Fragile X syndrome

What is fragile X syndrome?

Fragile X syndrome (FXS) is an inherited condition which presents with typical behavioural, developmental and physical problems.

Genetics [1] [2]

Fragile X syndrome is the most common cause of sex-linked general learning disability. It is one of a number of repeat expansion disorders. In DNA coding it is common to see repeated sequences of the nucleotides that make up the genetic strand. In fragile X syndrome there is an expansion of the number of repeat sequences in the fragile X mental retardation (FMR1) gene. This gene is on the X chromosome (Xq28). The nucleotides involved are cytosine (C) and guanine (G) and the repeated sequence is CGG. In the most common form of the condition, the CGG sequence is repeated more than 200 times. The metabolic result of this is to block production of a substance called fragile X mental retardation protein (FMRP).

In individuals without fragile X syndrome the trinucleotide sequence is repeated 6-54 times. People in whom the sequence is repeated over 200 times have the full mutation, which causes a deficiency in FMRP and thereby the full clinical syndrome. If there are between 55 and 200 repeats, there may be a 'premutation'. In these individuals, FMRP is produced but there is a risk of expansion in subsequent generations. The premutation alleles also confer a risk of associated fragile-X disorders (fragile X-associated tremor/ataxia disorder and fragile X-associated primary ovarian insufficiency).

Who gets fragile X syndrome? (Epidemiology)

Fragile X syndrome affects 1:5,000-7,000 men and 1:4,000-6,000 women [3] .

The premutation is far more common. Two to four times as many females as males carry the gene abnormality. This has an estimated prevalence of 1 in 130-260 females and 1 in 250-810 males [4] .

Fragile X syndrome symptoms [5]

- An individual with fragile X syndrome typically has learning difficulties (IQ less than 70) and delayed milestones, along with typical physical features such as a high forehead, large testicles (2-3 times normal size), facial asymmetry, a large jaw and long ears.
- There may be features due to changes in connective tissue including prominent ears, hyperextensible finger joints, mitral valve prolapse, soft skin and flat feet.
- There may be associated anxiety-related symptoms including obsessive-compulsive and perseverative behaviours, emotional lability and aggressive or self-aggressive behaviours. Affected girls and women are more likely to have problems with shyness or social withdrawal. In some cases, those affected may also have a diagnosis of attention deficit hyperactivity disorder (ADHD) or an autism spectrum disorder. Around 30% of affected males have autism and as many again may have an autism spectrum disorder [2] [6] .
- Other symptoms may include hand-flapping, repetitive actions, clumsiness, avoidance of gaze, seizures and sleep disturbance.
- Specific speech disorders may include echolalia and perseveration (the inability to complete a sentence due to repetition of words at the end of a phrase).

The diagnosis is usually made by the age of 3 due to delay in attainment of developmental milestones.

Differential diagnosis

- Other causes of general learning disability.
- Other chromosomal abnormalities causing learning difficulty, such as Down's syndrome and other sex chromosome anomalies such as Klinefelter's syndrome, Rett syndrome and Lujan-Fryns syndrome.
- Sotos syndrome.

- ADHD.
- Autistic spectrum disorder.
- Marfan's syndrome.

Investigations

- A detailed family history is useful as there may be features across the generations of premutation.
- A blood sample (or chorionic villus biopsy) can be sent for DNA analysis. Most laboratories currently use a combination of Southern blotting (detects full mutations) and polymerase chain reaction (PCR) testing (identifies pre-mutations and smaller CGG repeats). Southern blotting involves transferring DNA material from an agar gel on to a membrane. Electrophoresis applied to this membrane can then be used to identify a particular DNA sequence. PCR is used as polymerase enzyme to amplify a particular DNA region, making identification easier.
- A refinement of this technique, using capillary action to separate DNA fragments of differing size, enables the rapid testing of large numbers of samples, making the method suitable as a newborn screening test [7] [8] .
- Second-level analysis involves CGG methylation testing to evaluate lack of FMRP production ('silencing') and molecular techniques to identify loss of function mutations [3] .
- The development of long range-PCR-based protocols on DNA from either chorionic villi or amniocytes has made antenatal testing a possibility [3] .

Fragile X syndrome treatment and management [9] [10]

There is currently no cure for fragile X syndrome but a number of pharmacological, behavioural and cognitive interventions may improve quality of life.

Interventions include:

- Speech therapy.
- Special needs education.
- Behavioural therapy.
- Stimulants such as dextroamfetamine and methylphenidate for those with associated ADHD.
- Selective serotonin reuptake inhibitors (SSRIs) for symptoms of anxiety.
- Antipsychotics for mood stabilisation, improving attention and reducing anxiety - particularly aripiprazole.
- Anticonvulsants where seizures are present.
- Genetic counselling and support of the parents and other family members.

There is very little evidence for the efficacy of any of the pharmacological or behavioural therapies commonly used [11] [12] [13] .

Future prospects, however, look to have potential. A number of promising targeted clinical trials in recent years have had disappointing results due to a number of factors including variable phenotypes/characteristics of those with fragile X syndrome, difficulty in measuring outcomes and lack of translation of results in genetically altered mice to humans. Compounds for which trials have been completed with disappointing results have aimed to modify the FMRP targets and thus restore excitation/inhibitory signalling pathways. These include metabotropic glutamate receptor 5 antagonists, memantine, lithium, GABA/glutamate normalisers, minocycline and acetyl cholinesterase inhibitors. Folate therapy has been tried in the past and was the subject of a Cochrane review in 2011 but the evidence base was found to be poor and no conclusions could be drawn [14] .

As understanding of the role FMRP plays at cellular and molecular level continues to improve. Reduced FMRP production results in hyperactivation of the extracellular-signal-regulated kinase (ERK) signaling pathways as well as the mammalian target of rapamycin complex 1 (mTORC1). Behavioural and biochemical results in an FXS animal model (*FMR1* knockout mice) suggest that metformin could play a beneficial role in blocking these pathways [15] .

Prognosis

There is no shortening of life expectancy. Outcome in general varies with the degree of intellectual disability and expression of other characteristics, which vary widely.

Fragile X syndrome prevention

The UK National Screening Programme Committee decided not to institute a national newborn screening programme (January 2011). Likewise in the USA, fragile X syndrome is not part of the newborn screening programme but this remains a controversial issue [16] .

In 2019, the UK National Screening Programme Committee decided not to institute a national antenatal screening progamme on the grounds that there was lack of evidence that screening would improve outcomes in affected children compared to usual healthcare [17] .

Currently, the policy is to restrict screening to carrier identification within affected families. It may also be worthwhile screening children with learning difficulties, aiming to identify more families and to enable carriers to have prenatal counselling.

Further reading

- The Fragile X Society
- Sethna F, Moon C, Wang H; From FMRP function to potential therapies for fragile X syndrome. Neurochem Res. 2014 Jun;39(6):1016-31. doi: 10.1007/s11064-013-1229-3. Epub 2013 Dec 18.
- McCary LM, Roberts JE; Early identification of autism in fragile X syndrome: a review. J Intellect Disabil Res. 2013 Sep;57(9):803-14. doi: 10.1111/j.1365-2788.2012.01609.x. Epub 2012 Sep 14.
- Li Y, Zhao X; Concise review: Fragile X proteins in stem cell maintenance and differentiation. Stem Cells. 2014 Jul;32(7):1724-33. doi: 10.1002/stem.1698.
- Lozano R, Rosero CA, Hagerman RJ; Fragile X spectrum disorders. Intractable Rare Dis Res. 2014 Nov;3(4):134-46. doi: 10.5582/irdr.2014.01022.

Authored by:	Peer Reviewed by: Dr Hayley Willacy, FRCGP	
Originally Published: 20/11/2023	Next review date: 11/11/2021	Document ID: doc_2169

View this article online at: patient.info/doctor/fragile-x-syndrome

Discuss Fragile X syndrome and find more trusted resources at Patient.