

Full article

Fragile X syndrome



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Introduction

Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability. Fragile X is found in all races and the name of the syndrome comes from its location on the X chromosome, as the bottom of the chromosome appears to be broken or fragile when examined under a microscope. (See Figure 1.¹) Fragile X syndrome was first identified in 1969 (identifying the fragile site) and in 1991 the *FMR1* gene which is altered in patients with FXS was discovered. This condition affects males and females, although males are generally more severely affected. Individuals with FXS display a wide range of capabilities ranging from mild learning difficulties to severe intellectual disability with behavioural difficulties.

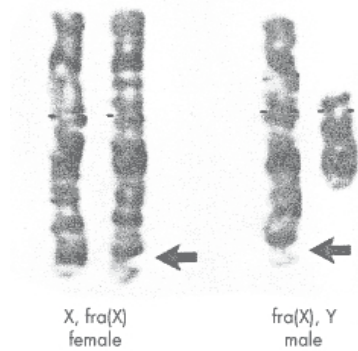


Figure 1: X chromosomes showing a fragile site from both a male and a female¹

What is fragile X syndrome?

Fragile X syndrome is a genetic condition caused by a change in the *FMR1* gene on the X chromosome. The *FMR1* has a key role in the brain to allow neuronal networks to respond and be modified by learnt experience. Approximately one in 4000 males and one in 6000 females are affected with this condition.

The disorder follows a pattern known as X-linked inheritance and males and females can be carriers for this condition. (See *Appendix 1*, p. 9, for information about 'X-linked inheritance'.) In general terms, a female carrier of an X-linked disorder has a one in four chance of having a male infant affected with the disorder. Fragile X syndrome is diagnosed by a specialised DNA test that looks at the length of a section of genetic code at the beginning of the fragile X gene. The diagnosis is important not only for the management and understanding of the child, but also to provide reproductive advice to the extended family.

Symptoms

Infants with fragile X syndrome often have delayed motor milestones and low muscle tone. Language development is often severely delayed in early childhood and is commonly referred to as being echolalic (child repeats words and phrases), with most children having little speech before three years of age.

Children with fragile X syndrome are often very good mimics. Anxiety symptoms and social avoidance are common. This may manifest as gaze avoidance and repetitive mannerisms such as hand flapping or rocking. Anxiety symptoms and poor communication skills may lead to behavioural difficulties.

¹ Greenwood Genetic Centre (2002). *Counselling Aids for geneticists*. Greenwood Genetic Center, USA.

Males often exhibit symptoms of hyperactivity and poor attention and stimulant medications are sometimes used. About 10% of males may have seizures which often resolve in childhood.

Language is usually established by the time of school entry and as adults, verbal communication is often satisfactory. Academic progress is usually slow, with most individuals struggling with complex concepts and mathematical skills. Literacy skills are variable, but some males with fragile X will be able to read. Anxiety symptoms and social avoidance, particularly of new situations, are prominent into adulthood and many find social interaction and regular employment difficult to manage and require support. Anxiety symptoms may be helped with medication like Prozac and Zoloft.

The disorder has a number of characteristic physical features, with some features being present only in adulthood. The features in males include a larger than average sized head (macrocephaly), a long face with prominent chin, and large prominent ears. In adulthood, males will be identified to have testicular enlargement (macro-orchidism). Low muscle tone and joint hypermobility are often present on examination and may affect classroom activities including writing.

The majority of males with fragile X syndrome and some females will require lifelong support, either living with their family and/or with accommodation support from a service provider. Life expectancy is not changed by this disorder and adult cognitive or physical decline is not characteristic of the disorder.

Symptoms in females with the disorder are variable, but commonly include anxiety concerns. Approximately 60% of females with fragile X syndrome have an intellectual disability which may vary from mild to moderate. It is not possible to predict the intellectual abilities of females by current genetic testing.

Prevalence

The prevalence of the disorder (the total number of affected people in the population) may be different depending on the racial group comprising the population. (For example, the prevalence of fragile X syndrome is lower in Korea compared with Australia, and higher in Israel compared with Australia.) Incidence describes the number of new diagnoses each year or fixed period of time. Local estimates based on a physical assessment of residents in institutional and special educational facilities in New South Wales estimated a prevalence of one in 4000 males in the early 1990s. Due to extensive testing in families where a diagnosis of fragile X syndrome has been made and subsequent prenatal testing, the incidence has significantly decreased in New South Wales.

Inheritance

The fragile X gene, FMR1, is located on the bottom of the X chromosome. Chromosomes are the physical structures that carry our genetic code. An individual with fragile X has an expansion in a section of their genetic code, which is in front of the FMR1 gene. The FMR1 gene is switched off when this section of genetic code increases beyond a critical point.

In most families the code remains stable from generation to generation, but in a small minority of people termed ‘carriers’ the code is able to grow in size when passed on from a carrier mother to her children. About one in 260 females are fragile X carriers. The change in gene size from carrier to fragile-X affected may take multiple generations. Although a carrier has an elongated copy of the FMR1 gene, they do not usually have learning difficulties but some may experience difficulty with abstract concepts like mathematics.

A female carrier who has one child with fragile X syndrome has a one in four chance of having a further affected male in each pregnancy and a one in four chance of having a female who has an abnormal copy of the fragile X gene. Prenatal diagnosis is an option for all female carriers of fragile X syndrome. Carriers are typically identified after the birth of an affected relative. (See *Appendix 2*, p. 11, for further information about ‘Carriers of fragile X’.)

Challenges for students with FXS

Almost all students with fragile X syndrome (FXS) will have some degree of learning disability. Girls will have milder academic difficulties than boys. Behavioural and cognitive difficulties are common in all students with FXS but are most severe in boys. The condition shares many similarities with autism but also important differences.

The most salient academic challenges, especially in males, include:

- delayed language acquisition and repetitive (perseverative) speech
- weak short and long-term memory for abstract information such as mental mathematical calculations (eg 2×6), often leading to anxiety around mathematics
- lack of spatial awareness and visuo–motor coordination, causing many children with FXS to appear clumsy and awkward
- difficulty maintaining attention over a long period for tasks that require abstract reasoning, such as mathematics
- extreme difficulty performing sequential tasks, such as problem-solving or planning ahead in a sequence; very impulsive
- becoming easily distracted in class by sudden noises, movements and routine transitions when attempting to focus on a given task.

Underlying many of the academic challenges that face students with FXS is a severe and pervasive attention deficit. In boys this is often coupled with hyperactivity and in girls anxiety. Attention skills form the essential building blocks for learning and academic outcomes and therefore it is critical that impairments are recognised and treated as early as possible in development beginning in preschool and continuing across the primary and secondary school years.

The most salient behaviour challenges include:

- *Feelings of being overwhelmed.* This can be brought about by the demands of social involvement, especially unexpected situations and changes, even by the common transitions of daily life. For example, for many students with FXS, especially boys, an unexpected transitioning from one classroom to another classroom can create intense feelings of anxiety resulting in challenging behaviour.
- *Autism-like characteristics.* These are present in most students with FXS but may be more intense in some students leading to a co-morbid diagnosis of autism in a minority of FXS children. However, it is important to note that students with FXS enjoy social interactions and have productive peer and parent relationships but struggle to maintain eye contact due to over-arousal mechanisms rather than a lack of desire to communicate.

Strengths for students with FXS

In addition to challenges, students with FXS also have strengths that provide teachers with important opportunities to minimise the effect of the academic challenges. These include:

- good visual memory skills that include strong face and emotion recognition skills
- good imitation skills
- good verbal skills especially vocabulary
- well-developed skills in verbal labelling and comprehension
- good short and long-term memory for meaningful information (eg stories, objects, names) with a particular ability to tap into a repertoire of acquired knowledge and vocabulary.

This array of strengths is a signpost for teachers to develop FXS specific intervention programs that focus on their proficiencies and weave those into the class curriculum. For example,

- by focusing on their strength in visual memory, many students with FXS will benefit tremendously from the use of visual timetables that present, in pictorial format, daily changes in the timetable in terms of different activities and environments
- by focusing on their strength in memory retention for meaningful information, critical skills such as number development and letter recognition can be taught using resources that promote learning in a meaningful context (eg colour and stories) rather than a traditional sequential approach of rote learning

- once engaged, many students with FXS can focus for long periods of time without experiencing too much distraction or hyperarousal, particularly if an activity is meaningful and non-sequential. An ideal teaching tool is the computer-assisted learning programs that develop academic techniques but are attractive, novel and fun for many students with learning difficulties. For the student with FXS, these programs engage attention, are interesting and visual in their presentation of information, and material can be given in a piece-meal ('chunking') format that plays to an FXS strength. Most importantly, these programs avoid one-to-one eye contact that many students with FXS find difficult and upsetting, and instead, allow them to view academic material in a positive and enriching format.

Key points for schools about fragile X syndrome

- Males are more severely affected than females.
- Social anxiety and hyperarousal are common, associated with reduced eye contact.
- Attention difficulties are common.
- Students may have reduced ability to sequence tasks.
- There is often difficulty with transitions, requiring student preparation.
- There is often difficulty with abstract learning so teachers should present information in a meaningful context to student.
- Visual learning is a common characteristic of students with fragile X syndrome.
- Computer-assisted learning projects may help to engage students.
- Low muscle tone and motor coordination difficulties may affect classroom activities, requiring planning for adjustments.

Glossary

carrier

a person who has inherited a genetic trait or condition but displays no symptoms

chromosomes

highly organised structures containing DNA located inside the nucleus of the cell. Normal nucleated human cells each contain 22 pairs of chromosomes, and two additional chromosomes, an X and Y chromosome in males, and two X chromosomes in females.

echolalia

involuntary parrot-like repetition of a word or sentence just spoken by another person.

gene

a sequence of DNA within a chromosome, which controls the production of a protein molecule, or controls the function of other genes.

incidence

the number of new diagnoses each year or fixed period of time.

joint hypermobility

joints that can be flexed or extended to a greater extent than usual.

macrocephaly

a head that is larger than normal in size.

macro-orchidism

testicles that are larger than normal in size.

prevalence

the total number of affected people in the population.

X-linked inheritance

a mode of inheritance in which the inherited trait is transmitted on the X chromosome.

Resources

Support organisations

NSW Genetics of Learning Disability Service (previously known as the NSW Fragile X Service)

Offering genetic counselling, carrier identification and coordination of prenatal testing.

Hunter Regional Genetics Service,

PO Box 84, Waratah NSW 2298

Ph: +61 2 4985 3136

Fragile X Association of Australia

PO Box 109, Manly, NSW 1655

Ph: 1300 FX INFO (1300 394 636)

www.fragilex.org.au

Fragile X Alliance Inc.

263 Glen Eira Rd, North Caulfield, VIC 3161

Ph: +61 3 9528 1910

www.fragilex.com.au

Web resources

Fragile X Trust (NZ)

Excellent education strategies for parents and teachers

<http://www.fragilex.org.nz/education>

Marcia Braden PhD

US psychologist who is recognised expert in education and psychological issues for people with FXS

<http://marciabraden.com/>

DET websites

Student Health in NSW Public Schools: A summary and consolidation of policy

https://www.det.nsw.edu.au/policies/student_serv/student_health/student_health/PD20040034.shtml

The role of the school community in supporting student health

The material in this section of the website provides advice on a wide range of issues relating to student health in public schools. It is particularly relevant to school staff and parents.

<http://www.schools.nsw.edu.au/studentsupport/studenthealth/index.php>

Curriculum planning and programming, assessing and reporting to parents K–12

This policy applies to all staff employed in NSW public schools, regions and state offices. It also applies to students who attend public schools and has implications for each school community.

https://www.det.nsw.edu.au/policies/curriculum/schools/curric_plan/PD20050290.shtml

Policy Standards for Curriculum Planning and Programming, Assessing and Reporting to Parents K–12

These policy standards are to be used for curriculum planning and teaching programs and are to be read in conjunction with the policy.

https://www.det.nsw.edu.au/policies/curriculum/schools/curric_plan/policystandards161006.pdf

Appendix 1 X-linked inheritance²



What is an X-linked genetic condition?

An X-linked genetic condition is caused by a change in a gene (mutation) located on the X chromosome. Genes located on the X chromosome are called X-linked genes. Women have two X chromosomes. Men have an X and a Y chromosome. If a woman has a gene change on one of her X chromosomes, she is usually unaffected because she has another X chromosome. If a man has a gene change on his X chromosome, he will usually be affected.

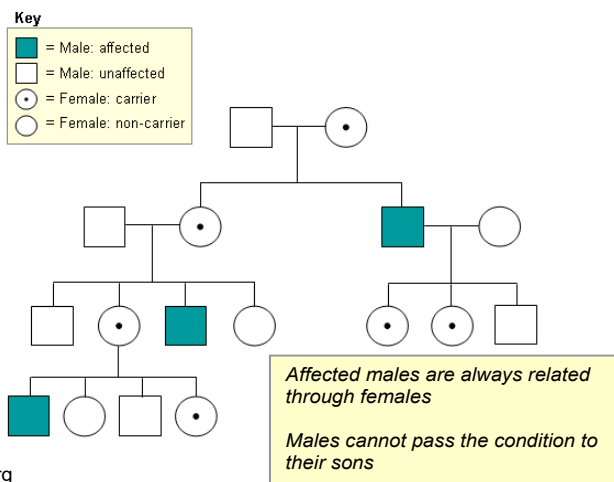
What does it mean if a woman is a carrier?

A woman who is a carrier of an X-linked condition has a gene change on one X chromosome and a normal copy of the gene on the other X chromosome.

Most carriers do not have symptoms of the condition. If they do, they are usually more mildly affected than the males in the family.

How are X-linked conditions inherited?

X-linked conditions are passed on through female carriers to male children. Usually there are affected males in more than one generation of the family as seen in the diagram below.



www.genetests.org
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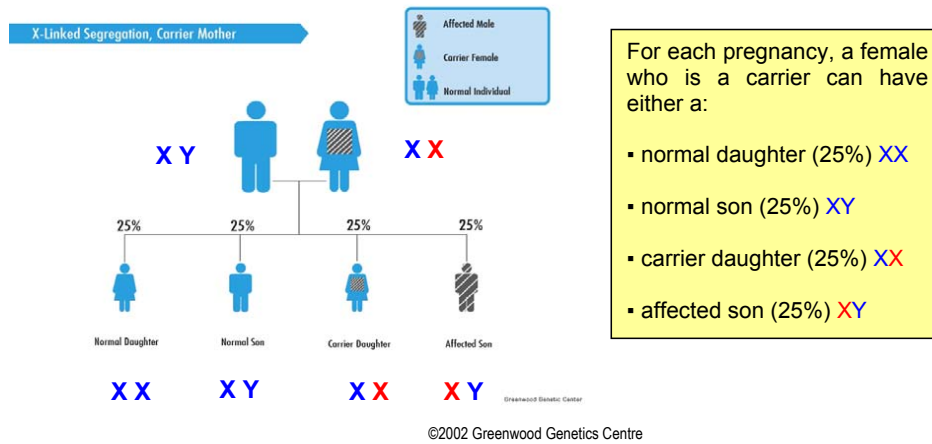
Genetics of Learning Disability Service (GOLD)
Hunter Genetics PO Box 84 Waratah NSW 2298
Phone: 02 49853136 Email: gold@hnehealth.nsw.gov.au

Mar 2010

² Genetics of Learning Disabilities Service, March 2010.

What are the chances of a female carrier having affected children?

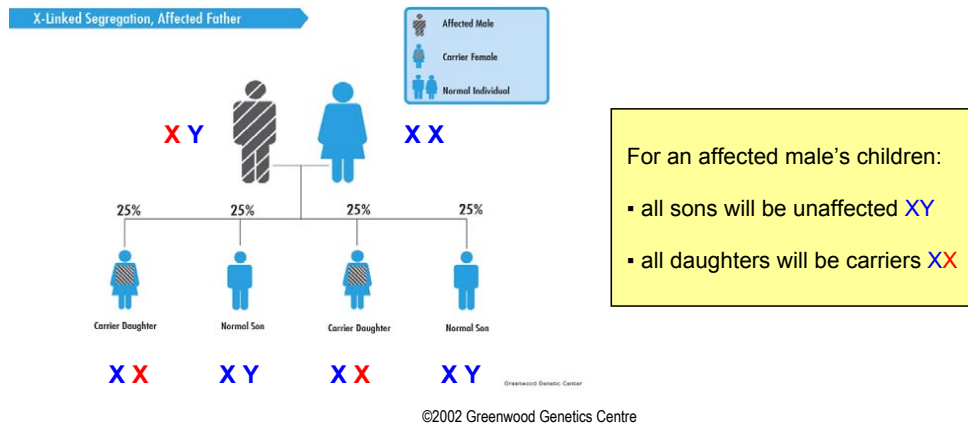
In each pregnancy there is a 50% (1 in 2) chance that the baby will receive the normal X chromosome and a 50% chance that the baby will receive the X chromosome with the gene change. Therefore, a female carrier has a 25% (1 in 4) chance of having an affected son and a 25% (1 in 4) chance of having a carrier daughter.




What are the chances of an affected male having affected children?

Males with an X-linked condition *cannot* pass it to their sons. Sons receive a Y chromosome from their father and an X chromosome from their mother.

Daughters receive an X chromosome from both their mother and their father. All daughters of affected males will be carriers and could have an affected son.



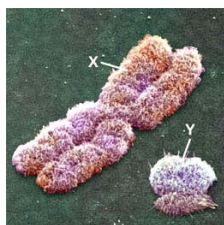
Appendix 2 Carrier of fragile X syndrome³



Genetics
Of
Learning
Disability

Carrier of fragile X Syndrome

What is Fragile X Syndrome?



Fragile X Syndrome is a genetic condition causing intellectual disability and behavioural problems. It is caused by a change in the FMR-1 gene on the X chromosome. The change is an increase in the size of a small section of the FMR-1 gene. This gene produces a protein, called FMR-1 protein which is necessary for brain functioning, especially in the areas of problem solving and comprehension. Individuals with fragile X display a wide range of capabilities ranging from mild learning problems to severe intellectual disability. The condition can affect both males and females but males tend to be more severely affected than females. There is no cure for this condition.

What are CGG repeats?

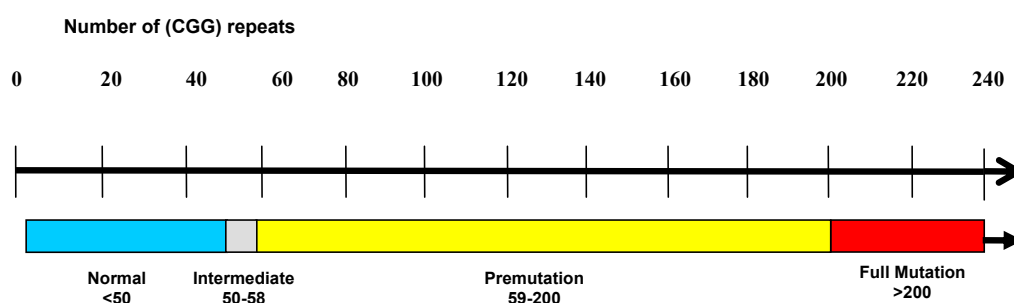
Part of the FMR-1 gene is made up of the chemical bases, CGG, repeated a number of times. The number of CGG repeats varies from one person to another and can be classified as being in the normal range (less than 50 repeats), the intermediate range (50-58 repeats), the premutation range (59-200 repeats) and the full mutation range (over 200 repeats). A premutation does not stop the gene from functioning and producing the FMR-1 protein.

What is a Full Mutation?

A large increase of over 200 CGG repeats is called a full mutation. The FMR-1 gene with a full mutation is switched off and can not produce the FMR-1 protein causing intellectual disability (*Figure 1*).

Figure 1

Normal, Intermediate, Premutation and Full Mutation



Fragile X Syndrome Testing

Since 1991, a DNA blood test has been available to test for the size of the CGG repeats within the FMR-1 gene. This shows if individuals are within the normal, intermediate, premutation or the full mutation range. Medicare covers the cost of the test, if there is a family history of fragile X syndrome or intellectual disability.

What does it mean to be a carrier?

Males and females can both be carriers of fragile X syndrome. A person with 59 - 200 CGG repeats is a premutation carrier. This means that although the repeat has increased in size, the gene is still functioning and producing protein. However, in female carriers, the repeat size can be unstable and increase in size as it is passed to future generations.

³ Genetics of Learning Disabilities Service, November 2009.

What does it mean to be a carrier? (cont.)

Most people do not have any learning problems associated with being carriers, although some experience psychosocial problems such as increased anxiety and depression. There are some identified health problems related to being a carrier of fragile X syndrome. Female carriers may have early menopause (20%), develop thyroid problems (20%) and experience muscle pains (25%).

FXTAS (Fragile X Tremor Ataxia Syndrome) is a neurological condition similar to Parkinson's disease, and may involve ataxia (unsteadiness), intention tremor (shaking) and memory problems. Male carriers over the age of 50 have a 20-40% chance of developing this condition. It is less commonly seen in females.

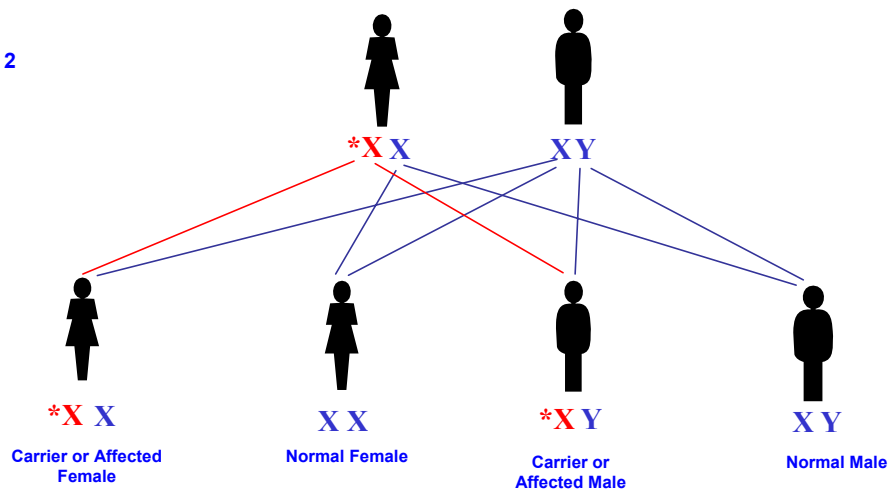
Female carriers

Females have two X chromosomes, one X inherited from their mother, and one X inherited from their father. Being a carrier of fragile X syndrome means that the female has a small increase in the number of CGG repeats (59-200 repeats) on one of her X chromosomes. Her other X chromosome has a normal number of CGG repeats.

When having children there is a 50% chance of passing on the X chromosome with the normal number of repeats and 50% chance of passing on the X chromosome with the increased number of repeats. If the X chromosome with the increased number of repeats is inherited, the number of repeats can increase to the premutation range (59-200 repeats) or the full mutation range (over 200 repeats). A repeat size of 100 or more is very likely to expand to full mutation range when inherited from a female.

A son or a daughter with a premutation will be a carrier. A son with a full mutation will have fragile X syndrome. A daughter with a full mutation will have a 65% chance of intellectual disability, ranging from mild to severe (Figure 2).

Figure 2



Male carriers

Males have one X chromosome inherited from their mother, and one Y chromosome inherited from their father. If a male is a carrier of fragile X syndrome, he has inherited his mother's X chromosome with a small number of CGG repeats (59-200 repeats). Carrier males are also referred to as normal transmitting males, or premutation males.

When a male carrier passes on his X chromosome with a small CGG repeat size to his daughters, it usually remains a similar size but it can decrease or increase in size. All daughters will be carriers and be at risk of having a son or daughter with fragile X syndrome. All sons of a male carrier receive a Y chromosome from their father and therefore, **will not** be carriers or have fragile X syndrome (Figure 3.)

Figure 3

