The Fragile X Association of Australia

Testing

Who should be tested?

- All people with an intellectual disability or ASD (Autism Spectrum Disorder)
- People with significant learning problems, mild cognitive deficits, ADHD and anxiety
- People with any of the physical or behavioural features of Fragile X syndrome, regardless of gender or family history
- Any individual who has a family member with a diagnosis of Fragile X syndrome or a family history of intellectual disability or developmental delay
- Women who experience early menopause and people with symptoms of Parkinson's type diseases

How to get tested?

A DNA blood test for Fragile X can be organised through your GP or paediatrician or any medical doctor. The blood may be collected by a doctor or at any pathology centre and be sent for testing. Test results are available approximately 4 to 8 weeks (NSW specifically) after the sample is taken. Result availability varies from state to state.

*The test to request is **"DNA studies for Fragile X syndrome".** 5 – 10 ml of blood should be collected into a lithium heparin or EDTA tube (ask your doctor to check which anticoagulant is required by the laboratory) and transported immediately without freezing.*

Are these tests covered by Medicare?

Fragile X DNA testing is funded by Medicare under the following conditions:

"Medicare **item 73300** in the following circumstances:

Detection of genetic mutation of the FMR1 gene by nucleic acid amplification (NAA) where:

(a) The patient exhibits intellectual disabilities, ataxia, neurodegeneration, or premature ovarian failure consistent with an FMR1 mutation; or
(b) The patient has a relative with an FMR1 mutation"

"Item 73305: Detection of genetic mutation of the FMR1 gene by southern blot where the results in item 73300 are inconclusive".

Prior to ordering these tests (73300 and 73305) the ordering practitioner should ensure the patient has given informed consent. Appropriate genetic counselling should be provided to the patient either by the treating practitioner, a genetic counselling service or by a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.

The Fragile X Association of Australia

FXAA

Who are we?

The Fragile X Association of Australia (FXAA) is a national organisation that aims to Improve the health and wellbeing of those affected by Fragile X syndrome.

Those affected include: full mutation, carriers, parents, caregivers, siblings, extended family and significant others.

What do we do?

The FXAA offers several services including:

Clinical Care and Support

Clinics:

FXAA provides access to multidisciplinary Fragile X clinics located in Melbourne and Sydney and mobile clinics located across the country. The clinics are normally composed of a medical doctor, psychologist, occupational therapist and speech pathologist. The emphasis at the clinics is to identify effective treatments and intervention strategies that will optimise the person's abilities and enhance their life.

Counselling:

The FXAA offers counselling to individuals and families that are affected by Fragile X syndrome. The counselling is free and confidential and is held on the premises of the association. Counselling is appointment based and can be conducted through telephone, Skype and face to face meetings. Counselling is available to all members and appointments or queries can be made through email and phone.

Casework:

Casework is offered to all families and individuals that are affected by Fragile X. The caseworker provides professional direction and case management to high needs families and carriers who are affected by Fragile X. The caseworker manages individual cases and acts as an advocate, source of referral and support for individuals and families.

Parent support:

The parent support arm of FXAA is through telephone support and social gatherings for families that are affected by Fragile X.

Carrier support:

The carrier support arm of FXAA is through telephone and email support.

Research and Education

Workshops:

Free workshops enable families and professionals to be educated on Fragile X syndrome and raise awareness within the community.

Research:

The FXAA supports research initiatives conducted in the academic community and maintains and relates up to date information to members of the Association.

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Fragile X

What is Fragile X Syndrome?

- Fragile X syndrome is the most common inherited cause of intellectual disability
- Fragile X syndrome appears in people of all ethnic, racial and socio economic backgrounds.
- It is estimated that as many as 100,000 Australians have Fragile X syndrome or are at risk of developing a Fragile X associated disorder.

Signs and symptoms may include:

- Anxiety
- Shyness
- ADHD
- Autistic like behaviours
- Poor eye contact
- Delayed speech development
- Tactile defensiveness
- Repetitive speech
- Aggression
- Hyperactivity
- Poor fine and gross motor skills

Physical characteristics

Physical features may be quite subtle or not present and because of this many children and adults with Fragile X syndrome appear to look normal, which may hinder diagnosis.

- Long narrow face
- Prominent ears
- High palate
- Large testicles (in post pubescent males)
- Abnormalities of connective tissues and muscle tone may result in:
    - Hyper-extensible joints (double jointedness)
    - Flat feet
    - Soft velvety skin
    - Mitral valve prolapse (heart murmur)
- Low muscle tone may cause:
    - Spinal curvature
    - Strabismus (crossed eyed or eyes)
    - Slack facial features

What causes Fragile X Syndrome?

Fragile X syndrome is caused by a mutation on the X chromosome. Females have two X chromosomes and males have one X and one Y chromosome. One specific gene near the end of the X chromosome normally contains between 6 and 50 repetitions of a specific genetic code.

For reasons which remain unclear, the regulation of the code breaks down in some people causing the number of repeats to increase. An expansion of the sequence from 50 to 200 repeats is called a premutation and may cause few or no symptoms of Fragile X syndrome. People with the premutation are known as carriers.

An increase to over 200 repeats (sometimes into the thousands) is called a full mutation and results in Fragile X syndrome. This full mutation stops production of a protein required for brain development and all brain functioning.

Will my child have a normal life?

Intellectual disability is the most significant characteristic of those with Fragile X.

Most males and approximately two thirds of females exhibit some intellectual disability. This is usually accompanied by poor fine and gross motor skills.

The range of learning problems is wide with some individuals affected by minor developmental delays. However, at the other end of the scale there can be severe intellectual disability. Most affected males fall somewhere in the middle. Males typically appear more severely affected than females, however, parents and educators are often surprised at their achievements.

Females appear less affected. However, they may experience difficulty with maths and tend to suffer from a range of anxiety disorders including social anxiety.

Strengths may include:

- Visual learning e.g. pictures, computers
- Whole word, number and pattern recognition, ‘Gestalt’ learning
- Long term and incidental memory
- Concrete, relevant tasks
- Strong imitation skills, drama
- Good functional life skills
- Friendly, good sense of humour

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Treatment

What is the appropriate treatment?

People with Fragile X syndrome generally have sensory and perceptual processing problems which distort the way they receive information and their ability to use it to learn and behave appropriately.

Currently there is no cure for Fragile X, but there are effective treatments that may improve these traits and quality of life. A multi-disciplinary therapeutic approach incorporating educational, medical, and behavioural management techniques is most beneficial. Psychological, occupational, physical and speech therapies can be incorporated as appropriate.

- A ***Doctor*** who is well-informed about the symptoms and implications of a Fragile X diagnosis is a critical member of any treatment. He/she may recommend some medications and appropriate therapies.

- A ***Psychologist*** works within a family support model, recognising the impact of disability on families across the life-span, and the importance of providing support and education across the individual's environments of school/work/day program, home and community. Focus is on a functional, practical approach in order to support individuals with Fragile X in their everyday life experiences including communication-behaviour support, social-emotional support, educational support and family support.

- An ***Occupational Therapist*** can utilise sensory integration techniques in collaboration with the child's teacher and other educational team members which can help improve these children's abilities to manage their behaviour, learn new information and increase their potential for a productive life. These strategies are especially effective when incorporated into an early intervention program.

- A ***Speech Pathologist*** aims to identify the communication needs of the individual with Fragile X syndrome within their environments and provide strategies to develop their understanding and expression of information. By doing so, the individual's understanding of their environment can increase often with a corresponding decrease in anxiety.

Are there any medical treatments available?

Medical treatment focuses on ADHD (hyperactivity) symptoms, tantrums, anxiety, mood instability and obsessive-compulsive behaviours.

- Stimulants may be prescribed alone or in combination with other medications.

- Serotonin agents target anxiety and obsessive-compulsive behaviours and often improve social behaviours and language.

- Atypical antipsychotic medications may help to stabilise mood or decrease aggression.

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Women

Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)

Female carriers may suffer from Fragile X-associated primary ovarian insufficiency (FXPOI) a problem which can lead to infertility and early menopause in some female pre-mutation carriers. Primary ovarian insufficiency (POI) is a condition in which the ovaries stop functioning normally in a woman younger than age 40. Common symptoms of POI include absent or irregular periods and infertility (http://www.fragilex.org/html/poi.htm).

POI is not menopause*, e*ven though women with POI may develop symptoms similar to those of menopause, such as hot flashes and vaginal dryness. POI differs from menopause in some important ways:

- Women with POI can still get pregnant in some cases because their ovaries may function now and then to release viable eggs; women who have completed menopause cannot get pregnant because their ovaries no longer release eggs.
- Women with POI can experience a return of menstrual periods; women who have completed menopause will not have menstrual periods again.
- Some women with POI will become pregnant without treatment, even many years after their initial diagnosis.

Women with POI and no known family history of Fragile X

Studies show that women who have FXPOI of unknown cause have a 1/50 chance of being a premutation carrier of the FMR1 gene, the gene that causes Fragile X syndrome. Given that carriers of the FMR1 premutation have a significant risk of having a child with Fragile X syndrome, testing for the FMR1 premutation in women with FXPOI is recommended.

Women with a known FMR1 premutation

Studies show that approximately 1 in 4 women with an FMR1 premutation experience FXPOI and another 1 in 4 experience early menopause. It is thought that all women with premutations have some decrease in ovarian function. However, many women with premutations are able to conceive and family planning is recommended rather than assuming decreased fertility.

Family Planning

Prenatal Testing

Prenatal diagnosis (testing for the Fragile X mutation in a baby before it is born) is available to any person shown to be a carrier of a Fragile X mutation. Prenatal fragile X testing is usually performed on the developing baby using one of two methods: either chorionic villus sampling (CVS), performed at approximately 10 weeks of pregnancy: or amniocentesis, performed between 16-20 weeks of pregnancy. All couples considering prenatal diagnosis should meet with a genetic counsellor before becoming pregnant in order to discuss the most current prenatal techniques, their limitations and benefits (http://www.fragilex.org/html/prenatal.htm).

Preimplantation Genetic Diagnosis (PGD)

If you have a child diagnosed with Fragile X, have a family history of Fragile X or you are a carrier and are considering conceiving, preimplantation genetic diagnosis may be an option in terms of future family planning.

In a normal IVF cycle, the embryologist chooses which embryo (or embryos) will be transferred to the uterus based on visual observation of the embryos as they develop. Preimplantation genetic diagnosis (PGD) allows the scientist to base their choice on the results of detailed genetic tests on the embryos, excluding those embryos that contain an obvious genetic abnormality.

For more information regarding the IVF cycle process for PGD please contact FXAA on 1300 394 636.

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Carrier Information

What is a carrier?

A **carrier** is an individual who carries an altered form of a gene which can lead to having a child or offspring in future generations with a genetic disorder. 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.

What are CGG repeats?

Fragile X Syndrome 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. 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-1protein.

What does it meant to be a carrier?

Female carriers of Fragile X Syndrome have a risk of having a child, male or female, with the premutation or full mutation. A male carrier will pass on the premutation to all of his daughters; he cannot pass on Fragile X in any form to his sons. It is estimated that as many as 1 in 280 males and 1 in 125 females are carriers.

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 issues related to being a carrier of Fragile X syndrome:

Female carriers with a premutation

- Female carriers may suffer from Fragile X-associated primary ovarian insufficiency (FXPOI) a problem which can lead to infertility and early menopause in some female pre-mutation carriers.
- In general, IQs of females with the premutation fall into the average range although some females may have difficulties with arithmetic and vocabulary
- Females may develop Fragile X Tremor Ataxia Syndrome (FXTAS). Although research is still very new in this area, some females with the premutation have been diagnosed with FXTAS. However, it is less commonly seen in females compared to males.
- Females may develop thyroid problems (20%) and/or experience muscle pains (25%)

Male carriers with a premutation

Male carriers over the age of 50 have a 20-40% chance of developing FXTAS (Fragile X Tremor Ataxia Syndrome) which is a neurological condition similar to Parkinson's disease, and may involve ataxia (unsteadiness), intention tremor (shaking) and memory problems. Initial signs of the disorder may include difficulty writing, using utensils, pouring and walking.

The symptoms progress over years or decades, until many daily tasks become extremely difficult. There may be short term memory loss, anxiety, decreased sensation to touch in the lower extremities and rigidity in movement. It is common to find these carriers misdiagnosed as having Parkinson's disease, senile dementia or Alzheimer's disease.