The fragile X syndrome

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Abstract
The fragile X syndrome is characterised by mental retardation, behavioural features, and physical features, such as a long face with large protruding ears and macro-orchidism. In 1991, after identification of the fragile X mental retardation (FMR1) gene, the cytogenetic marker (a fragile site at Xq27.3) became replaced by molecular diagnosis. The fragile X syndrome was one of the first examples of a "novel" class of disorders caused by a trinucleotide repeat expansion. In the normal population, the CGG repeat varies from six to 54 units. Affected subjects have expanded CGG repeats (>200) in the first exon of the FMR1 gene (the full mutation). Phenotypically normal carriers of the fragile X syndrome have a repeat in the 43 to 200 range (the premutation).

The cloning of the FMR1 gene led to the characterisation of its protein product FMRP, encouraged further clinical studies, and opened up the possibility of more accurate family studies and fragile X screening programmes.

Keywords: fragile X syndrome; FMR1 gene; mental retardation

History
In 1943, Martin and Bell described sex linked mental retardation without dysmorphic features in a family in which both affected males and females were observed. Thirty-six years later, Lubs' reported a marker X chromosome (later to be known as the fragile X chromosome) as an inconsistent finding in cytogenetic studies in leucocytes of some mentally retarded males. The folic acid and thymidine depleted cell culture medium was identified as the essential factor for the induction of this fragile site at Xq27. During the seventies, the combination of X linked mental retardation and macro-orchidism was recognised.4 Later, other clinical characteristics were established, for example, a long face with large, protruding ears, and behavioural features, including avoidance of eye contact, hyperactivity, hand flapping, and perseverative speech.1

The fragile X syndrome was diagnosed at that time by cytogenetic detection of the fragile site at Xq27.3. It had some special features for an X linked disorder. Approximately 30% of the obligate carrier females were mildly or moderately retarded and a large portion (±50%) had no cytogenetic fragile X expression. Also, mentally normal grandfathers linking two family branches with the fragile X syndrome were observed. These "normal transmitters" had no clinical or cytogenetic features that could apparently transmit the fragile X syndrome.

The gene involved in the fragile X syndrome, the Fragile X Mental Retardation (FMR1) gene, was identified in 1991.6-11 The gene defect was the first expansion of a trinucleotide repeat to be discovered and a whole class of disorders is now known to be associated with this type of mutation.12

Clinical studies
The original "Martin-Bell family" was restudied in 198113 and the typical cytogenetic and clinical features were found. The "Martin-Bell phenotype" was proposed as an eponym for the phenotype of affected males. Additional clinical features include high arched palate (52%), strabismus (36%), hyperextensible metacarpophalangeal joints (67%), hand calluses (29%), double jointed thumbs (53%), single palmar creases (25%), pes planus (71%), and heart murmur or click (10%) (figs 1 and 2, table 1).13-16 The facial features are often less noticeable, particularly in affected females and children (fig 3). The macro-orchidism often develops during or after puberty and is frequently absent in young patients.7-8 Seizures are observed in approximately 20% of young affected males, with a lower prevalence in adults.8,13-16

Fragile X infants often have relative macrocephaly persisting into adult life.17 However, the adult height of affected males is below the norm.17-18 A few patients present with either overweight or general persisting overgrowth which can be confused with either Prader-Willi syndrome or Sotos syndrome.19-24 Associations with other syndromes are reported; examples are the Robin sequence (micrognathia, glossoptosis, and cleft soft palate),25 the FG syndrome (congenital hypotonia, macrocephaly, distinctive face, and imperforate anus),26,27 and the DiGeorge anomaly (defects of thymus, parathyroids, and great vessels).28 However, there is no definite evidence for a causal relationship between the FMR1 gene...
Although several neuroimaging and a few neuropathological studies have been done on the central nervous system in fragile X patients, knowledge on specific structural and cellular defects is still limited. Reduced size of the posterior cerebellar vermis on MRI in male patients and increased size of the caudate nucleus, thalamus, and hippocampus have been reported. These findings have neither been confirmed nor refuted by others.

Neuropathological studies of three fragile X males' brains showed immature, thin, and long dendritic spines in different regions, with a reduction in mean synaptic contact but with preservation of neuronal density in the neocortex. Similar abnormal dendritic spines were observed in fragile X knockout mice. Interestingly, in normal mouse brain, high FMRP expression is observed in the synaptonematosomes which could be related to the high transcriptional activity necessary for function of neuronal spines. However, abnormally long, thin dendritic spines are also seen in cases with chromosomal abnormalities or unspecified mental retardation. Apparently, these are non-specific neuropathological changes, as is the neuronal heterotopia observed in two affected males and linked to their epilepsy. In the testes, macro-orchidism seems to be associated with increased tubular length and interstitial oedema.

The FMR1 gene
The identification of the FMR1 gene principally elucidated the special characteristics of the transmission of the defect in fragile X families rather than explaining the mental retardation itself. The FMR1 gene has a size of 38 kb with 17 exons and an untranslated polymorphic CGG repeat in the first exon. The normal population, this CGG repeat varies from six to 54 units (fig 4) with an average of 30 units. The mutations in the FMR1 gene can be divided into a major and a minor class (table 2). The major class of FMR1 gene mutations affects the CGG repeat, whereas mutations in the coding region are infrequently observed.

CGG REPEAT EXPANSIONS
On the basis of the size of the CGG repeat and its effect on protein and phenotypic expression,
two types of mutations within the CGG repeat can be distinguished: the premutation (size 43 to 200 units) apparently without clinical effect and the full mutation (size > 200 units) which, if fully methylated, is associated with mental retardation in all male and in 50–70% of female patients. At the protein level, FMR1 is absent from cells in cases with a fully methylated mutation only.

The mutations in the CGG repeat are dynamic. They may change from generation to generation as well as within a single person during early embryogenesis. Stable alleles with a CGG repeat < 55 units are defined as normal, and unstable alleles ranging from 43 to 200 repeat units are regarded as premutation alleles.

The premutation and its intergenerational instability
The premutation with repeats in the range of 43 to 200 units causes no phenotypic abnormalities in (male and female) carriers (Fig. 4). The intergenerational (in)stability of the premutation is dependent on the sex of the transmitting parent and on the size of the repeat. Only women with a premutation have a risk of having affected offspring with a full mutation. This risk of expansion into a full mutation depends on the size of their premutation; it is less than 20% for smaller premutation alleles (< 70 CGG repeats), but more than 80% for larger premutation alleles (> 80 CGG repeats).6, 65

The CGG repeat is generally interspersed with two AGG triplets61, 66 and their position at the 3' end influences repeat instability, with an instability threshold of 34–38 uninterrupted CGG repeats.61, 65 The potential predictive value of the size of the uninterrupted CGG repeat for risk prediction in the offspring of female premutation carriers has not been adequately evaluated until now.

In the 43 to 55 CGG repeat range, there is an overlap between normal and premutated alleles, often referred to as the “grey zone”. Only the observation of intrafamilial instability identifies these “intermediate” alleles as premutation alleles.61, 62, 66 However, such premutation alleles can also be stably inherited through many generations.67, 68 Alteration in one generation from alleles of < 43 to > 43 repeats is unknown, suggesting that such changes are very gradual. However, regressions from premutation to normal size (< 43 repeats) have been observed within one generation.69–71

The timing of any transition from pre- to full mutation is not fully understood. The presence of full mutations in the ovary of female fetuses, without evidence of a premutation, and simulation studies support the hypothesis of preconceptional enlargement.72–74 This seems to conflict with the finding of only premutations in the sperm of four males with a full mutation in somatic cells.75 The latter observation might be explained by regression of a full mutation to a premutation in a limited number of cell
lineages. In the germline, we have then to assume a selection for those cells with a premutation.

The full mutation

Subjects with the fragile X syndrome have CGG repeats above 200 units, the “full mutation” (fig 4). The expansion into full mutation is usually accompanied by hypermethylation of the repeat and its flanking regions, resulting in a shut down of transcription and the absence of the FMR1 protein. The latter causes the mental retardation. All males and a majority of the females with a hypermethylated full mutation are mentally retarded.

In somatic cells of fragile X patients, the mitotic instability of the repeat of the full mutation causes longer and shorter expansions, so all fragile X patients are somatic mosaics. The instability occurs during early embryogenesis and results in this somatic heterogeneity.

In fragile X patients, two special subclasses of mosaicism can be distinguished on the basis of size and methylation pattern.

1. “Size mosaics” are those patients with both a full and a premutation, which is observed in 20-40% of the male patients.
2. Also, males with somatic mosaicism for a full mutation and a (partial) deletion of the FMR1 gene have been reported.

2. “Methylation mosaics” are subjects with variations between cells in the methylation status of a full mutation. The proportion of leucocytes with an unmethylated full mutation may vary from low (=10%) to 100%. A few intellectually normal males with a high proportion (>60%) of leucocytes with an unmethylated full mutation have been reported.

OTHER MUTATIONS

Mutations other than CGG repeat expansions are most often large deletions (partial or complete) of the FMR1 gene, with or without surrounding regions. Several unrelated cases have been reported.

The first intragenic mutation in the FMR1 gene, a de novo point mutation (an Ile304Asn substitution) in exon 11, was reported in a profoundly retarded male with fragile X features. The missense mutation resided in one of the important domains of the FMR1 protein.

Intragenic mutations may result in an absence of FMRP and thereby cause the fragile X syndrome. One single de novo base pair deletion in exon 5 and an inherited two base pair substitution in exon 2 resulting in a loss of protein production have been described. A C to T point mutation in the 14th nucleotide of intron 10 of the FMR1 gene causing a deletion of exon 10 was reported in three unrelated fragile X patients. All five male patients showed the mental retardation and physical features characteristic of the fragile X syndrome.

Molecular diagnosis

Before the cloning of the FMR1 gene, cytogenetic detection of the fragile site at Xq27.3 (FRAXA) was the only method for (prenatal) diagnosis and carrier detection. However, this method was inadequate for carrier detection and other fragile sites localised near FRAXA caused diagnostic confusion, like FRAXE.

Table 2 Mutations in the FMR1 gene and their effect

<table>
<thead>
<tr>
<th>Mutation</th>
<th>No of cases</th>
<th>FMRP</th>
<th>MR</th>
<th>Physical features</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGG repeat expansion</td>
<td></td>
<td></td>
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<tr>
<td>Premutation (43-200 CGGs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full mutation (&gt;200 CGGs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;60% methylated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ premutation</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>+ deletion</td>
<td></td>
<td></td>
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<td>8</td>
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<td>&lt;40% methylated</td>
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<tr>
<td>16</td>
<td></td>
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<td></td>
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<tr>
<td>Other mutations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 base pair change (exon 2)</td>
<td>1</td>
<td>Absent</td>
<td>+</td>
<td>+</td>
<td>115</td>
</tr>
<tr>
<td>1 base pair deletion (exon 5)</td>
<td>1</td>
<td>Absent</td>
<td>+</td>
<td>+</td>
<td>115</td>
</tr>
<tr>
<td>1 base pair change (exon 11)</td>
<td>3</td>
<td>Present</td>
<td>+</td>
<td>+ (less typical)</td>
<td>113</td>
</tr>
<tr>
<td>1 base pair change (intron 10)</td>
<td>3</td>
<td>Truncated</td>
<td>+</td>
<td>+</td>
<td>116</td>
</tr>
<tr>
<td>Partial or complete deletion of FMR1 gene</td>
<td>14</td>
<td>Absent</td>
<td>+</td>
<td>+ (some atypical)</td>
<td>100-112</td>
</tr>
</tbody>
</table>

*For additional references see text.
The CGG repeat has been status (< product after methylation of chorionic sample because it might be amplified and used in prenatal PCR analysis.58 Repeat detection of The methylated full mutations is island methylation sensitive restriction fragment production. An alternative method for determining CGG repeat size is the polymerase chain reaction or PCR analysis. However, CGG repeats of more than ≈150 units are generally difficult to amplify and will often not give a detectable product after the PCR.

Most laboratories use both methods (restriction enzyme and PCR analysis) for prenatal and prenatal diagnosis.121 When a premutation is found in a chorionic villus sample, confirmation in amniotic fluid or a cord blood sample might be considered to ascertain the stability of the premutation during fetal life.125 In the (near) future, when sufficient information about stability becomes available, this precaution may become unnecessary. Absence of methylation of the fully expanded mutation in chorionic villi at 11 weeks of gestational age has been observed in a fetus with hypermethylation of the full mutation in fetal tissue.126,127 Methylation status is therefore unreliable in an early (≤12 weeks of pregnancy) chorionic villus sample because it may differ from the fetal tissue. Nevertheless, testing of methylation status may be useful in amniotic cells.

The methods described above can identify repeat amplifications in the CGG repeat and large deletions in the FMR1 gene. Subtle mutations outside the CGG repeat will not be detected. At present, only a limited number of mutations in the coding region of the FMR1 gene have been found using sequencing techniques.111,115,116 It is conceivable that other rare mutations in the FMR1 gene will be detected in the future.

**FMRF ANTIBODY TEST**

Recently, an FMRF protein antibody test was developed for detecting the presence or absence of FMRF in lymphocytes.115 This rapid detection method allows the diagnosis of fragile X syndrome from a blood smear; cells from fragile X males with a methylated full mutation produce no FMRF.130 The proportion of cells with FMRF production allows a distinction between males with the fragile X syndrome (<30% staining cells) and normal subjects (>40% staining cells).127 The test does not detect dysfunctional proteins, neither does it differentiate between normal and premutation alleles.

As a result of lyonisation, females with a full mutation may have staining of up to 80% of the lymphocytes, overlapping with 40% of the normal females who have staining in less than 80% of their lymphocytes.127 The test is therefore not suitable for detecting females with a full mutation or a premutation.

The main application for this rapid and cheap test is screening for the fragile X syndrome among mentally retarded males or male neonates. DNA studies are needed to confirm the diagnosis and to ascertain carrier status in their relatives.

Recently, the antibody test was successfully used in the prenatal diagnosis of at risk male

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**Figure 4** Part of the FMR1 gene and its CGG related mutations in the first exon of the FMR1 gene that contains the CGG repeat (grey) (see text for further details).
Table 3
Overview of DNA screening programmes among institutes and schools for the mentally retarded*

<table>
<thead>
<tr>
<th>Persons studied</th>
<th>Persons with grey zone allele</th>
<th>Persons with premutation</th>
<th>Persons with full mutation</th>
<th>Characteristics of population studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>F</td>
<td>M+F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>England</td>
<td>219</td>
<td>—</td>
<td>219</td>
<td>—</td>
</tr>
<tr>
<td>Australia</td>
<td>472</td>
<td>—</td>
<td>472</td>
<td>—</td>
</tr>
<tr>
<td>England</td>
<td>180</td>
<td>74</td>
<td>254</td>
<td>(41–49)</td>
</tr>
<tr>
<td>United States</td>
<td>299</td>
<td>140</td>
<td>439</td>
<td>(41–60)</td>
</tr>
<tr>
<td>Hagerman et al (1994)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>England</td>
<td>103</td>
<td>51</td>
<td>154</td>
<td>(50–60)</td>
</tr>
<tr>
<td>England</td>
<td>1013</td>
<td>1013</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>United States</td>
<td>888</td>
<td>591</td>
<td>1279</td>
<td>(41–60)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>870</td>
<td>661</td>
<td>1531</td>
<td>(43–60)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>3353</td>
<td>1317</td>
<td>4670</td>
<td>75 (1.8%)</td>
</tr>
</tbody>
</table>

*For references see text.
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The FMRP has RNA binding capacity owing to characteristic sequence motifs in the protein: an RGG box and ribonucleoprotein particle (RNP) K homology domains (designated KH domains). A patient with a severe phenotype and a missense mutation in one of these KH domains had quantitatively normal FMRP production in lymphoblastoid cells.

FMRP binds its own FMR1 transcript and, with unknown selectivity, 4% of fetal brain transcripts. Recently, a more specific binding of FMRP was found via RNA with the 60S ribosomal subunit, suggesting a function of FMRP in ribosomal function and in translation of certain proteins. A nuclear localisation signal encoded by the 3' part of the gene, as well as a nuclear export signal encoded by exon 14, were seen. Eberhart et al. postulated an interaction of FMRP with mRNA(s) in the nucleus, followed by export to the cytoplasm as part of a mRNP particle where it associates with ribosomes. A role of the FMRP in the translation machinery could explain the high expression in (some) actively dividing pre- and postnatal tissues.

Effects of the absence of FMRP were studied in knockout mice. These mice showed relevant learning deficits, hyperactivity, and macroorchidism as observed in fragile X patients. The knockout mice brain and testes lacked pathological abnormalities, except for enlargement of the testes.

Mental retardation

Fragile X males show some variability in intellectual disability: in most prepubertal boys it is moderate (IQ=35-55), and in adults moderate to severe (IQ=20-40). This apparent decline in IQ probably reflects a slowing of cognitive development, stabilising after puberty.

In affected males, a methylated, full mutation will lead to mental impairment whatever the repeat size of the mutation. It has been suggested that males with a “size mosaic” DNA pattern (premutation together with the full mutation with an associated residual FMR1 protein production) might have better mental functioning than fragile X males with a full mutation only. However, others found no mean IQ differences. Apparently, the proportion of brain neurones producing FMRP in “size mosaic” males is insufficient for normal cognitive functioning. This is also shown by the presence of mental retardation in a male mosaic for a partial deletion of the CGG repeat and a full mutation, who had FMRP production in 28% of his lymphocytes.

An indication of the proportion of cells expressing FMRP needed for normal mental functioning is shown in mentally normal males with incompletely methylated full mutations in more than 60% of their leucocytes.

An insufficient proportion of FMRP producing cells also explains cognitive impairment (IQ<85) in females who have a full mutation; 52-62% of the women with a full mutation who are to have mental impairment (IQ<85). In these heterozygotes, the proportion of abnormal FMR1 alleles on the active X chromosome (which are unable to produce FMRP) has an influence on cognitive development. Apparently, there is no large scale transmission/passage of corrective molecules from FMRP producing cells to non-FMRP producing neurones.

Management

Mental retardation and behavioural problems dominate the clinical presentation. The mental retardation is not amenable to intervention. However, careful medical follow up and sometimes intervention are required as the physical and behavioural problems of fragile X patients are related to their stage of development (table 1). Seizures observed in approximately 20% of males and 5% of females necessitate timely diagnosis and treatment. During infancy, connective tissue abnormalities, such as congenital hip dislocations and inguinal hernia, may be present. In late life the connective tissue dysplasia may lead to scoliosis, flat feet, and mitral valve prolapse. The mitral valve prolapse requires evaluation by a cardiologist and a recommendation for antibiotic prophylaxis before surgical or dental procedures.

Some children fail to thrive because of gastro-oesophageal reflux, tactile defensiveness, or difficulties in sucking. The latter of these problems requires attention from a specialised speech therapist or physiotherapist, while the gastro-oesophageal reflux can be treated by dietary advice or medication or both. Surgery is rarely needed. The frequent otitis media and sinusitis in approximately 50% of affected children require adequate intervention (antibiotics or polyethylene tubes or both). Approximately 30-50% of cases need ophthalmological help for strabismus, myopia, or hyperopia.

Behavioural problems include attention deficit and hyperactivity at a young age. Although fragile X patients are generally friendly, some may show aggressive behaviour in adulthood. Influencing these behavioural problems is difficult, although behavioural therapy and avoidance of overwhelming stimuli may alleviate some of the symptoms. In some countries, pharmacological intervention for the behavioural problems is common. However, adequately controlled studies on their effectiveness in the fragile X syndrome are scarce.

The need for special education and training, especially in the younger child, is of primary importance. Speech therapists and physiotherapists can help with language and motor development.

Conclusions

Since the original observation of the fragile X syndrome as a familial sex linked mental retardation syndrome in 1943, its clinical and molecular diagnosis has greatly improved. The biological basis for the unique phenomena of normal transmitting males and the “Sherman paradox” became evident after the cloning of the FMR1 gene in 1991, as well as the nature of the CGG repeat at the 5' end of the FMR1 gene and its intergenerational instability. The precise mechanism of the repeat expansion is...
still unknown. The FMR1 protein shows widespread expression in nearly all tissues studied, with both nuclear and cytoplasmic localisation. The protein seems to shuttle between nucleus and cytoplasm and it can bind to ribosomes via mRNA. Why the major clinical symptoms are restricted to the brain and testis remains unresolved.

The intellectual disability is the most consistent clinical symptom in males with the methylated full mutation. FMR1 protein expression in less than 30% of lymphocytes is associated with mental retardation and other clinical symptoms. Size mosaicism (combined presence of premutation and full mutation) does not seem to mitigate mental retardation while it is likely that at least 50% of (brain) cells expressing FMRP will be required to function at a normal IQ level.

The identification of the gene defect enabled screening programmes to be implemented, but the practicability and desirability of screening the mentally retarded or young adult females is still under debate. Testing mentally retarded subjects leads to diagnosis and improved support for newly diagnosed fragile X patients and allows identification of all premutation carriers in the proband's family. Subsequently, a fragile X diagnosis assists the parents in coping with problems and eventually accepting their mentally handicapped child. The diagnosis in a child will generally result in parents looking for treatment options. Some parents ask for pharmacotherapy to suppress the behavioural problems. However, its value is still a subject of debate. Most parents hope for a cure, either through protein replacement or gene therapy or both. However, before studying such future therapy strategies, one should consider that protein production probably needs to be restored in at least 50% of the cells (based on studies in blood) to achieve normal cognitive function. Before this long term aim, efforts should be concentrated on improving the diagnostic rate and subsequently the diagnostic certainty for fragile X syndrome patients. In the meantime, (basic) research can concentrate on increasing our understanding of the actual mechanism(s) of the neuronal dysfunction underlying the mental retardation.

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Willemsen R, Los F, Moh kms S, et al. Rapid antibody test for prenatal diagnosis of fragile-X syndrome on amni-

Willemsen R, Moh kms S, de Vries B, et al. Rapid anti-

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