THE GENETIC OF MENTAL RETARDATION

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Abstract

Mental retardation is a common problem with major implications for a nation's health, education and community services. The causes of mental retardation have been found to have a definite etiological basis, which may be biochemical, chromosomal, Mendelian genetic disorders, or due to environmental effects such as toxins, infections, trauma or perinatal anoxia. The underlying causes remain unknown in a significant percentage of cases, but genetic causes account for 25-50% of such cases.

Chromosome aberration is a genetic abnormality which is usually a de novo or a spontaneous mutation. Recurrence risk is very low and not inherited if parent is not balanced carrier. Chromosomal disorders can be detected using light microscope, but cryptic chromosomal aberration less than 4 Mb cannot be seen. Fluorescence In Situ Hybridization (FISH) techniques using fluorescence labeled DNA sequence can be used for identifying a small abnormality in chromosomal DNA.

Biochemical disorders and other Mendelian inheritance are inherited from generation to generation depending on their recessive or dominant type. Their mutation can only be detected by molecular analysis such as DNA amplification using Polymerase Chain Reaction (PCR). These disorders carry high risk of recurrence. Individuals with dysmorphic features and a family history of mental retardation without chromosomal abnormalities are possibly due to cryptic/submicroscopic chromosomal aberration as well as Mendelian disorders.

Introduction

Mental retardation is a clinically and etiologically heterogeneous group of conditions, whose pathogenesis is poorly understood. In the past, mental retardation (MR) was classified according to the severity of cognitive impairment (on the basis of IQ test score) as mild (50-70), moderate (35-50), severe (20-35) and profound (<20) MR (Beirne-Smith et al 1994)

In 1992 the AAMR (American Association on Mental Retardation) replaced this categorization by one that is more functional in nature. The emphasis shifted to a person's capability, taking into account the environments in which the person functions and need for varying levels of support (Luckasson et al, 1992). In this definition MR refers to substantial limitations in present functioning i.e. a fundamental difficulty in learning and the performance of certain daily life skills. It is characterized by significantly sub-average intellectual functioning (IQ<70-75) which exists concurrently with related limitations in two or more of the following applicable adaptive skill areas: communication, self care, home living, social skills, community use, self direction, health and safety, academic progress, leisure and work.

Approximately 3% of the populations have an intelligence quotient (IQ) of less than 70, among whom a cause for the mental retardation can be established in less than half of all cases (Harper et al, 2002; Flint et al, 1995).

Some of the disorders have been found to have a definite etiological basis, which may be biochemical, chromosomal, Mendelian genetic disorders, or due to environmental effects such as toxins, infections, trauma or perinatal anoxia, but in a significant percentage of cases the underlying cause remains unknown. A number of studies of mild mental retardation have shown high rates of chromosomal abnormalities (Curry et al, 1997). This raises the possibility that at least a proportion of individuals who appear to have idiopathic mental retardation will be accounted for by previously undetected chromosomal aberrations, single gene defects as well as by other specific causative agents or by combinations of the above.

Chromosome disorders and Mental retardation

It is particularly important to recognize chromosomal disorders among the non-Mendelian genetic causes of mental retardation. Mental retardation associated with congenital malformations, developmental delay and abnormal dermatoglyphics are characteristic findings with chromosomal aberrations (Scriver et al, 1995). The most common chromosomal cause of mental retardation is trisomy 21 syndrome (= Down syndrome), followed by trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome**).** The frequency of Down's syndrome with typical clinical features was 12.3% of the population in Semarang Special Schools and 11% of the population in rural area special schools in Central Java which was lower when compared with other previous studies 15% in most Caucasian studies (Faradz et al 1996 , Rimoin et al 2002). MR can be caused by sex chromosome abnormalities, as also mentioned that the more X chromosome is the more mentally retarded (Miller et al 2001).

Almost all chromosomally unbalanced autosomal disorders are associated with mental retardation (Harper, 2002). Routine cytogenetic analysis (400-500 band level) has shown that chromosomal anomalies constitute 40% of severe (IQ<55) and 10-20% of mild mental retardation (IQ 55-70) (Flint et al, 1995). Curry et al (1997) claimed 4-28% of individuals with mental retardation had chromosomal abnormalities the frequency of which increased with the severity of mental retardation and the presence of congenital anomalies.

Chromosomal subtelomeric rearrangements involving less than 4 megabases (Mb) of chromatin (such as William, Angelman and Di George syndrome) are cytogenetically undetectable even at the highest resolution but could account for a substantial number of apparently idiopathic cases (Flint et al, 1995, Rimoin et al 2002). Individuals with dysmorphic features and a family history of MR without chromosomal abnormalities are possibly due to cryptic chromosomal translocations resulting in submicroscopic subtelomeric deletions or duplications (Ledbetter, 1992). Approximately 6% of unexplained mental retardation may be accounted for by these relatively small chromosomal abnormalities (Flint et al, 1995).

Molecular analysis and molecular cytogenetics: fluorescent in-situ hybridization (FISH) is beginning to identify small, cytogenetically invisible deletions in some cases. Telomere specific DNA FISH probes can be used to detect subtle deletion and

translocation events. Since the majority of subtelomeric repeats are shared by several chromosomes, unique sequence clones flanking the subtelomeric repeats are employed for FISH probes (Ledbetter, 1992). Multiplex ligation dependent probe amplification (MLPA) has been used recently in the Netherlands to screen patients with unexplained mental retardation for subtelomeric rearrangements (Koolen et al, 2004). This technique is fast and inexpensive to screen some common genetic diseases such as trisomy 21, 13, 18 and sex chromosome abnormalities (Klinefelter syndrome).

X-linked mental retardation (XLMR) and non specific XLMR (MRX)

Lehrke (1972) was the first to suggest that there may be genes coding for intellectual function located on the X chromosome after finding an excess of males with mental retardation. It is believed that XLMR is responsible for the documented excess of males in the mentally retarded population rather than Y linked genes. About 40% of XLMR and 4% of all mental retardation has been attributed to Fragile X syndrome (Vogel and Motulsky, 1997). Fragile X syndrome was included in XLMR recessive disorders.

In the XLMR Genes Update of 1996 (Lubs et al) classified XLMR according to the genetic origin of the group of disorders into 3 main categories: (1). X-linked recessive and partly dominant disorders (including syndromes, neuromuscular disorders and metabolic disorders), (2). Dominant lethal disorders and (3) non specific XLMR. The 1996 XLMR listing shows 105 XLMR disorders, 34 of which have been mapped and 19 (including one MRX FRAXE) that have been cloned (Lub et al, 1996). This list is increased every year and updated every 2 years in XLMR international workshop.

In the XLMR Genes Update of 2005 (Stevenson et al) reported that 11 new additional genes for XLMR and 20 candidate genes for MRX (MRX63-84) has been identified and 28 genes have already been cloned.

Non-specific mental retardation (MRX) is conditions where mental retardation appears to be the only significant clinical finding, without any clear underlying causative factor or associated clinical features that suggest a syndromic diagnosis, the absence of abnormalities on standard diagnostic laboratory tests and no relevant pedigree information (Harper, 2002; Neri et al, 1994). MRX is a very common disorder, clinically homogenous but genetically heterogeneous which affects ~1 in 600 males (Herbst and Miller, 1980).

MRX is most appropriately approached by molecular analysis. This disorder can only be diagnosed if there are multiple cases in a family. This stresses the importance of taking adequate family histories. The diagnosis depends further on a thorough standardized clinical examination of affected patients. Molecular diagnosis as a final proof has to be done using linkage analysis. Studying patients with XLMR and structural X chromosomal abnormalities is important way to localize and clone genes. Mapping studies (linkage of the MRX gene to the X chromosome in each family) have led to a systematic nomenclature for MRX based on regional localization between markers detecting the closest flanking recombinants (Gedeon et al, 1996). Lubs et al (1996) indicated 42 known regional localization's for MRX families (including FRAXE) which can be grouped in 8-12 non overlapping loci, suggesting the involvement at least of 8 X-linked genes in MRX. Stevensen et al (2005) reported 55 MRX families which have been mapped.

The Fragile-X (FRAXA) and FRAXE Syndrome

Fragile-X mental retardation (FRAXA) is an X-linked recessive disorder with unusual pattern. Fragile X syndrome cannot unequivocally be assigned to either dominant or recessive categories because carrier females may or may not be mentally retarded and may or may not reveal the fragile site after cytogenetic lymphocyte culture. The non MR carrier females are presumably protected from the effect of the full mutation by the other normal X chromosome (female has two X chromosomes), which is likely to be the result of random X-inactivation pattern.

A typical affected male is mentally retarded but heterozygous females also have a 30-35% chance of being retarded. Surprisingly, whereas other X-linked disorders are virtually always expressed in the hemizygote and unaffected males never transmit the disease to descendants of either sex, there are some Fragile X males who are obligatory carriers of the Fragile X mutation by virtue of their position in the pedigree but who are not retarded and who do not express the fragile site on cytogenetic analysis. A normal transmitting male (NTM) passes the gene to all his daughters, who are usually intellectually normal themselves but have the expected proportion of retarded sons.

Fragile-X is the most common cause of heritable mental retardation which has prevalence in Caucasians populations of 1:2,000 (1:1,500 in males and 1:2,500 in females). The introduction of specific molecular genetic testing for Fragile X syndrome has lead to a downward revision of the prevalence of this diagnosis in the Australian population from 0.08% (1:1,250) to 0.025% (1:4,000) in predominantly Caucasian males with intellectual disability as the result of improved discrimination between fragile sites molecularly and prenatal diagnosis (Turner et al, 1996).

Our first screening in MR children has shown that the frequency of fragile X syndrome in Indonesia to be 2% in Central Java (Faradz, et al 1999), which is comparable to Caucasian data. In the same study, 53% of the male and female Fragile X patients in an institution of isolated village in central Java could be retraced to one ancestor (Faradz et al, 2002). In unselected male population of 10 ethnic groups in Indonesia carriership rates has shown to be 0.3% (Faradz et al, 2001).

The phenotype is currently viewed as including; mild to moderate mental retardation, coarsening of facial features, long and narrow face, macroorchidism, large and prominent ears, prominent jaw, high forehead, high pitched and jocular speech. (Hagerman,2002). Cytogenetically the fragile-X syndrome is characterized by the presence of a break (fragile site) at the end of long arm of the X chromosome after culturing peripheral blood lymphocytes in a folate-deficient medium. The molecular basis of the diseases is an expanded trinucleotide repeat in the 5' untranslated region of the *FMR-1* gene (Fragile X Mental Retardation -1 gene). The length of the trinucleotide repeat is polymorphic in the population. Normal individuals have fewer than 50 copies of the trinucleotide repeat (CGG)n. Carriers of premutation alleles have between 52 and 230 (CGG)n repeats and affected people have greater than 230 repeats up to-2,000(CGG)n. When the trinucleotide repeat expands beyond 230 copies the repeat array becomes methylated, which results in transcriptional silencing of the *FMR-1* gene. It is assumed that FMR-1 protein is essential for the normal development of central nervous system and

the loss (or reduction) in *FMR-1* transcription is the critical event leading to mental retardation in people with fragile-X syndrome. Mental retardation is present in all males with more than 230 copies of the trinucleotide repeats, but only in 30% of females with such a repeat length are affected.

The Fragile XE syndrome (FRAXE) was described by Sutherland and Baker (1992) as a form of X-linked mental retardation associated with a fragile site on the X chromosome 600 kb telomeric to *FMR1*. Fragile XE syndrome is caused by an expansion of a GCC repeat. The clinical features of this syndrome are debated but include mild mental retardation or developmental delay without evidence of dysmorphic features (Hamel et el., 1994). Most studies of developmentally delayed populations have found a low prevalence of FRAXE, in the range of 1-2/100,000 live births (Holden et al., 1996; Murray et al., 1997). Trinucleotide repeat expansion is a cardinal feature of both Fragile XE and Fragile XA syndromes. In contrast to Fragile XA, where repeat instability occurs predominantly by transmission through the female line, instability of the FRAXE repeat is observed in transmissions through both males and females (Hamel et al., 1994). Murray et al. (1997) have categorized FRAXE allele sizes as follows: "common" alleles, with 11-30 GGC repeats; intermediate alleles, with 31-60 GCC repeats; premutation alleles, with 61-200 repeats; and full mutation alleles with >200 repeats and methylation of the repeat.

Summary and Future Directions

Cytogenetic diagnosis is still useful and affordable for the diagnosis of mental retardation in developing countries. However cytoggenetic analysis cannot always detect genetic diseases, MR caused by Mendelian inheritance cannot be seen by microscopic examination. So that sensitive molecular diagnosis is a useful tool for detecting some genetic diseases and is important for determining the risk of having children with genetic diseases. Therefore the establishment of molecular diagnostic detection is a high priority. This will be a significant challenge for a developing country such as Indonesia, where the cost of genetic testing is still relatively expensive in comparison to the average wage of the population.

There are many genes in X chromosome that cause mental retardation; it seems that X chromosome is important chromosome for developing IQ. As we know all of our X chromosome comes from our mother or grand mother, therefore we should appreciate and thanks to our mothers for giving us intelligence. Many more candidate genes will become available in the near future. The mutational and functional testing of these genes in patients and families will be facilitated by the availability of new techniques. Multidisciplinary and international cooperation are needed to elucidate the molecular and cell biological basis of mental retardation. Eventually, this will enhance understanding of the physiology of central nervous system formation and function, improve pre and post natal diagnostic possibilities and lead to the development of novel therapeutic strategies.

The molecular era for diagnosis of genetic diseases in Indonesia has in fact just begun. The molecular laboratory diagnosis of mental retardation in Indonesia will become possible in major centers in Indonesia over the next few years. However, prenatal diagnosis is still controversial, and there is an on-going debate as to whether

pregnancy termination is acceptable to any of the major religions in Indonesia. There is a legal dilemma as to the practice of pregnancy termination after prenatal diagnosis. Unless this legal issue is resolved, prenatal diagnosis for genetic diseases will be hindered, as there is little point in undertaking prenatal diagnosis if one of the major therapeutic options is not available. In spite of this prenatal genetic diagnosis (preconception genetic diagnosis) and gene therapy are progressing in the developed country. In the absence of legal terminations, prenatal diagnostic information will have a limited role in preparing parents for the birth of a child with a genetic disorder whilst enabling earlier interventions. The competence of professional genetic counsellors will also have to be addressed if diagnostic services are provided. The availability of experienced genetic counsellors in Indonesia is therefore essential to assist the clinicians

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