

# MORE ABOUT...GENETICS

## UNRAVELLING THE FRAGILE X SYNDROME

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### Introducing fragile X

Fragile X syndrome is one of the most common *inherited* causes of significant intellectual disability. This disorder is transmitted in an atypical X-linked pattern and occurs in both men and women. The diagnosis was initially delineated following cytogenetic demonstration of a 'break' or fragile site at the tip of the X chromosome in a group of intellectually disabled boys. Discovery of the molecular mechanism of fragile X syndrome has allowed explanation of a number of the unusual inheritance and clinical phenomena encountered in the condition.

### What are the clinical features of fragile X?

Fragile X syndrome occurs in all ethnic groups and has an estimated prevalence of 1 in 4 000 - 6 000 men and about half that in women. The disorder is characterised by intellectual disability, facial dysmorphology and behavioural disturbances. Some of the clinical manifestations encountered are listed in Table I.

Table I. **Clinical manifestations of fragile X syndrome**

| Physical features            | Neurodevelopmental features   |
|------------------------------|-------------------------------|
| Macrocephaly                 | Disproportionate speech delay |
| Long face                    | Intellectual disability       |
| Protruberant ears            | Poor eye contact              |
| Prominent jaw                | Hyperactivity                 |
| Large testes (after puberty) | Autistic-like features        |
| Joint laxity                 | Mood disturbance              |
| Mitral valve prolapse        | Epilepsy (16%)                |

### More about the genetics of fragile X

#### Molecular mechanism of fragile X mutations

Fragile X syndrome was the first condition shown to occur as a result of a dynamic mutation. Previously known as triplet repeat disorders, this group of conditions occur as a result of instability in an area of the responsible gene in which a repeating DNA sequence occurs. The gene that is mutated in fragile X syndrome is the familial mental retardation (FMR) 1 gene. In most affected individuals there is an increased number of CGG repeat trinucleotides in the 5' untranslated region of the FMR1 gene. The remaining affected individuals have a point mutation or deletion in the same gene.

In normal individuals there are between 10 and 45 of these CGG repeats. If the number of copies of the CGG trinucleotides is > 200, fragile X syndrome may be present. This number of repeats results in methylation of the gene, stopping its transcription. In men, who have only a single X chromosome, fragile X syndrome is virtually inevitable. In women, however, the clinical outcome will depend in part on the pattern of X inactivation. If the majority of active X chromosomes in the brain are those with the mutation,

intellectual disability is likely to occur. For women with a repeat number of > 200, there is a risk of approximately 50% of manifesting the disorder.

Individuals who have a number of CGG copies between the normal and affected range are termed 'premutation carriers'. The expansion of the CGG region in these individuals results in instability of the region, allowing increased expansion when transmitted to the next generation by women. For reasons not entirely clear, men will transmit the premutation to their daughters, but the mutation never expands into the fragile X syndrome range after male transmission. Premutation 'carriers' can show clinical abnormalities different to those of fragile X syndrome.

#### How is fragile X syndrome passed on in families?

Both boys and girls with fragile X syndrome will have a mother with a premutation or a full mutation. These women will have a 50% risk of passing on the abnormal X chromosome to each child. Sons inheriting the X chromosome carrying a full mutation will have fragile X syndrome, while daughters who inherit the mutation have about a 50% risk of showing features of this syndrome. For women carrying smaller premutations (< 100 repeats) the risk of expanding to a full mutation

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in the next generation is a little lower, depending on the number of CGG repeats.

A woman who carries a fragile X premutation could have inherited the mutation from her mother or her father. For men with a premutation all their daughters, but none of their sons, will be carriers.

**Can premutation ‘carriers’ have symptoms?**

A number of men, who have an increase in the CGG repeat number in the FMR1 gene in the premutation range, have developed a late-onset neurological disorder characterised by tremor, ataxia and cognitive decline. A small number of female premutation carriers have been described with similar symptoms but without dementia. Women who carry premutations are also at increased risk of developing premature ovarian failure.

**How is fragile X syndrome diagnosed?**

The clinical features of fragile X syndrome can be subtle, particularly in young children and in girls. The diagnosis should be considered in all individuals with intellectual disability or developmental delay, especially if there is a compatible family history.

Cytogenetic demonstration of a fragile site is diagnostic but less sensitive than molecular testing. Reliable DNA test-

ing is available for diagnosis, carrier detection and prenatal diagnosis.

**Genetic counselling in fragile X families**

Diagnosing an individual with fragile X syndrome is only the beginning. The family should be evaluated and family members at risk identified for genetic counselling and testing where appropriate. Genetic counselling in this disorder is complex, but carries the hope of reducing the burden of this condition for families and communities.

**MEDICAL INFORMATICS AND BIO-INFORMATICS: THE INFORMATION REVOLUTION AND MEDICINE**

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As knowledge of the human genome brings us nearer to realising the dream of understanding the underlying causes of many disorders, ranging from straightforward genetic conditions such as cystic fibrosis (CF)<sup>1</sup> and Tay-Sachs disease (TSD),<sup>2</sup> through to the complex interaction of genes and environment that contribute to the individualised risk of heart disease or asthma, it is becoming increasingly important that we are aware of the resources making it easier to handle the overwhelming array of data available on the Internet.

Similarly, advances in medical informatics are set to change the practice of medicine at all levels. Advances such as personal databases for the compilation and analysis of patient records and related information, practice management software,<sup>3</sup> online libraries of drug interactions,<sup>4,5</sup> dis-

ease-specific support sites,<sup>6,8</sup> and continuing medical education,<sup>9,10</sup> to name but a few, completely refashion the toolset available to the GP in the practice of medicine.

The importance of information technology (IT) in medicine is nowhere more evident than in our medical schools. The University of Cape Town has made IT skills one of the cornerstone abilities of its new medical students. In fact, the first evaluation of new MB ChB students is an IT literacy evaluation on day one of their first year. The underlying principle is not only that it is important to know which resources are available now (such as the list of support sites for individuals afflicted with rare genetic conditions),<sup>6,8</sup> but also to equip the GP with the know-how to track down new resources as they become available. In this regard search engines like Google<sup>11-13</sup> and a range of others are becoming some of the most used electronic tools. One correctly placed query can save endless hours of wading through old journals, textbooks or antique lecture notes (heaven forbid).

As an example try to find the contact details of the South African Inherited Disorders Association'. Then try 'South African Inherited Disorders Association as a Google<sup>11-13</sup> search. (Note that entering SAIDA is not nearly as efficient, although the link is still on the first page of results.)

An important caveat needs to be placed on the use of Internet resources for clinically important information: remember that unless the information is from a proven (that means proven to your standards of proven, not anyone else's) source, the information available from the majority of sites should be regarded as having back-of-breakfast-box reliability. This means that it may sound right, and it may even be right, but it cannot be accepted as scientific fact simply because some person has decided to place it on a website. This does not mean that useful and factual information is not available; it only requires that you apply the same level of judgement that you