

Genetics of Learning Disability

Definition of mental retardation

The definition of Mental Retardation (MR) requires there to be significant subaverage general intellectual functioning (Criterion A) that is accompanied by limitations in adaptive functioning in at least 2 of the following skill areas: communication, self care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health and safety (Criterion B). The onset must occur before age 18 years (Criterion C). General intellectual functioning is defined by the intelligence quotient, IQ. Adaptive functioning refers to how effectively individuals cope with common life demands. These are less objective measures and rely on information gathered from independent sources e.g. teacher evaluation and educational, developmental and medical history, nevertheless these assessments are extremely useful. In the UK, the ICD-10 Classification of Mental and Behavioural Disorders, WHO, Geneva 1992 is used whilst in the USA the DSM-IV diagnostic classification is used which is broadly similar to the WHO classification^{1,2}.

IQ across the population is normally distributed and is set at 100 and an IQ <70 is classified as intellectual impairment or mental retardation. In approximately 0.5-1% of the population mental retardation is severe, defined as an IQ<50, and in 2-3 % of the population the mental retardation is mild to moderate (IQ 50-70) which defines them as having special needs.

Etiology of mental retardation

In many cases (40%) the underlying aetiology remains unknown but with improved technology and understanding this figure is gradually reducing. Both environmental and genetic causes lead to MR and frequently coexist in an individual. *Environmental* exposure divides into pre-, peri- and postnatal exposure. The longterm consequences of extreme prematurity and the associated medical complications accounts for an increasingly significant proportion of children with mental retardation whereas the proportion of children suffering from post natal infections is diminishing. Perinatal injury due to birth problems remains common as does prenatal exposure to teratogens during pregnancy. These include fetal exposure to sodium valproate, anticoagulants, alcohol and high levels of blood glucose in diabetic mothers. A small proportion of children also suffer from accidents or

infections beyond the postnatal period that results in mental retardation.

The *genetic* contribution to severe MR is high as empiric recurrence risks for siblings of severely affected individuals are 5-8% if a single case is observed and 12-15% if 2 siblings are affected³. This includes both chromosomal abnormalities and single gene defects. The relative excess of males in the population with severe mental retardation (1.3-1.7:1) suggests that X-linked disease genes are a significant contribution to the overall genetic aetiology⁴. Recent studies using modern cytogenetic techniques, to exclude chromosome abnormalities, suggest that where 2 male siblings are severely retarded, in the absence of a chromosome abnormality, the likelihood of this being due to an X-linked gene abnormality is as high as 80%⁵.

Investigation of the patient with mental retardation

The assessment of an individual with mental retardation relies heavily on a good clinical history and examination. A detailed 3 generation pedigree may reveal histories of fetal loss, miscarriage or a history of medical problems in other family members which may provide clues to the underlying aetiology. Details of maternal health, pregnancy history and birth history noting birth weight, height and head circumference are invaluable. A profile of developmental milestones and education history will help to distinguish the individual with slow development from those with developmental regression associated with neurodegenerative conditions. There have been several consensus papers recently recommending base line investigations for a developmentally delayed child (see table 1)⁶.

Chromosomal abnormalities associated with mental retardation

Routine Karyotype

This is in effect a visual inspection of the whole genome at the resolution of approx 5-10 Mb. This will detect large gain or loss of chromosome material and rearrangements which are almost always of clinical significance. Although the technique is ultimately limited by the resolution of the microscope the quality of the chromosome preparations have gradually improved over the last 10 years and re-evaluation of a patient's chromosomes where a chromosome abnormality is suspected is well worthwhile.



Lucy Raymond is a university lecturer and honorary consultant in medical genetics, University of Cambridge. She has a special interest in the genetics of learning disability and has established an international collaborative study (GOLD study) that aims to identify abnormalities in novel genes that cause mental retardation.

Table 1
Investigation of a child with developmental delay based on Shevell *et al* 2003

Investigation of the child with developmental delay
<ul style="list-style-type: none"> ● 3 generation pedigree and details of development of all possibly affected individuals ● Obtain a detailed clinical history of maternal health pre-pregnancy ● Pregnancy history ● Birth history and birth height, weight and head circumference ● Developmental milestones ● Educational history (special schools and IQ) ● Neonatal PKU and hypothyroidism ● Karyotype (550 G banded resolution) ● Fragile X ● Telomere screen ● MRI of brain ● EEG if epilepsy present ● Metabolic screen if clinically indicated

Review Article

Microdeletion syndromes and subtelomeric deletion analysis
There are recurrent small microdeletions of the genome that are associated with characteristic syndromes. Routine chromosome analysis would appear normal as these microdeletions are too small to be detected by G banding and light microscopy and would only be detected using specific genomic DNA fluorescent probes which fail to bind where there is deletion. The common deletion syndromes are Wolf-Hirschhorn, Cri du Chat, Williams, Prader-Willi, Angelman, Rubinstein-Taybi, Miller-Dieker lissencephaly, Smith-Magenis, Alagille, DiGeorge or 22q11 deletion syndrome (see table 2 for the chromosomal location).

In 1995 Flint *et al.* extended this technique to develop a strategy to screen for the abnormal inheritance of subtelomeric DNA polymorphisms in individuals with mental retardation⁷. They found 3/99 patients had an abnormality at the end of one of the chromosomes. Since then the technology has been developed to provide this as a clinical service for suitably selected patients. The range of diagnostic yield is approximately 3.5 to 11%⁸.

Genomic Microarrays

The principle is therefore well established that small deletions or duplications of chromosome material can lead to mental retardation. The recent challenge has been to identify small deletions and duplications in the whole genome in a single or few procedures. The use of multiple probes simultaneously is now possible using probes of known location on the genome 1 Mb apart¹⁴. Recent publications have established that a further 10% of patients with mental retardation carry deletions or duplications^{9,10}. Although this technique is not yet in routine clinical practice it is likely to be soon.

Single gene disorders associated with mental retardation

There are 3 broad phenotypic groups of diseases where mental retardation is a significant feature: progressive neurodegenerative conditions; syndromic mental retardation where the mental retardation accompanies other physical features and non-syndromic mental retardation where the mental impairment is the only significant and constant feature. Research to identify the causes of non-syndromic mental retardation has been predominantly confined to characterising disease causing genes on the X chromosome. This has been due to the relative excess of males in the population with severe mental retardation⁵, the availability of large kindreds with X linked disease and

the relative experimental ease of identifying recessive genes on the X chromosome.

Fragile X syndrome was the first single gene in this category to be identified and since 1991 a further 16 X-linked genes have been associated with a non-syndromic mental retardation phenotype although some of these genes are also associated with a specific syndromic diagnosis: *FMR2*, *PAK3*, *OPHN1*, *GDI*, *IL1RAPL1*, *RSK2*, *ATRX*, *ARHGEF6*, *MECP2*, *TM4SF2*, *SLC6A8*, *FACLA*, *ARX*, *AGTR2*, *PQBPI*, *DLG3*. All the genes identified to date are rare causes of X-linked mental retardation as only a small number of families have ever been found to carry mutations in the same X linked gene and there remains a large number of X linked families where the causative mutation have not yet been identified. To account for the remaining unresolved X linked families, it has been estimated that as many as 75 additional genes on the X chromosome remain to be assigned to a mental retardation phenotype¹¹. The provision of a molecular genetics service for all these rare X linked genes is indeed a challenge and currently relies on research groups with a special interest.

Future work

The identification and characterisation of many more genes responsible for mental retardation over the coming few years is likely with the development of large-scale corroborative research endeavours. This means that for many families more appropriate diagnostic investigations will be available and families will have the possibility of understanding the basis of the disability in their child. This knowledge will also ensure that accurate and appropriate genetic information is available to the family. Over the next 10 years, it is hoped that many of the 40% of children where a diagnosis is not yet achieved will have the benefit of an accurate diagnosis.

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Table 2

Common microdeletion syndromes identified by FISH at specific chromosome locations.

Syndrome	Chromosome location
Wolf-Hirschhorn	4p16.3
Cri du chat	5p15.2-p15.3
Williams	7q11.23
Prader-Willi	15q11-q13(paternal)
Angelman	15q11-q13 (maternal)
Rubinstein-Taybi	16p13.3
Miller-Dieker lissencephaly	17p13.3
Smith-Magenis	17p11.2
Alagille	20q12.1-p11.23
Di George, 22q11 syndrome	22q11.21-q11.23

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Correspondence to:
 Dr. F Lucy Raymond
 Cambridge Institute for Medical Research, University of Cambridge, Cambridge, CB2 2XY
 E-Mail: flr24@cam.ac.uk

GOLD study details see
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