Understanding your results:
Fragile X disorders

INVITAE

WHAT ARE FRAGILE X DISORDERS?

Fragile X-associated disorders are a family of inherited genetic conditions caused by changes in the gene *FMR1*, which is located on the X chromosome. *FMR1* has a set of three letters of DNA, CGG, that repeat over and over (CGG-CGG-CGG, etc.). Each set of CGGs is called a "repeat."

The number of CGG repeats determines whether a person will have a fragile X disorder. If a condition does develop, the number of CGG repeats influences the symptoms and severity. It also determines whether a person is at risk of having a child with a fragile X disorder.

WHAT DOES THIS MEAN FOR ME?

PREMUTATION (55-200 REPEATS)

Premutation carriers are individuals with 55 to 200 CGG repeats.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that can occur in premutation carriers. Symptoms typically begin after age 50 and include tremors, memory loss, dementia, lower limb weakness, and mental or behavioral changes.

Though FXTAS occurs in both genders, males are more frequently affected than females.

Not all fragile X premutation carriers develop FXTAS, but it's still important to discuss your test results with your healthcare provider or a genetic counselor to understand your risks.

Fragile X-associated premature ovarian insufficiency (FXPOI) is a reproductive condition that causes early menopause in women who are premutation carriers.

Women who are carriers of a premutation have a 20% chance of developing FXPOI. Men are not affected.

FXPOI may affect your response to IVF medications. If you are a premutation carrier, it is important to talk with your healthcare provider about your FMR1 *test result and how it may impact your ability to get pregnant.*

FULL EXPANSION (200+ REPEATS)

A full expansion occurs when an individual has 200 or more CGG repeats. Males with a full expansion do have fragile X syndrome. Females with a full expansion may or may not have symptoms of fragile X syndrome.

Fragile X syndrome (FXS) affects the nervous system and is the most common cause of inherited intellectual disability. Affected individuals display intellectual disability, behavioral and learning challenges, and various facial characteristics.

Though fragile X syndrome occurs in both genders, males are more frequently affected than females, and generally with greater severity.

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HOW ARE FRAGILE X DISORDERS INHERITED?

Depending on which parent has the premutation, future children are at risk of inheriting different CGG repeat lengths. The *FMR1* gene is located on the X chromosome. Females inherit two copies of the X chromosome and have two copies of *FMR1*. Males inherit one X and one Y chromosome and have one copy of *FMR1*. Fragile X disorders are more common and more severe in males than females because males do not have a functioning second copy of the gene to offset the effects of repeats in the first gene.

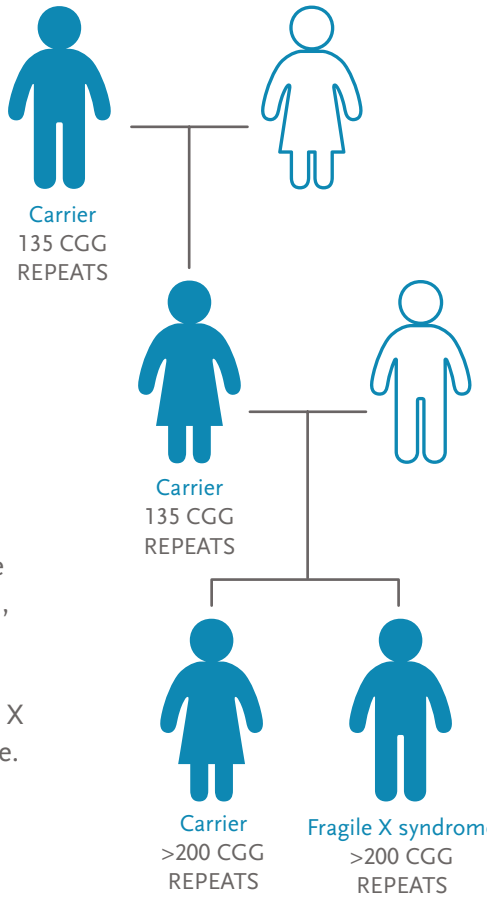
WHAT IS REPEAT EXPANSION?

Repeat expansion occurs when the number of CGG repeats increase from one generation to the next. Repeats are more likely to expand when the premutation is passed from a female carrier to her child. The repeat number typically stays the same when a male carrier passes the premutation down to a child. As the number of repeats increases, the risk of having a child with a full expansion also increases.

THE INHERITANCE OF FRAGILE X SYNDROME

The number of CGG repeats can increase from one genration to the next. When this happens, it is called an expansion. The fragile X mutation is more likely to expand when the mutation is passed from a woman to her children, as shown in this diagram. As the number of repeats increases, the risk of having a child with fragile X syndrome increases too.

When a man carries the fragile X mutation, the repeat number typically stays the same when it is passed on to his daughters.



Women have two copies of the fragile X gene (one on each X chromosome), so females with a mutation in one of their fragile X genes have a second normal copy of the gene on the other X chromosome, which may compensate. Approximately 50% of females with fragile X mutations will show some symptoms of disease.

Males only have one X chromosome, thus only one copy of the fragile X gene. Males with a mutation in their fragile X gene will have the disease, as they do not have another copy of the gene to compensate.

WHAT DOES MY CARRIER SCREENING TELL ME?

Carrier screening tells you how many CGG repeats are in your *FMR1* gene(s) so you can understand your risk of developing a fragile X disorder as well as your child's risk of inheriting a fragile X disorder.

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MALE CARRIER SCREENING RESULTS AND IMPLICATIONS

Fragile X syndrome is typically inherited from the mother so screening for men is generally not necessary. However, if you have a blood relative who is a carrier for fragile X disorders, or have tested positive on a fragile X carrier screen, talk with your healthcare provider or genetic counselor as there may be health risks to you and your daughters.

FEMALE CARRIER SCREENING RESULTS AND IMPLICATIONS

Since females have two copies of the *FMR1* gene, the result listed on your report will show two repeat length numbers, one for each copy. Each result will fall into one of four categories of repeat length listed in the table below: normal, intermediate, premutation, and full expansion. You and your future children are at risk for the conditions associated with the highest number of repeats that you carry.

Number of CGG repeats	What does this mean for me?	What does this mean for my children?
5-44 **Normal**	▪ You are not at risk of developing a fragile X disorder.	▪ Very low risk of fragile X disorders.
45-54 **Intermediate**	▪ You are not at risk of developing a fragile X disorder.	▪ Very low risk of fragile X syndrome. ▪ Each pregnancy carries a 50% chance that a child will inherit an intermediate repeat. ▪ Intermediate repeats can expand to a premutation in a child; however, they are not known to expand to full expansion range
55-200 **Premutation**	▪ You are not at risk of developing fragile X syndrome. ▪ You are at risk of developing FXPOI and/or FXTAS.	▪ Increased risk for fragile X syndrome. ▪ Each pregnancy carries a 50% chance that a child will inherit a premutation, which can increase to a full expansion in a child. ▪ The risk of expansion depends on the size of the premutation.
>200 **Full expansion**	▪ About 50% of women with a full expansion have symptoms of fragile X syndrome. It is possible to be symptom-free and carry a full expansion. ▪ You are not at risk of developing FXPOI or FXTAS.	▪ Increased risk for fragile X syndrome. ▪ Each pregnancy carries a 50% chance that a child will inherit the full expansion. ▪ A male child who inherits the full expansion will have fragile X syndrome. ▪ A female child who inherits the full expansion may or may not have fragile X syndrome.

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SHOULD I INFORM MY FAMILY IF I AM A CARRIER FOR FRAGILE X DISORDERS?

Since fragile X disorders are inherited, your close family members may be carriers as well. You may want to inform them of your carrier status to give them the opportunity to be tested.

WHERE CAN I GET MORE INFORMATION ABOUT FRAGILE X DISORDERS?

National Fragile X Foundation: www.fragilex.org
Genetics Home Reference: www.ghr.nlm.nih.gov/condition/fragile-x-syndrome

The inheritance of fragile X disorders is complex, even for genetic experts, so you may have questions. Discuss your carrier screening results with your healthcare provider or genetic counselor to better understand your test results and your options.

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