Guidance Statement for Females with the Fragile X Premutation

This statement is intended for use by medical practitioners to discuss with their patients.

Key Points

The Fragile X premutation does not cause Fragile X syndrome.

Females with a Fragile X premutation are generally healthy but may have an increased chance of having:

- **children with Fragile X syndrome**
- **fertility problems and/or early menopause**

Risk and counselling advice vary with the size of the premutation, and many women will not develop any symptoms or be affected. Information in this statement is mainly derived from studies of families who have a member with the full mutation and so may not apply to women ascertained from population screening.

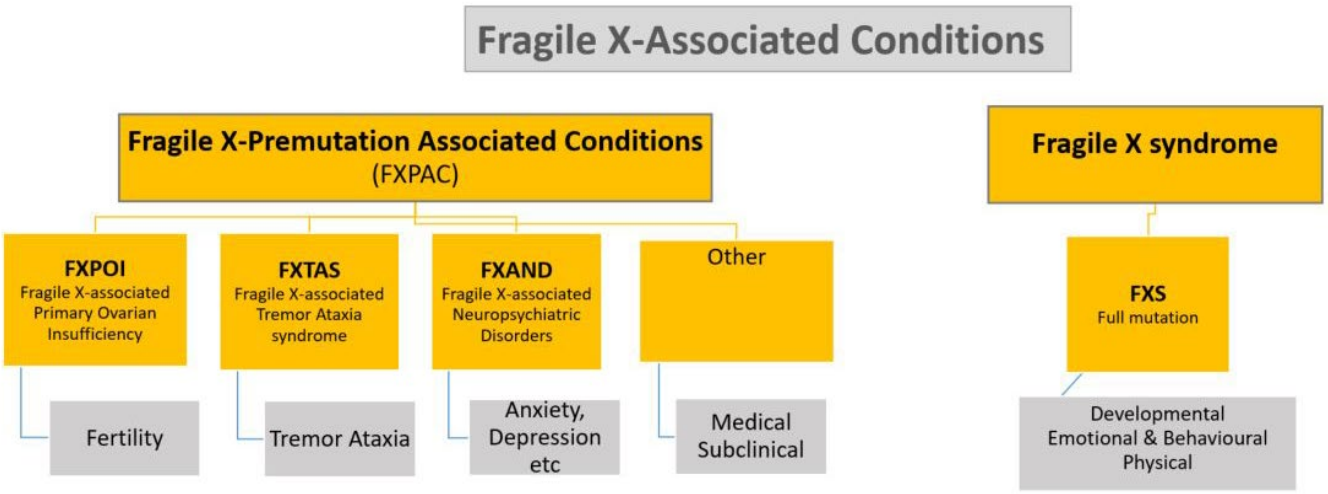


Figure: courtesy Fragile X Alliance Inc

Fragile X Full mutation	> 200 CGG repeats	Fragile X syndrome
Fragile X Premutation	55- 199 CGG repeats	FXPAC (FXPOI, FXTAS, FXAND, other)
Intermediate (Grey zone)	40 – 54 CGG repeats	Not generally considered to be associated with Fragile X syndrome or FXPAC. Not reported by all labs.

Points for medical professionals to be aware of:

1. A Fragile X premutation is a type of result that comes from Fragile X carrier testing. People with a 'premutation' (PM) have a genetic change in a gene called *FMR1*. The *FMR1* gene is associated with Fragile X syndrome (FXS) or Fragile X Premutation Associated Conditions (FXPAC). The premutation change can occur in both males and females and is an expansion of 55 to 200 CGG repeats.

2. Females with a PM have a 50% chance of passing the genetic change to their offspring. If the premutation expands to over 200 repeats in their offspring, the child can have Fragile X syndrome. This chance increases with the number of CGG repeats of the female. If a female with 55-69 CGG repeats also has 'AGG interruptions', their chance of having children with Fragile X syndrome may be lower. Only some Fragile X screening providers include AGG testing in their Fragile X carrier screen.

3. All females with the PM can have an unaffected child. Depending on their CGG expansion size and AGG interruptions, some may need to discuss with a genetic counsellor or appropriate medical practitioner reproductive options such as: Prenatal testing to see if the *FMR1* gene with the normal number of CGG repeats is inherited; IVF with pre-implantation Genetic Testing (PGT-M); Donor egg or embryo; Surrogacy; Adoption

4. Females with the PM in general do not have developmental delay as seen with Fragile X syndrome.

5. Females with the PM have a chance of developing **FXPAC** (**F**ragile **X** **P**remutation-**A**ssociated **C**onditions). This includes **FXPOI, FXTAS, FXAND** and a range of general medical conditions:

- **FXPOI** (**F**ragile **X**-associated **P**remature **O**varian **I**nsufficiency) occurs in approximately 20 - 30% of females with the PM, a third of whom will develop early menopause by age 40. The chance is lower in women with smaller CGG expansions. Because of this risk, females with the PM should seek medical advice regarding FXPOI and discussion of options including egg freezing and timing of pregnancy.

- **FXTAS** (**F**ragile **X**-associated **T**remor/**A**taxia **S**yndrome) is a Parkinsonian-like neurological disorder affecting a percentage of older PM males and less often older PM females. The chance may be lower in women with smaller CGG expansions.

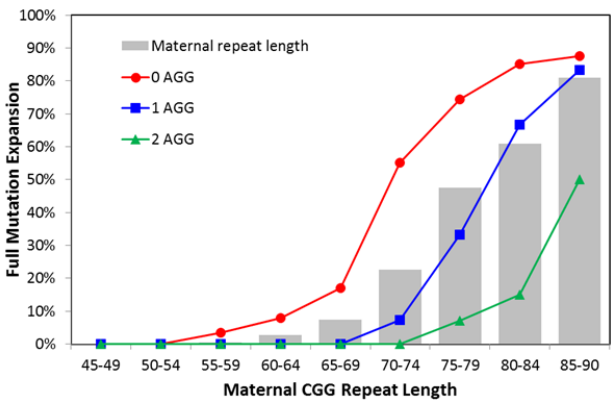
- **FXAND** (**F**ragile **X**-associated **N**europsychiatric **D**isorders) are present in a percentage of females and males and include a range of anxiety disorders, depression, insomnia, OCD, ASD, ADHD, executive function deficits, chronic fatigue and chronic pain conditions. Many of these are 'subclinical' conditions ie do not meet the criteria for a definitive disorder per se. **Other** general health conditions that may be associated with the premutation include hypertension, thyroid disorders, sleep disorders, migraine and immune-mediated disorders. FXAND and other conditions may not apply to women ascertained from population screening.

6. **Testing** of extended family members should be offered with appropriate genetic counselling to those at risk of also having the PM. In general, biological parents of someone found to carry a Fragile X gene expansion (greater than 55 CGG repeats) are tested first. If the *male parent* is found to carry the PM, then he will pass the PM to all of his daughters and none of his sons. His parents, siblings and relevant cousins should be offered testing. If the *female parent* is found to carry the PM, then all her offspring should be offered testing to determine if they have the PM, full mutation or do not carry the gene expansion. Her parents, siblings and relevant cousins should be offered testing. If possible, **use the same laboratory to request the "DNA test for fragile x syndrome"** and provide the laboratory number of the family member initially found to carry the gene. Testing for family members is covered by Medicare.

7. Management and preventive strategies are important for providing advice regarding reproductive options, ovarian insufficiency, movement and psychiatric symptoms and associated psychological issues if present.

8. CGG repeat ranges and chance of expansion to Fragile X syndrome; Maternal CGG/AGG repeat length

Maternal repeat ranges	Chance of expansion to long repeat
55 – 59[1]	0.5%
60 – 64[1]	1.7%
65 – 69[1]	7%
70 – 74[1]	21%
75 – 79[1]	47%
80 – 84[1]	62%
85 – 89[1]	81%
90 – 99[2,3]	80 – 100%
100+[2,3]	~100%



1Nolin et al, 2014; 2Nolin et al, 2003; 3Berkenstadt et al, 2017

Note: *"The term "female" in this factsheet refers to a person who has two X chromosomes and is therefore of female sex, this term does not reflect what gender the person may identify with.*

Further information:

1. Fragile X Association of Australia – www.fragilex.org.au
2. USA National Fragile X Foundation - https://fragilex.org/understanding-fragile-x/fragile-x-101/premutation-carriers/
3. *Ref:* Tassone F, et al Insight and Recommendations for Fragile X-Premutation-Associated Conditions from the Fifth International Conference on *FMR1* Premutation. Cells. 2023 Sep 21;12(18):2330. doi: 10.3390/cells12182330
4. Hagerman RJ, Protic D, Rajaratnam A, Salcedo-Arellano MJ, Aydin EY, Schneider A. Fragile X-Associated Neuropsychiatric Disorders (FXAND). Front Psychiatry. 2018 Nov 13;9:564. doi: 10.3389/fpsyt.2018.00564
5. Johnson K, Herring J, Richstein J. Fragile X Premutation Associated Conditions (FXPAC). Front Pediatr. 2020 May 27;8:266. doi: 10.3389/fped.2020.00266. PMID: 32537445; PMCID: PMC7267017.

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