. The genes that are known to date are collectively responsible for about 50% of all cases of non-syndromic XLMR.

**Autosomal recessive genetic defects**

Metabolic defects are the best studied cause of mental retardation of autosomal recessive inheritance. Phenylketonuria (PKU) is the most common inborn error of metabolism in Germany, with an incidence of 1 in 10,000 births. In PKU, there is impaired degradation of the amino acid phenylalanine, and, if the disorder remains untreated, the accumulation of toxic metabolites impairs brain development. Nearly all PKU patients in Germany are identified in the first few days of life by neonatal screening, and strict adherence to a low-phenylalanine diet enables them to undergo normal mental development. PKU is thus one of the few monogenic diseases that can be successfully treated (20).

There are also many other autosomal recessive MR syndromes (including Bardet-Biedl syndrome and Cohen syndrome) whose underlying genetic defects have been identified in recent years. These defects cause abnormalities in multiple organs (21, 22). To date, however, only a few of the genes responsible for the common non-syndromic (non-specific)
types of mental retardation are known. An investigation of more than 100 consanguineous (inbred) Iranian families with MR revealed a marked degree of genetic heterogeneity (diagram 4) (23, 24). Just as is the case for X-chromosomal defects, testing for individual gene defects will be possible as a part of routine diagnostic evaluation only when cheaper methods of mutation screening become available.

**Autosomal dominant mental retardation**

The genetic defects that have so far been found to cause mental retardation of autosomal dominant inheritance are almost exclusively connected to syndromic types of MR. Non-specific autosomal dominant MR is more difficult to study, because the affected persons usually do not procreate, and thus no large family trees are available for linkage studies. Most of these mutations presumably arise de novo. Nearly all of the genes that have been found to date have been identified through the analysis of balanced chromosomal aberrations or of very small chromosomal deletions.

**Genetic diagnosis of MR patients**

Once any evident non-genetic causes have been ruled out, patients with mental retardation should be referred to a physician specializing in human genetics or to a pediatrician specializing in medical genetics. The specialist will first perform a clinical genetic examination enabling diagnosis of the known syndromic types of MR, if one of these is present. If the clinical evidence points to a particular syndrome, directed cytogenetic, molecular genetic, or biochemical testing may follow, to the extent that such tests are available.

Many patients, however, display no additional dysmorphisms or other abnormalities, or else these abnormalities are so non-specific that they cannot be connected to any particular known syndrome. Families in Germany tend to be small; thus, mental retardation usually arises sporadically, and family trees only rarely provide evidence of a particular inheritance pattern.

All patients with non-syndromic (non-specific) mental retardation should undergo chromosomal analysis. It is reasonable to test boys for fragile X syndrome even if they do not (yet) display any of the typical clinical features. In families that can be identified as suffering from X-chromosomal mental retardation (at least two affected males, with inheritance through a healthy mother), testing for the detection or exclusion of all known X-chromosomal genetic defects can be considered; for financial reasons, this may best be done in the setting of the international research projects that are currently in progress (the authors can provide further information on request). Even when all of the available diagnostic techniques are applied, a cause can now be clearly identified in only about 50% of patients with severe MR; in those with mild MR, the percentage is even lower (2). Although no causal therapy is yet available for most types of genetically determined MR, the effort to make a diagnosis is justifiable, even aside from the question of family counseling with regard to prognosis, risk of recurrence in future children, etc. The identification of a genetic defect helps parents accept the illness and actively contend with it, e.g., by participating in self-help groups.

**Genetic counseling and the risk of recurrence**

The parents of a mentally retarded child often ask about the risk of recurrence in future children. If the patient is suffering from an identifiable syndrome, the risk of recurrence can usually be stated fairly precisely. If a genetic defect has been found, the opportunity for prenatal diagnosis exists. For children with non-syndromic MR as well, the demonstration of a genetic defect allows a precise statement of the risk of recurrence and enables prenatal genetic testing. In most cases, however, no genetic defect can be found. If there is no positive family history, then the risk of mental retardation in each future child is ca. 8%, as long as the ill child has a non-specific type of mental retardation (25, e1). This risk is elevated in relation to the baseline risk level of 2% and often leads parents to choose not to have any more children. A more precise estimation of the risk will be possible only after more MR genes have been characterized and more comprehensive tests have been developed to diagnose or exclude defects within them.

**Summary and prospects**

The diagnostic possibilities for genetically determined mental retardation have considerably expanded in recent years because of the introduction of new techniques for chromosomal
analysis with higher resolution and the identification of the genetic defects underlying many monogenic diseases. Nonetheless, the etiology of genetically determined MR can still only be found in about half of all patients. The greatest problem lies in the area of non-syndromic mental retardation, which, though very common, has not been very intensively investigated to date. Many different genetic abnormalities can cause non-syndromic MR. The study of individual MR-related genes is hindered by the rarity of large enough kindreds for linkage analysis and by the fact that chromosomal aberrations are either rare (e.g., translocations) or rarely diagnosed (e.g., microdeletions). It is, therefore, all the more important that patients and families who are suitable for study should be referred to specialized research centers. This is the decisive step that must be taken if new MR genes are to be identified.

Studying the molecular causes of MR will be important, in future, not only for the purposes of genetic counseling and diagnosis; the knowledge gained can be expected to further our understanding of the central nervous system. Successful experimental drug trials in animal models of MR give hope that long-term, effective treatment will one day be possible for human beings as well. In a Drosophila model of fragile X syndrome, treatment with antagonists of metabotropic glutamate receptors led to correction of structural neuronal changes as well as of pathological behavior patterns (e2). Behavioral studies have shown that a stimulating environment has a beneficial effect on cognitive ability in murine models of Down syndrome and fragile X syndrome (e3). These observations imply that mentally retarded children stand to benefit from intensive special education that is provided to them as early as possible; this, in turn, underscores the importance of early diagnosis.

Conflict of Interest Statement
The authors state that they have no conflict of interest as defined by the Guidelines of the International Committee of Medical Journal Editors.

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REFERENCES
For e-references please refer to the additional references listed below.

ADDITIONAL REFERENCES


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