Fragile X syndrome (FXS) is the most commonly known inherited cause of intellectual disability often associated with autism (~1 in 2000 males and ~1 in 4000 females in the general population). Its other prominent features may include, but are not limited to, learning and speech difficulties, mood disturbance or anxiety associated with a number of minor physical anomalies. There is a high degree of variability in presenting symptoms between affected individuals. These symptoms may also overlap with other disorders and can lead to missed or mistaken clinical diagnosis. It is therefore, not possible to diagnose FXS based on clinical features alone. Genetic testing of the FMR1 gene is essential to confirm the diagnosis of FXS. Such testing targets a portion of this gene which usually has an abnormal ‘expanded’ sequence in FXS affected individuals. This expanded sequences leads to the gene being ‘turned off’ and to abnormal function of brain cells.

**Genetics and Clinical Involvement**

**FXD**
An abbreviation used to refer to Fragile X-associated disorders.

**FXS**
An abbreviation used to refer to Fragile X syndrome (‘syndrome’ is not capitalized).

**FXTAS**
An abbreviation for Fragile X-associated Tremor/Ataxia syndrome, a neurodegenerative condition that may occur in older male and female carriers. Symptoms include problems with balance, walking, shaking or tremors in body parts when performing activities of daily living, cognitive deficits including problems with memory, and mood disturbance. These symptoms are sometimes misdiagnosed as Parkinson’s disease or some form of dementia and the condition progresses at varying rates amongst individuals.

**FXPOI**
An abbreviation for Fragile X-associated Primary Ovarian Insufficiency, a condition that affects about 20 - 25% of premutation carriers in which ovarian reserve is reduced compared to other similar aged women. It can also cause infertility leading to complete cessation of periods before the age of 40. Associated symptoms can range from irregular or absent periods and hot flushes. A proportion of carriers with a diagnosis of FXPOI can still fall pregnant so receiving a diagnosis does not eliminate the need for considerations including contraception and family planning. Newly diagnosed carriers interested in having a family should consult their medical practitioner regarding levels of follicle stimulating hormone (FSH) levels and an ultrasound to assess their fertility.

**FMR1 gene**
An abbreviation of the term Fragile X Mental Retardation 1 gene— also referred to as “Fragile X gene”.

**mRNA**
An abbreviation of messenger Ribonucleic Acid, a molecule which carries a copy of genetic information from the Fragile X (or any other gene’s) DNA in the nucleus to the protein manufacturing apparatus in the cell, in order to make the fragile X or other proteins. The gene is in the nucleus and the protein manufacturing apparatus is in the cytoplasm of the cell. So a “messenger” is required to transfer the information.

**FMRP**
An abbreviation for Fragile X Mental Retardation protein. It is the product of the FMR1 gene and is essential for normal communication between brain cells. It is silenced in FXS.

**Gene**
An hereditary unit consisting of a unique sequence of DNA that occupies a specific location on a chromosome and determines a particular characteristic in an organism. Each unit is made up of a specific sequence of four chemical bases (adenine, thymine, cytosine, guanine).
**Trinucleotide repeat**
A sequence of three of the chemical bases that is repeated over and over again.

**CGG**
Refers to three chemical bases (cytosine, guanine, guanine) that are normally included in the genetic code and make up the Fragile X gene trinucleotide repeat.

**Repeat**
In the particular case of the Fragile X gene this refers to CGG repetition which occurs repetitively one after another within the DNA code of the FMR1 e.g. CGG-CGG-CGG-CGG is four repeats.

**Expansion**
This sometimes refers to an increase in the number of repeats from one generation to the next which occurs during genetic transmission. The term is also used to refer to an increase in the number of repeats over the (normal) common range.

**Chromosome**
Is a structure of packaged DNA that contains many genes. Normally each person has 23 pairs of chromosomes. The sex of an individual is determined by one pair of these chromosomes, termed sex chromosomes, known as X and Y. Females have two X chromosomes while males have one X and one Y chromosome. The Fragile X gene is located on the X chromosome. This means that females have two copies of this gene while males have only one copy.

**Pedigree**
A diagram based on family history which presents information about genetic relationships between family members and identifies individuals affected with Fragile X and other disorders. It also identifies those relatives of affected individuals who are, or have, an increased risk of being the carriers of the Fragile X gene with CGG repeat expansion.

**Note:** Everyone has the Fragile X gene, it is just that, in some people the gene changes (expands) which leads to Fragile X-associated Disorders.

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**Testing for Fragile X syndrome**

**Alleles**
An allele is one of the copies of a gene or region of a chromosome. In females there are two copies of the X chromosome and therefore there are 2 alleles that contain the FMR1 gene. The term allele is used interchangeably to refer to the FMR1 gene and the DNA code in close proximity.

**Typical repeat number**
6-45 CGG repeats.

**Grey zone**
45-54 CGG repeats.

**Premutation (carrier)**
55-200 CGG repeats.

**Full mutation**
Greater than 200 CGG repeats.

**Methylation**
A chemical change ‘on top’ of the genetic code acting as a switch that can turn off genes.

**Nonmethylated or unmethylated**
Refers to lack of the chemical signal that can turn genes off. The FMR1 gene is typically unmethylated in people without fragile X syndrome.

**Mosaic**
When someone has “mosaicism” it means that they have different groups of cells; one group with a specific genetic change and another group (or more) with either no, or different, genetic changes. In FXS the different types of mosaicism that may occur include: repeat size mosaicism (different cell groups in the body have different repeat sizes), and methylation mosaicism (different cell groups in the body have different methylation status).
Repeat mosaic  Refers to premutation and full mutation and/or grey zone in different cells but in the same tissue of the same person.

Methylation mosaicism  The FMR1 gene is turned on in some cells and turned off in other cells, but in the same tissue of the same person. In other words, the FMR1 gene in some cells is unmethylated and in other cells is methylated.

Tissue mosaic  Repeat and/or methylation mosaic between different tissues in the same person.

Activation ratio (AR)  In women there are two copies of an X chromosome and two copies of the FMR1 gene; one of which is active (unmethylated). This means that in women with a FM, there is only one copy of ‘unaffected’ FMR1 gene that has a typical repeat number. Activation ratio is the proportion of FMR1 alleles that has a typical repeat number and is active (unmethylated). Higher AR has been related to more favorable cognitive outcomes in FM females.

Genotype  Information on a genetic make-up of an individual or group of individuals with relevance to a single or many traits, or the whole organism.

Phenotype  Information on an organism's body normal and/or abnormal features.

PCR  An abbreviation of polymerase chain reaction — highly effective/sensitive approach to amplify small amounts of genetic code. It forms the basis of the diagnostic test used to determine the number of repeats and the range in which an individual with the Fragile X gene falls, i.e. in the grey, premutation or full mutation.

Southern Blot  A diagnostic test to determine number of repeats which is particularly effective in establishing full mutation repeat numbers. A modified version of this test known as methylation sensitive Southern Blot can also be used to provide information of the methylation status of the FMR1 gene and to determine the activation ratio.

Proband  The first individual in a family identified as having a FXD.

Cascade testing  Voluntary diagnostic testing of immediate and extended family members whom are suspected of having FXS or are at risk of being carriers based on pedigree information.

FXTAS: Fragile X-associated Tremor/Ataxia syndrome

mRNA toxicity  Too much mRNA is made and accumulates in the cell leading to premature cell death. This is thought to be the leading cause of FXTAS and FXPOI, as well as other premutation related disorders.

Toxic gain of function  This term implies that the elevated levels of FMR1 mRNA with CGG repeat expansion, within the premutation range, leads to severe changes in cells which may cause premutation-related disorders such as FXTAS, FXPOI, or some other reported problems.

Tremor  Fine, repetitive shaking of a body part.

Intention tremor  A hand tremor (or other part of the body such as legs or tongue) that is seen or worsens when that part of the body is moving to do something with intention.

Ataxia  Balance problems, tripping, weaving, reaching out to walls or other supports to steady oneself when mobilizing.
**IVF**
Abbreviation for in vitro fertilization — the use of specialist medical technology in a bid to achieve a pregnancy, following the retrieval of gametes (sperm and ova), from a consenting male and female.

**PGD**
Abbreviation for preimplantation genetic diagnosis — testing of laboratory embryo prior to implantation into the uterus. Pre-implantation genetic diagnosis is an optional genetic test used in an IVF setting that involves the biopsy or analysis of cells taken from an embryo between day 3 and 5, so that doctors can exclude those with a genetic abnormality from being implanted into the uterus. The test represents an additional cost on top of standard IVF costs and has a high percentage of accuracy. Despite this, couples may still elect to go on to have other prenatal testing including amniocentesis and/or CVS. The test does have risks so couples should be counselled prior to consenting to the procedure. The test can only be performed on viable embryos.

**ICSI**
Abbreviation for intracytoplasmic sperm injection — an IVF technique in which a single sperm specially selected is injected into an egg in an attempt to achieve fertilization.

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**Where to get help**
Further fact sheets and information are available from the Fragile X Association of Australia

[www.fragilex.org.au](http://www.fragilex.org.au) or call 1300 394 636 or email support@fragilex.org.au

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