

8. Fragile x syndrome

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Dr Jonathan Cohen, Medical Director (Fragile X Alliance Clinic)

Ms Tarli Hall, Associate Genetic Counsellor (Genetic Health Services Victoria)

Dr Samantha Wake, Principal Genetic Counsellor (Genetic Health Services Victoria)

8.1 Key points

What is fragile x syndrome?

- Fragile X is the most common known inherited cause of intellectual disability.
- Fragile X syndrome is an X-linked condition.
- Between one in 2500 and one in 4000 males have fragile X syndrome.
- Between one in 250 and one in 500 females are estimated to carry the altered gene for fragile X.

Why is it important?

- Intellectual impairment is a life-long disability
- Early diagnosis can facilitate strategies that will enable individuals to achieve their maximum potential.
- Detection of carriers allows families to make informed decisions regarding family planning.
- While there is no cure, a wide range of specific treatment and management strategies is available.

Clinical features*

Individuals with fragile X syndrome may demonstrate the following characteristics:

- Developmental delay
- A range of physical characteristics
- Medical conditions:
 - ✦ Up to 20% have epilepsy
 - ✦ Eye problems, such as strabismus or squint
 - ✦ Recurrent ear infections
 - ✦ Joint laxity
 - ✦ Mitral valve prolapse
- **Behavioural or emotional problems including:**
 - ✦ Autistic-like behaviour; for example, hand flapping, gaze aversion, repetitive speech mimicry (echolalia)
 - ✦ Anxiety disorders
 - ✦ Aggressive outbursts
 - ✦ Attention deficit disorders.

*See *Background* for more details.

Who is at risk?

Individuals of either sex with:

- Intellectual disability.
- Developmental delay.
- Autistic-like characteristics.
- Learning disabilities of unknown causes, including borderline cases.
- A family history of fragile X syndrome or relatives with developmental delay of unknown cause.
- A previous fragile X cytogenetic test result that was inconclusive.

Who should be offered testing?

- *All individuals at risk* (see above).
- *Preconceptual*: any woman with a personal or extended family history of fragile X syndrome or intellectual disability of unknown cause.*
- *Obstetric*:
 - ✦ Pregnant women or their spouses with a family history of fragile X syndrome or an intellectual disability of unknown cause.*
 - ✦ Fetus of a woman known to be a fragile X carrier.
 - ✦ Women with a family history of premature menopause.

* Whenever possible, the affected person should be tested to determine if fragile X syndrome is the cause of the intellectual disability.

Which tests?

Testing should always be performed with appropriate pre- and post-genetic test counselling.

Investigating developmental delay/intellectual disability

- *DNA studies and karyotyping*: DNA studies offer a definitive result for affected individuals as well as carriers. Karyotyping should also be requested as other chromosomal explanations may be identified. Requests must specify fragile X syndrome.

Preconception testing

- *DNA studies*: to determine carrier status.

Prenatal testing

- *DNA studies*: testing can be offered to pregnant women using chorionic villus sampling.

Results generally take up to four weeks; however, prenatal test results can be back in two weeks. At present, there is no cost to the individual.

Testing for fragile X cannot determine the degree of intellectual disability, and the level of intellectual disability varies greatly between individuals.

Informing family

The patient/parents should be encouraged to:

- Inform family members that they may be at risk of inheriting or passing on fragile X syndrome.
- Give their family members written information about fragile X.
- Advise family members to discuss their risk with their own GP and/or contact the local Clinical Genetics Services.

8.2 Background

(The following material has been adapted from Lennox, N & Diggins, J (eds) 1999, *Management guidelines: people with developmental and intellectual disabilities*, Therapeutic Guidelines Limited.)

What is fragile X syndrome?

Fragile X syndrome is the most common known inherited cause of intellectual disability and it has a wide variety of presentations. It is the second most common genetic cause of intellectual disability. (Down syndrome is the most frequent and only ~1% of Down syndrome is inherited.) Intellectual problems can vary from mild learning difficulties, to emotional and behavioural problems, through to severe intellectual disability.

Fragile X is an X-linked disorder with a population frequency of between one in 2500 and one in 4000 in men. The population frequency in females is one in 5000 to 8000, and females show varying degrees of the condition.

Genetics

Fragile X is caused by an alteration in a gene on the X chromosome (the FMR1 gene: Fragile X Mental Retardation 1). The FMR1 gene produces a protein, FMRP, which is thought to be necessary for normal neurological functioning.

It is inherited as an X-linked condition although, due to the type of genetic abnormality involved, the pattern of X-linked inheritance is atypical.

The condition is a result of an increase in size (expansion) of a certain part of the gene due to a tri-nucleotide sequence being repeated over and over again. Most people have an expansion of between six to 50 repeats, with an average of 30. Males who are unaffected only have a small expansion (premutation), and those who are affected have a much larger expansion. Once the gene is above a certain size it generally 'switches off' production of FMRP, which results in an individual having fragile X syndrome.

Table I. Repeat numbers and variable presentation of fragile X syndrome

No. of repeats	Gene status	Effect	Estimates of frequency in the general population ^a
6–50 (average 30)	Normal	Unaffected	
50–230	Premutation	Females usually unaffected carriers	1 in 250 to 1 in 500 ^b
		Males usually unaffected carrier	1 in 750
>230	Full mutation	At least half of females are affected	1 in 5000 to 8000 females
		Generally affected if male	1 in 2500 to 4000 males

^a Turner, G, Webb, T, Wake, S & Robinson, H. 1996, 'The prevalence of fragile X syndrome', *Am J Med Genet*, 64:196–97.

^b Hagerman, RJ & Cronister, A (eds) 1996, *Fragile X syndrome: diagnosis, treatment and research*, Johns Hopkins University Press, Baltimore. Note: understanding of fragile X is constantly evolving and one very recent report suggested this frequency could be as high as one in 70.

Source: Lennox, N & Diggins, J (eds) 1999, *Management guidelines: people with developmental and intellectual disabilities*, Therapeutic Guidelines Limited.

Pattern of inheritance

The size of the expansion in the FMR1 gene is not stable and can change across generations. Both men and women with an expansion may pass it on to their children.

- Mother to child transmission is unstable, and the expansion may increase in size.
- Father to daughter transmission is stable for premutations; that is, the expansion will not increase.
- There are limited data on men with full mutations; however, it appears that daughters inherit a premutation from their affected fathers (that is, expansion decreases in size).

Women have a 50% chance of passing a premutation or full mutation on to each of their children.

Men can only pass a premutation or mutation on to their daughters but to none of their sons, as the sons receive only their father's Y chromosome.

A male identified with fragile X syndrome could have inherited this from:

- A mother with a full mutation
or
- A mother with a premutation.

A large proportion of the extended family across the generations may be found to carry an expansion in the FMR1 gene, and there may or may not be other affected family members. Genetic counselling is important and allows families to make informed decisions about family planning.

Presentation

Carriers (premutation)

- Carriers of the fragile X syndrome are generally considered to be unaffected and will only be detected following DNA testing.
- For a female carrier, the risk of passing on the expansion is 50% for each pregnancy. Since the premutation is unstable, the severity of the condition in the child is influenced by the size of the mother's premutation.
- It is difficult to distinguish between a normal version of the gene and a small premutation. There is a 'grey zone' in which the upper end of the normal number of repeats can change into a premutation when passed on to children.

Fragile X syndrome (full mutation)

- Males with the full mutation of the fragile X gene demonstrate developmental, physical, behavioural and emotional characteristics of fragile X.
- Females may also be affected despite the X linkage, but usually appear less so than males because of skewed X inactivation.

Clinical characteristics of fragile X

Males with a full mutation

Typical features may not always be present, and these features may vary in severity.

Medical conditions

- Up to 20% have epilepsy
- Mitral valve prolapse
- Recurrent ear infections
- Eye problems; for example, strabismus, squint

Developmental delay

- Intellectual disability (100% of males).
- Speech delay
- Fine and gross motor delay
- Coordination difficulties
- Hypotonia

Physical characteristics

- Large prominent ears
- Long face
- Large testicles
- High, broad forehead
- High arched palate
- Connective tissue problems, for example:
 - Flat feet
 - Loose joints
 - Scoliosis

Behavioural or emotional problems

- Attention-deficit disorders with or without hyperactivity
- Speech disturbances including variable pitch, perseverative speech (repetition of word or phrase) and cluttering (rapid speech with repetitions and tangential remarks)
- Autistic-like features; for example, hand flapping and biting, gaze aversion, repetitive speech mimicry (echolalia) and preoccupation with objects
- Sensory defensiveness (aversion to touch, loud noises, bright lights and strong smells)
 - Hyperarousal or anxiety
 - Mood instability with aggression and depression, especially in post-pubertal males

Females with a full mutation

At least 50% of females with a full mutation have intellectual disability.

Issues related to genetic testing

- Fragile X testing should be considered for all people with an unknown cause of developmental delay. A karyotype is necessary to detect chromosome abnormalities that may be causes of the developmental delay.
- If an individual tests positive for the fragile X full mutation or premutation, the family should be referred to a genetic service for counselling, and testing should preferably be offered to the extended family.
- Detection of carriers allows families to make informed decisions regarding family planning.
- In the case of prenatal testing, there is the option of termination of pregnancy if the fetus is affected. Genetic counselling is best provided by the specialists in the field (see *Where to refer*).

Management

Specific treatment and intervention strategies are available, which integrate multiple health professionals as well as the parents and carers, and are of great benefit to affected individuals and their families.

These include:

- Genetic counselling.
- Grief and anger counselling.
- Support for families, including the assistance of a community worker or social worker.
- Early intervention, and ongoing speech and occupational therapies.
- Management of behavioural issues (sensory defensiveness, hyperarousal and attention problems). Some clinicians find that behavioural symptoms may respond well to SSRIs (selective serotonin re-uptake inhibitors) and psychostimulants.
- Educational strategies.
- Maximising strengths.
- Pharmacological management of medical issues including epilepsy, attention disorders, aggression and mood disorders.

Role of the GP**The GP's role includes:**

- Providing support.
- Managing co-existent disease.
- Providing referral for routine hearing, vision and dental review.
- Facilitating access to allied health services.
- Providing of preventive health strategies.

For most adults with fragile X syndrome, medical management is coordinated by the GP.

8.3 Patient and further information

Support groups

Fragile X Association of Victoria
Call: (03) 9569 0858

Information

A wide range of medical and multidisciplinary assessment for children and adults, as well as educational resource material for professionals and parents, is available from:

The Fragile X Alliance Inc
263 Glen Eira Road, North Caulfield 3161
Call: (03) 9528 1910
Fax: (03) 9532 9555

Websites

The Fragile X Association of Australia: <http://www.ozemail.com.au/~fragilex>

FRAXA: <http://www.fraxa.org> (includes the very helpful listserv)

The National Fragile X Foundation: <http://www.nxf.org>

Carolina Fragile X Project: <http://www.fpg.unc.edu/~fx>

Better Health Channel: <http://www.betterhealth.vic.gov.au>
Relevant topic: Fragile X syndrome

³ High-pressure liquid chromatography.

8.4 Where to refer

Assessment of children with developmental delay

Child Development and Rehabilitation Department
Royal Children's Hospital
Flemington Road, Parkville 3052
Call: (03) 9345 5898

Developmental Disability Clinic
Department of Paediatrics
Level 4, Monash Medical Centre
Clayton Road, Clayton 3168
Call: (03) 9594 6666
For appointments, fax letter to Dr Philip Graves:
(03) 9594 6925

Early childhood intervention services

For information regarding local intervention services contact:

Disability services
Department of Human Services
Level 2, 555 Collins Street, Melbourne 3000
Call: (03) 9616 8654
Fax: (03) 9616 7403
TTY: 1300 131 525 *during business hours, for people who are deaf or have a hearing, speech or communication impairment (for the cost of a local call)*

Assessment of adults with developmental delay

Centre for Developmental Disability Health Victoria
Suite 202, 3 Chester Street, Oakleigh 3166
Clinics are held at a number of locations
For appointments, call (03) 9564 7511

Medical and multi-disciplinary assessment for children and adults

There are costs associated with attending this service.

The Fragile X Alliance Inc
263 Glen Eira Road, North Caulfield 3161
Call: (03) 9528 1910
Fax: (03) 9532 9555

Genetic testing and counselling services

Genetic Health Services Victoria
Clinics are held at a number of locations:
Royal Children's Hospital
Flemington Road, Parkville 3052
Call: (03) 8341 6270
Fax: (03) 8341 6390

Monash Medical Centre
Clayton Road, Clayton 3168
Call: (03) 9594 2026
Fax: (03) 9594 2022

Rural and regional services

(Ballarat, Bendigo, Frankston, Geelong, Mildura, Sale, Shepparton, Traralgon, Warragul, Warrnambool)

Genetic Health Services Victoria
Call: (03) 8341 6201
Fax: (03) 8341 6390