MENTAL RETARDATION: 
A REVIEW OF THE GENETIC CAUSES

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Introduction

Unravelling the genetic causes of mental retardation is one of the greater challenges of molecular genetics for the next decade. Mental retardation, defined as a failure to develop a sufficient cognitive and adaptive level, is one of the most common human disorders. Mental retardation is either the only consistent handicap (called non-syndromic mental retardation) or is combined with other physical and/or behavioural abnormalities (called syndromic mental retardation). According to estimates, 1-3% of the human population (Curry et al., 1997; Roeleveld et al., 1997; Croen et al., 2001) has an IQ below 70 and suffers from learning and adaptive disabilities. It is an unrivalled lifelong burden that has a predominating impact on the life of the patient, his relatives and even on society as a whole.

The causes of the impairment are extremely heterogeneous and although a cause for mental retardation has been diagnosed in only half of the cases, it has been estimated that half of all cases are due to environmental factors and half to genetic factors (FIGURE 1). Environmental factors include prenatal exposure of the foetus to toxic substances (e.g., alcohol, drugs), environmental contaminants, radiation, infection, malnutrition, illness of the mother (e.g. exposure to rubella, cytomegalovirus) etc. In addition, multiple problems during or after birth may cause mental retardation. Although any unusual stress during birth may cause brain damage, especially premature birth and low birth weight may predict mental retardation. During childhood, factors such as disease (e.g. measles), a blow on the head, environmental toxins, etc. may cause irreparable damage to the brain and the nervous system. Genetic factors
FIGURE 1
Overview of causes of mental retardation. The prevalence is adapted from Curry et al., 1997.

TABLE I
Overview of the types of genetic causes of mental retardation

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<th>Chromosomal abnormalities</th>
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include chromosome abnormalities, monogenetic disorders and polygenic factors (TABLE I).

As the impact of mental retardation on life is so dramatic, determination of the cause of the disease is of uttermost importance. Only if the cause of the disease is known, a prognosis of the disease, a risk assessment and, if needed, a prenatal diagnosis is possible. The current paper summarizes the progress achieved in identifying the genetic causes of mental retardation and shortly issues on some diagnostic and therapeutic methods.

**Identified Genetic Causes**

**Chromosomal abnormalities**

Chromosomal abnormalities are responsible for up to 28% of all mental retardation cases (Curry *et al.*, 1997). Chromosomal abnormalities include numerical chromosome abnormalities, partial chromosome abnormalities and microdeletions.

**Numerical chromosome abnormalities**

A numerical chromosome abnormality is caused by additional (=polyplody) or missing (=monosomy) chromosomes from the normal set of 46. Aberrations in the number of chromosomes are easy to detect by counting the chromosomes in spreads obtained from blood cells under a microscope. Reported live-born autosomal chromosome polyploidies are restricted to trisomy 13 (Patau’s syndrome), 18 (Edwards’ syndrome) and 21 (Down syndrome). Though the former two are rare, trisomy 21 (=Down syndrome) is the most frequent cause of mental retardation, affecting on average 1 in 1500 but the risk increases exponentially with the age of the mother. Patau’s syndrome and Edwards’ syndrome share many features in common. Patients are always severely mentally retarded and most affected children die during the first weeks after birth. The fact that chromosome 13, 18 and 21 are among the three gene-poorest chromosomes of the human genome (www.ncbi.nih.gov), may explain why only these polyploidies are viable. Monosomy of any autosomal chromosome is invariably lethal at the earliest stage of embryonic life. Numerical sex chromosome abnormalities are more common than numerical autosomal abnormalities, but not necessarily associated with mental retardation. Turner syndrome (females possessing only one X chromosome) and Klinefelter patients (XXY males) may be intellectually normal. However, once the number of X-chromosomes exceeds two, such as in the triple X syndrome, patients are always mentally retarded.

**Partial chromosome abnormalities**

Deletions, insertions, inversions, translocations etc. may occur on any part of any chromosome. Translocations can remain without clinical consequences as long as they are balanced, without loss or gain of genetic material and do not interrupt an important gene. A well-known example is the Robertsonian translocation, which results from the breakage of two acrocentric chromosomes (13, 14, 15, 21 or 22) at or close to their centromeres followed by a fusion of the long arms. The resulting hybrid chromosome consists of two long arms of for instance chromosomes 14 and 21. As the short arm of these acrocentric
chromosomes contains abundant ribosomal sequences only, the carrier of this Robertsonian translocation remains unaffected. However, the progeny of such a patient may inherit an extra copy of the long arm of chromosome 21 on top of chromosome 14 and suffer from Down syndrome, or may inherit an extra copy of the long arm of chromosome 14 and not be viable.

Deletions may cause diverse phenotypes, depending on both the size and location of the deletion, but almost invariably including mental retardation. As a general rule, deletions spanning more than 2% of the total genome are not viable. Deletions with a minimum size of roughly a single chromosome band, or 5-15 Mb, can be detected under a microscope on chromosome spreads made of blood cells. Examples of such cytogenetically visible deletions include cri-du-chat syndrome, characterised by mental retardation and cat-like crying in childhood. Upon karyotype examination of patients, a deletion of varying size of the short arm of chromosome 5 (or even a total truncation), but invariably including the region 5p15.2-p15.3, may be identified.

Cytogenetically invisible microdeletions

Interstitial microdeletions

However, not all deletions are cytogenetically visible. Some deletions are too small to detect under a microscope. By definition, such so-called submicroscopic deletions involve the loss of only a limited chromosomal segment, taking away a few genes only and causing so-called contiguous gene syndromes. Such deletions do not occur at random positions in the genome but tend to cluster in specific regions. A submicroscopic deletion involving a segment on chromosome 7q11.23 causes Williams-Beuren syndrome, associated with mental retardation in combination with recognisable phenotypic features and an asymmetric cognition profile. Another contiguous gene syndrome is the Smith-Magenis syndrome, in which a deletion of a portion of 17p11.2 is associated with a striking phenotype including psychomotor and growth retardation, and behavioural problems. In addition, the velocardiofacial syndrome, caused by a 22q11 microdeletion, is characterised by cleft palate, cardiac anomalies, typical faces, and learning disability. Such deletions are not routinely detected by karyotype analysis, but may be detected by fluorescence in situ hybridisation (FISH) with probes specific for that chromosomal region upon request by an experienced clinician.

Subtelomeric deletions

A specific subcategory of cytogenetically invisible deletions includes deletions at the end of chromosomes. Chromosomal rearrangements involving the ends of chromosomes (telomeres) are emerging as a significant cause of idiopathic (Flint et al., 1995) as well as familial mental retardation (Holinski-Feder et al., 2000). Telomeres are composed of a TG rich repeat (TTAGGG)_n which is similar in all vertebrates. This simple sequence is repeated several hundred to several thousand times and the number of repeats is variable between individuals and with age. Immediately adjacent to these repeats lie complex families of repetitive DNA that may be shared among several chromosomes (Mefford and Trask, 2002). The function of these subtelomeric sequences, which may
extend over a few hundred kilobases, remains unknown. The high degree of sequence similarity could cause “cross-talk” between telomeric regions, a process from which the rearrangements may arise (FIGURE 2). The telomeric regions are extremely gene-rich which explains why the relatively small deletions of subtelomeric sequences frequently cause mental retardation such as observed in the Miller-Dieker syndrome (deletion of the 17p telomere) and the α-thalassemia/mental retardation syndrome (deletion of the 16p telomere).

Though initial studies reported identification of subtelomeric deletions in 5-10% of all cases of idiopathic mental retardation (Knight et al., 1999) the exact frequency of these mutations still remains unknown due to the fact that it is not possible to detect these cytogenetically invisible subtelomeric deletions by routine karyotyping. The most frequently used technique to detect these rearrangements is FISH in which fluorescent telomere-specific probes for each telomere are hybridised to genomic DNA. As this is a laborious technique, relatively few laboratories have screened more than a selected series of patients. However, alternative techniques are being developed that make use of a variable

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**FIGURE 2**

Schematic presentation of the structure of a telomere

All human chromosomes end with the (TTAGGG)$_n$ sequence repeated hundreds to thousands of times. Adjacent to these repeats lie various telomere associated repeats (indicated by black and white shaded blocks A-E) with a high degree of sequence similarity. Each chromosome end contains different subsets of a limited set of subtelomeric repeats (here indicated as A-E). The subtelomeric rearrangements may be a result of the cross talk between these highly similar regions.
mixture of 4-5 fluorescent dyes to label all human telomeres with a different combination of dyes. The karyotype may subsequently be visualised with the aid of a digital camera resulting in images of all chromosome ends in a different colour. This facilitates the identification of subtelomeric deletions in patients, but at present the resolution of none of these techniques is significantly higher than light microscopy. However, in the future, adaptations of these fluorescent techniques might enable screening for subtelomeric deletions on a routine basis.

Molecular methods under development to screen patients for a large number of subtelomeric deletions include multiplex amplifiable probe hybridisation (MAPH), which recovers short amplifiable probes after hybridisation to genomic DNA. A first set of probes containing all chromosome ends has recently been completed (Hollox et al., 2002). In our laboratory, we focus on multiplex quantitative PCR reactions to screen approximately 12 telomeres at the same time. Quantitativity is assured by the fluodosage technique, measuring the incorporation of fluorescently labelled primers.

If successful, this technique would allow us to screen all telomeres with only 4 multiplex sets of primers.

Monogenic causes of mental retardation

Mutations in a single gene may disrupt its function and may cause mental retardation or a variety of phenotypes associated with mental retardation, depending on the function of the mutated gene and the impact of the mutation on its function. A subdivision within this group of disorders is based on the mode of inheritance.

Autosomal dominant mental retardation

As patients with mental retardation rarely reproduce, pedigrees of autosomal dominant mental retardation are infrequently observed. However, patients with an autosomal dominant form of mental retardation may arise as a consequence of a novel mutation, as is for instance the case for patients with Rubinstein-Taybi syndrome (Petrij et al., 1995). This disorder, characterised by developmental delay, stature, characteristic facial features, and broad thumbs and big toes, is caused by mutations in the CREB gene located on chromosome 16p13.3. Milder forms of autosomal dominant mental retardation with variable phenotypic expression may remain hidden if patients are so mildly affected that their diagnosis is made only after the identification of the disorder in a more severely affected family member.

Autosomal recessive mental retardation

Autosomal recessive transmission is often observed in metabolic disorders, where a loss of function of both alleles has to occur before enzyme levels become too low to fulfil their function. These deficits of an enzyme may cause an intracellular storage of unprocessed substrates, a shortage of their products, a depletion of cellular energy or the release of excessive amounts of metabolites, causing all kinds of disorders. Phenylketonuria (PKU), an inborn error of metabolism resulting from a deficiency of phenylalanine hydroxylase,
is the most frequent cause of autosomal recessive mental retardation. As a result of the enzyme defect, there is a shortage of tyrosine while phenylalanine accumulates. Another example is the Smith-Lemli-Opitz syndrome, characterised by mental retardation and multiple congenital abnormalities. The disease is caused by mutations in both copies of the sterol delta-7-reductase (DHCR7) gene.

In addition, many isolated cases of mental retardation may be caused by rare autosomal recessive mutations, though it was only recently that the first causative gene involved in such isolated cases of non-syndromic mental retardation was cloned. A four base-pair deletion within the PRSS12 neurotrypsin gene was shown to be associated with mental retardation in a large pedigree with non-syndromic autosomal recessive mental retardation (Molinari et al., 2002). However, little is known with certainty about the frequency of such autosomal recessive mutations in the population.

X-linked mental retardation

X-linked forms of mental retardation are estimated to cause 10-20% of all inherited cases of mental retardation and thus may occur as frequently as 1 in 600 males. The relatively high frequency of X-linked mental retardation explains the excess of males over females observed among the mentally retarded (Chelly and Mandel, 2001; Leonard and Wen, 2002). As X-linked disorders may be transmitted by unaffected carrier mothers, large X-linked mental retardation families are occasionally observed, facilitating genetic analysis of these disorders (FIGURE 3).

At least 209 different X linked mental retardation disorders have been described (Chiurazzi et al., 2001). 140 forms of syndromic mental retardation are discerned and causative genes were identified for 27 of them. In addition, more than 87 forms of non-syndromic mental retardation have been described and causative genes have been identified in 11

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**FIGURE 3**

Examples of disease transmission in a family (MRX79) with X-linked mental retardation

Circles indicate unaffected females, squares unaffected males. Filled in squares indicate male patients. Carrier females, indicated by a circle with a dot in the middle, may transmit the disease to their progeny but are themselves unaffected. Squares with a diagonal line through represents deceased family members.
non-syndromic forms of mental retardation. The localisation of presently cloned X linked mental retardation causing genes is shown in FIGURE 4.

Despite the impressive progression in unravelling the underlying causes of X-linked mental retardation, diagnosis of individual cases remains problematic. Many X-linked mental retardation disorders have been observed only in a relatively limited number of patients. Moreover, the prevalence of many mutations is so rare, that some families almost seem to have their own, private mutation. Therefore, none of these mutations can be considered as candidates for routine screening, with the exception of the CGG repeat expansion in the fragile X-syndrome and possibly the A140V mutation in the MECP2 gene (see further).

In the future, gene expression analysis using microarray technology might significantly enhance the diagnostic possibilities of cases suspected from X-linked mental retardation. The majority of known mutations in X-linked genes are loss-of-function mutations. Spotting all genes of the X-chromosome on a microarray would enable simultaneous screening of hundreds of loss-of-function mutations by simply hybridising RNA of a patient to a single grid.

**Fragile X syndrome, the most common form of inherited mental retardation**

The fragile X syndrome is the most frequent and best-studied X-linked syndrome, which on its own has a prevalence of 1 in 4000-6000 (Kooy et al., 2000). It is a disorder characterised by mental retardation and typical physical and behavioural abnormalities. Adult patients suffer from mild to severe mental retardation in addition to very specific phenotypic features (macroorchidism, a long face, prominent ears, a high-arched palate, and flat feet). Behavioural problems include hyperactivity, eye-contact avoidance and repetitive speech as well as autistiform features in a subgroup of patients. On chromosome spreads of cells grown under specific cell culture conditions, fragile X patients show a gap or break on the X chromosome, the so-called fragile site FRAXA. At the molecular level, the disorder is due to a dynamic mutation caused by the expansion of a CGG repeat located in the promotor region at the 5' end of the FMR1 gene (Verkerk et al., 1991). In the normal population, the CGG repeat is polymorphic, ranging from 5 to 50 copies, but is stably inherited without size changes upon transmission from generation to generation. However, in carrier females, the CGG repeat is enlarged, ranging from 50-200 repeats, and is unstably inherited. Such an expanded CGG repeat is longer than in the normal population but is not disease causing. Therefore it is called a premutation. So, although female carriers themselves are unaffected, upon transmission from mother to progeny the CGG repeat may expand up to 200 repeats or more, resulting in fragile X syndrome once this threshold is reached. Such an enormous expansion is called a full mutation. Upon expansion of the repeat in fragile X patients, the promotor region of FMR1 becomes hypermethylated resulting in the transcriptional silencing of the gene. Consequently, FMR1 mRNA and protein is absent in fragile X patients. In females carrying a premutation, the promotor region remains unmethylated and FMR1 protein is being produced.

In addition to the fragile X syndrome, expansion of a CGG repeat at other fragile
G-banded map of the X chromosome showing the localisation of cloned genes responsible for syndromic (MRXS, only genes responsible for ‘pure’ syndromic mental retardation syndromes are shown) and non-syndromic (MRX) X-linked mental retardation. In some cases, different mutations in the same genes (indicated by an asterisk) can cause both syndromic and non-syndromic forms of mental retardation.
sites has been reported to cause mental retardation, including FRAXE (Gecz et al., 1996), associated with a milder form of mental retardation and FRA11B associated with Jacobsen syndrome, characterised by mental retardation and severe malformations (Jones et al., 1995). In addition to these fragile sites that have been cloned and proven to be associated with mental retardation, a variety of other fragile sites has been reported in patients with mental retardation, including FRA2A, FRA11A, and FRA12A. However, at present it is unknown whether in these cases the fragile sites are also causative of the disorder.

Mutations in the MECP2 gene may be a frequent cause of X-linked mental retardation

Mutations in the MECP2 gene cause Rett syndrome in females, characterised by severe neurodevelopmental decay and mental retardation (Amir et al., 1999). Male patients with Rett syndrome are extremely rare as the Rett causing mutations in the MECP2 gene are lethal in hemizygous males. Yet, MECP2 mutations differing from those that cause Rett syndrome were identified in as much as 2% of male patients with non-syndromic mental retardation (Couvert et al., 2001). This suggested that mutations in the MECP2 gene might be a frequent cause of mental retardation. However, this study did not discriminate between a disease causing mutation and rare polymorphisms and it was subsequently argued that the observed variations in the MECP2 gene in mentally handicapped patients are not disease causing mutations but rather rare polymorphisms, unrelated to the disease in the patient (Yntema et al., 2002). So far, the only well established frequent mutation in the MECP2 gene is the A140V mutation, recently postulated to be a recurrent mutation with an estimated prevalence of 1 in 100 in X-linked families (Winneppeninckx et al., 2002).

Mitochondrial mental retardation

In addition to errors on the autosomes or sex chromosomes, defects in mitochondrial genes may also cause mental retardation. Such pedigrees may be apparent because of the maternal inheritance.

Polygenic mental retardation

It is generally assumed that polygenic, e.g. forms of mental retardation that are caused by more than a single gene, are a frequent cause of mental retardation, especially amongst those patients that are more mildly affected. In contrast to the more severe forms of mental retardation that are caused by defects in a single gene, mild mental retardation does not follow a clear pattern of Mendelian inheritance. It is common among descendants with a sub-average socio-economic status. Although nothing is known about the genetic causes of mild mental retardation as yet, it is generally assumed that a multitude of genes neither of which is necessary nor sufficient for the development of the phenotype contributes to the disorder (Plomin, 1999).

The Diagnostic Process

In most cases, a diagnosis begins with a thorough clinical evaluation of the patient. The clinician tries to obtain some
insights in the severity of the disease, physical and behavioural abnormalities, family history, prenatal risks to which the patient was exposed, problems during birth, developmental milestones of the patient etc. Based on the outcome of this clinical evaluation, a diagnostic route is set up for each patient. A first step will be a thorough investigation of the chromosomes of the patient by checking chromosome numbers and the presence of chromosome abnormalities. If negative, DNA screening for the fragile X syndrome will be performed. Depending on the outcome of the chromosome and fragile X screening and on the clinical evaluation of the patient, a further screening for mutations in specific genes or for the presence of specific microdeletions may be performed. Metabolic testing is performed only in rare cases.

**Therapeutic Intervention**

*Therapy today . . .*

There is no drug intervention possible for most forms of mental retardation and therapy is limited to the treatment of the anomalies or complications accompanying the mental retardation, such as the correction of physical malformations. In addition, it has become apparent that the mental development and the cognitive capacities of mentally retarded patients may benefit from good education and support. Recent studies have shown that it is possible to boost the IQ of mentally retarded children by changing their environment (Duyme et al., 1999). By well-adapted programmes including socialisation, physical development, language development and occupational therapies, mentally retarded people may attain a certain degree of autonomy.

As possibilities for therapy for mental retardation disorders are still limited at present, current strategies focus on prevention of the disorder. If detected early in life, the mental retardation caused by phenylketonuria can be prevented by a lifelong diet without phenylalanine. This is why in many countries newborns are routinely screened for this enzyme deficiency shortly after birth. Another mental retardation disorder that can be prevented following early diagnosis is congenital hypothyroidism. This disorder can be treated by thyroid hormone replacement therapy. In addition, if a genetic cause of the disorder is known, prenatal diagnosis may be offered to the family.

. . . and in the future

Perhaps due to its high prevalence, most therapeutic studies have focussed on the fragile X syndrome. Recently, it was discovered that intellectually normal or minimally affected individuals with an unmethylated full mutation still produce FMR1 proteins (Smeets et al., 1995). It was concluded that the silencing of the FMR1 gene is caused by the methylation following the repeat expansion and not by the expansion itself. Inspired by the discovery of these exceptional individuals, demethylating agents were used to demethylate the expanded repeat in patients. In vitro reactivation of FMR1 expression in lymphoblastoid cells of fragile X patients was obtained by treatment with the demethylating agent 5-azadeoxycytidine, which unfortunately is toxic for use on humans (Chiurazzi et al., 1998). As this experiment demonstrates the feasibility of restoring
protein expression at least in cultured cells from patients, one of the future challenges is the search for less toxic demethylating reagents that are specific for the fragile X gene.

In addition, fundamental research on the fragile X mouse model has demonstrated that the AMPA receptor is potentially up regulated in the hippocampus (Huber et al., 2002). The AMPA receptor is a neurotransmitter receptor that is activated by neurophysiologic processes and is involved in memory and learning. Drugs that directly interfere with the AMPA receptor in the brain, called Ampakines™ have been on the market for some time, and this has inspired clinicians to start to test whether those drugs may be used to ameliorate the condition of a selected group of fragile X patients.

However, speaking in general terms, the development of rational therapies for mental retardation disorders is more difficult than for any other type of disorder. This is due to the extreme genetic heterogeneity. As drug targets will have to be identified for each disease gene separately, this would in no rare cases require almost an independent approach for many individual mental retardation families. Perhaps a more realistic approach to develop therapy would be to increase our insights in how mutations in these mental retardation genes leads to disease. Common pathways might be involved in more than a single disorder (Ramakers, 2002). Interfering in such pathways could perhaps be exploited to ameliorate the condition of patients suffering from more than a single mental retardation disorder at once. Therefore, increasing our insight in the molecular causes of the mental handicap might lead towards realistic therapies for mental retardation disorders in the future.

**Summary**

Mental retardation, defined by an intelligence quotient (IQ) below 70, is the most frequent cause of serious handicap in children and young adults with an estimated prevalence up to 3% of the population. The handicap may be mild to severe and may occur either as an isolated phenomenon or in the company of other maladies. Yet, as the handicap interferes with the performance of essential skills at each age, the impact of mental retardation on patient’s life and his environment is always dramatic. Therefore, mental retardation is one of the more important topics in medical science. The current paper summarises the advances made in unravelling the genetic causes of mental retardation, estimated to be responsible for 50% of all cases, and issues on the current diagnostic and therapeutic possibilities.

**Glossary**

**5' end of a gene**
Definition of the beginning of a gene segment (3' represents the end of the segment).

**Acrocentric**
Chromosome in which the centromere is very near one end.

**Allele**
Alternative form of a gene found at the same locus on homologous chromosomes.

**AMPA**
Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor. This neurotransmitter receptor is involved in memory and learning processes.
Autosomal
Any chromosome other than a sex chromosome (i.e. not an X or Y chromosome).

Centromere
The point at which two chromatids of a chromosome are joined. This region is important for separation during the production of a new copy.

CGG repeat expansion
Repeated sequence CGG at the DNA level. When the number of repeats increases this is referred to as an expansion.

Chromosomal regions (p & q, centromere)
A chromosome consists of two parts (arms), a long and a short arm that are labelled q and p, respectively that are linked by a region known as a centromere.

Contiguous gene syndrome disorder
A disorder resulting from the deletion of adjacent genes.

CREB
Activator protein of gene expression.

Cytogenetics
The study of chromosome structure usually by direct observation.

Cytomegalovirus
A Herpes virus that causes pneumonia, retinitis (an infection of the eyes) and gastrointestinal disease in immunosuppressed people.

Deletions
Loss of a DNA sequence.

Dominant
A trait that is expressed in individuals who are heterozygous for a particular allele. Heterozygotes are individuals who possess two different alleles at one particular locus on a pair of homologous chromosomes.

Fluorescence in situ hybridisation (FISH)
A method for directly observing regions on chromosomes.

FMR1
Gene that causes fragile X mental retardation if it is shut down.

Gene-poorest chromosomes
Chromosomes carrying a less than normal number of genes (the rest of the chromosome consisting of apparently non-coding (non-gene) DNA).

Genotype
Genetic constitution of an individual.

Hemizygous
Loss of one of the usual two copies of a gene (or multiple genes). This term also refers to genes carried by the X chromosome in males where only one copy of this chromosome is present.

Hippocampus
Region of the brain involved in learning, memory and generation of emotions.

Hybridising
A single strand DNA/RNA probe sequence complementary to a target single strand DNA/RNA sequence can hybridize to form a double strand. If the probe sequence is labelled in some way, it can be used to detect the target sequence.

Hypermethylated
Methylation is the chemical modification of DNA (addition of a methyl group). DNA methylation affects the ability of DNA to direct the production of a protein. Hypermethylated (overmethylation) DNA is often not able to produce the protein whereas hypomethylated (undermethylated DNA) is.

Idiopathic
A term used in medicine to describe a disease or condition for which no known cause can be identified.

In vitro
Used to describe experiments carried out in the test tube.

Insertions
The additions of DNA sequences.

Interstitial
Region between two other defined regions.

Inversions
When DNA sequences are excised from the genome, turned back to front and then reinstated at the same spot, they are said to be inverted.

Karyotype
The observed pattern of chromosomes in cells of an individual.

Loss-of-function mutation
A mutation that results in the loss of function of a gene i.e. the loss of the ability to produce a specific protein.
Lymphoblastoid
Dividing cells of lymphocyte (white blood cell) like origin.

Microarray
A matrix consisting of very many spots each consisting of one gene sequence that can be used to hybridise to a specific probe or to the labelled RNA from an individual.

Metabolic
Biochemical reactions required for the synthesis of biopolymers such as proteins or lipids.

Mitochondria
The cells power station, generating energy.

Monogenetic
Only one gene involved.

mRNA
Intermediate copied from DNA and used to direct protein production.

Multiplex
Multicomponent reaction.

Neuronal receptor
Receptor on the surface on neurons (cells of the brain).

Neurotrypsin (PRSS12)
Neuronal multidomain serine protease neurotrypsin (PRSS12), an enzyme that digests proteins in the brain.

PCR
Polymerase chain reaction, a method to amplify small amounts of a gene or gene product.

Phenotypic
Observable characteristics.

Polygenic
Controlled by more than one gene.

Polymorphic
A gene that can exist in many forms or lengths.

Polymorphism
The occurrence in a population of two or more genetically determined forms.

Promoter
Control region of a gene that drives the production of a protein.

Recessive
A trait that is expressed in individuals who are homozygous for a particular allele. Homozygotes are individuals who possess two identical alleles at one particular locus on a pair of homologous chromosomes.

Ribosomal
A subcellular structure involved in protein production.

Rubella
German measles.

Sex chromosome
X or Y chromosome, determining gender.

Sterol delta-7-reductase (DHCR7)
An enzyme involved in hormone regulation.

Substrate
The reactant in any enzyme-catalysed reaction.

Subtelomeric
Region just before the end of the chromosome.

Telomere
The end section of a chromosome.

Transcriptional silencing
Turning off of protein production from a gene.

Translocations
Incorrect rejoining of two broken chromosomes so that genetic information that is normally located in two different areas becomes juxtaposed.

Trisomy
Three copies of a chromosome, instead of the usual two copies.

Unmethylated
Nonchemically modified form of DNA that is more likely to be active in directing protein production.

X-linked
Located on the X chromosome.

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