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My46 Trait Profile

Fragile X-associated premature ovarian insufficiency

Other Names: Fragile X-associated premature ovarian failure

Fragile X-associated premature ovarian insufficiency is a condition that causes a woman's ovaries to stop functioning properly earlier than is normal. It is caused by a premutation in the FMR1 gene.

Characteristics of Fragile X-associated premature ovarian insufficiency

Fragile X-associated premature ovarian insufficiency (FXPOI) is characterized by the end of menses (periods) prior to age 40 in females caused by ovaries (the reproductive organ in females) that are not functioning to their normal capacity. Thus, females with FXPOI may not produce the normal amounts of certain hormones (e.g., estrogen) and do not release eggs regularly. Common symptoms of FXPOI include irregular or absent menses, infertility, and symptoms of menopause such as hot flashes and night sweats. Approximately 1 in 250 females are FMR1 premutation carriers, however only about 20-25% of them develop FXPOI. The onset of FXPOI is usually in adults, although FXPOI has been reported in younger women (i.e., teenagers).

Diagnosis/Testing

Females with FXPOI have a specific change called a premutation in the FMR1 gene. FMR1 contains a three-letter code, CGG, that is repeated over and again, and thus it is known as a "CGG repeat." The number of CGG repeats can be different from one person to another. Females who do not have FXPOI usually have between 5 CGG repeats (e.g., CGG-CGG-CGG-CGG-CGG) and 44 CGG repeats. However, females with FXPOI have a larger number of CGG repeats between 55 and 200. These larger repeat sizes are referred to as premutations. Premutations are considered "unstable" when transmitted by a mother. This means that when a premutation is passed down from a mother to her child, the premutation may expand into a full mutation in the child (e.g., a mother with 80 CGG repeats may have a child who has over 200 CGG repeats). Repeat sizes over 200 CGG repeats are called full mutations and cause a different, but genetically related condition called fragile X syndrome (see trait profile).

The FMR1 gene makes a protein called fragile X mental retardation 1 protein. In individuals with FMR1 premutations, high levels of abnormal FMR1 substance are produced. It is not entirely understood why or how this overproduction causes FXPOI in female FMR1 premutation carriers.

Management/Surveillance

Evaluation of FXPOI often includes a reproductive endocrine evaluation (e.g., this may include blood tests to check hormone levels as well as ultrasounds of the pelvic area). It is suggested that female FMR1 premutation carriers keep a log of their menstrual cycles, note any unusual patterns, and share this log with their healthcare provider.

Females with FXPOI may still get pregnant; it is estimated that approximately 5-10% of females with FXPOI get pregnant after being diagnosed.

In addition to FXPOI, female FMR1 premutation carriers have an increased risk of developing thyroid disease (e.g., underactive thyroid gland) and chronic muscle pain. Both males and females with a FMR1 premutation have an increased chance to develop fragile X-associated tremor/ataxia syndrome (see trait profile).

Mode of inheritance

FXPOI is inherited in an X-linked dominant pattern. Since the FMR1 gene is located on the X-chromosome, females have two copies of the gene. This means that females with a premutation in one copy of their FMR1 genes are at risk of developing FXPOI. Not all females with a FMR1 premutation develop FXPOI.

Risk to family members

Female premutation carriers have a 50% chance of passing on their abnormal FMR1 gene copy with every pregnancy. If a female FMR1 premutation carrier passes on the abnormal FMR1 gene to her child, there is a chance the premutation will either expand to a full mutation, potentially causing fragile X syndrome, or the premutation will not expand and remain a premutation in the child.

Male FMR1 premutation carriers have a 100% chance of passing on their abnormal FMR1 gene copy to all of their daughters. Premutations do not usually expand when passed from fathers to daughters. This means that the daughters are usually premutation carriers and are at risk of developing FXPOI.

Special considerations

None

Resources

National Fragile X Foundation
http://www.fragilex.org/fragile-x-associated-disorders/fxpoi/
Genetics Home Reference: Fragile X-associated primary ovarian insufficiency
http://ghr.nlm.nih.gov/condition/fragile-x-associated-primary-ovarian-insufficiency

References

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Saul RA, Tarleton JC. (Updated 26 April 2012). FMR1-Related Disorders. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.ncbi.nlm.nih.gov/books/NBK1384/. Accessed [02/13/2013].

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