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My46 Trait Profile

Fragile X-associated tremor/ataxia syndrome

Fragile X-associated tremor/ataxia syndrome (FXTAS) is an adult-onset genetic condition characterized by movement and cognitive problems. It is caused by a premutation in the FMR1 gene.

Characteristics of Fragile X-associated tremor/ataxia syndrome

Common features of fragile X-associated tremor/ataxia syndrome (FXTAS) include ataxia (i.e., balance problems), intention tremors (i.e., rhythmic shaking only during purposeful movement such as when writing), memory loss, mood changes, and cognitive decline (i.e., decreased intellectual function). Individuals with FXTAS often have abnormalities detected by brain imaging tests (e.g., MRI) that include characteristic findings (e.g. white matter lesions) in specific areas of the brain and/or brain stem. FXTAS is more common in males, and symptoms usually occur after 50 years of age. Females can also develop FXTAS, although the symptoms tend to be less severe. Studies suggest that, approximately 40-45% of males and 8-16% of females over the age of 50 who have a FMR1 premutation develop symptoms of FXTAS.

Diagnosis/Testing

Individuals with FXTAS have a specific change called a premutation in the FMR1 gene. This gene 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. Individuals who do not have FXTAS usually have between 5 CGG repeats (e.g., CGG-CGG-CGG-CGG-CGG) and 44 CGG repeats. However, individuals with FXTAS have a larger repeat size between 55 and 200 CGG repeats. These larger repeat sizes are referred to as premutations. Both males and females with a FMR1 premutation have an increased chance to develop FXTAS.

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). Thus, female premutation carriers have an increased risk of having a child with fragile X syndrome.

The FMR1 gene makes a protein called fragile X mental retardation 1 protein. In individuals with FMR1 premutations, high levels of an abnormal FMR1 protein are produced and may accumulate in the brain and nerve cells in individuals with FXTAS. This overproduction and accumulation is thought to explain the features seen in FXTAS.

Management/Surveillance

Management of FXTAS often involves neurological evaluations, brain imaging tests, and behavioral and psychological assessments. Certain medications to treat or reduce tremors may be helpful. Because loss of balance is a common feature seen in FXTAS, creating a safe home environment is important.

Intention tremors and ataxia are often the first signs of FXTAS. As the condition progresses, resting tremors (i.e., rhythmic shaking when the muscles are relaxed and at rest), stiffness or rigidity, and bradykinesia (i.e., very slow movements) are often seen. Many individuals with FXTAS are misdiagnosed as having Parkinson’s disease because the symptoms can appear very similar.

Since FXTAS is more common in males, more is known about how often symptoms develop in males as compared

to females. As illustrated below, the chance of a male with a FMR1 premutation developing FXTAS increases with age.

Age of a male FMR1 premutation carrier	Approximate risk for him developing FXTAS
50-59 years	17%
60-69 years	38%
70-79 years	47%
Over 80 years	75%

For example, a male FMR1 premutation has a 17% chance of developing FXTAS at age 50. This chance increases to 75% at 81 years of age.

Signs of FXTAS are found in approximately 8-16% of female FMR1 premutation carriers who are over the age of 50. The neurological symptoms (i.e., tremor and/or ataxia) seen in females with FXTAS are usually less severe than the symptoms seen in males. In addition to FXTAS, female FMR1 premutation carriers have an increased chance to develop fragile X-associated premature ovarian insufficiency (see trait profile), thyroid disease (e.g., underactive thyroid gland), and chronic muscle pain.

Mode of inheritance

FXTAS is inherited in an X-linked dominant pattern. Since the FMR1 gene is located on the X-chromosome, males have one copy of the gene, and females have two copies of the gene. Having one copy of an abnormal FMR1 gene is enough to increase the chance of developing FXTAS. This means that males with a premutation in their one and only copy of the FMR1 gene are at risk of developing FXTAS. Similarly, females with a premutation in one copy of their FMR1 genes are also at risk of developing FXTAS. However, females usually have less severe symptoms than males. Not all individuals with a FMR1 premutation develop FXTAS.

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 FXTAS.

Special considerations

None

Resources

National Fragile X Foundation
http://www.fxtas.org
Genetics Home Reference: Fragile X-associated tremor/ataxia syndrome
http://ghr.nlm.nih.gov/condition/fragile-x-associated-tremor-ataxia-syndrome

References

Apartis, E. et al. (2012)."FXTAS: new insights and the need for revised diagnostic criteria." Neurology, 79(18): 1898-1907.
Berry-Kravis, E. et al. (2007)."Fragile X-Associated Tremor/Ataxia Syndrome: Clinical Features, Genetics, and Testing Guidelines." Movement Disorders 22(14): 2018-2030.
Finucane, B. et al. (2012)."Genetic counseling and testing for FMR1 gene mutations: practice guidelines of the national society of genetic counselors." Journal of Genetic Counseling, 21(6): 752-760.

Rodriguez-Revenga, L. et al. (2009)."Penetrance of FMR1 premutation associated pathologies in fragile X syndrome families." European Journal of Human Genetics 17(10): 1359-1362.
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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