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My46 Trait Profile

Fragile X syndrome

Fragile X syndrome is a genetic condition mainly characterized by intellectual disability and caused by mutations in the FMR1 gene on the X chromosome.

Characteristics of Fragile X syndrome

Fragile X syndrome is the most common inherited cause of intellectual disability. Males with fragile X syndrome usually have moderate intellectual disability, while females with fragile X syndrome usually have mild intellectual disability. Developmental delays (i.e., delays in speech, language, motor, social, or thinking skills) are seen in almost every individual with fragile X syndrome. Individuals with fragile X syndrome may also have behaviors (e.g., poor eye contact, repetitive use of language, hand-flapping) commonly observed in children with autism, impulsivity, hyperactivity, and social anxiety. Mild heart abnormalities such as mitral valve prolapse (i.e., a leaky heart valve), strabismus (i.e., problems aligning the eyes), very flexible fingers, and flat feet are common features of the condition. Most adult males with fragile X syndrome have characteristic craniofacial features including macrocephaly (i.e., a large head), a long and narrow face, a prominent chin, and large ears.

Diagnosis/Testing

Changes or mutations in a gene called FMR1 cause fragile X syndrome. This gene makes a protein called the fragile X mental retardation 1 protein (FMRP) that plays an important role in normal brain development. The FMR1 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 fragile X syndrome usually have between 5 CGG repeats (e.g., CGG-CGG-CGG-CGG-CGG) and 44 CGG repeats. However, individuals with fragile X syndrome usually have an abnormally high number of CGG repeats that can range from over 200 to several thousand repeats. A large number of CGG repeats is known as an expanded CGG repeat and is referred to as a “full mutation.” These full mutations may have another chemical change called “methylation.” This means a chemical called a methyl group (a carbon atom and three hydrogen atoms) attaches to it. When a gene is “methylated,” it has been “turned off” and does not make a protein. Individuals with fragile X syndrome typically have a methylated full mutation, so the FMR1 gene is turned off and does not make the FMRP.

Management/Surveillance

Management of fragile X syndrome often involves intensive educational and behavioral therapies. Treatment with certain medications may also help with the behavioral features seen in fragile X syndrome. Regular physical exams including monitoring for high blood pressure and the development of mitral valve prolapse are also recommended.

Mode of inheritance

Fragile X syndrome 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. Thus, if males have a methylated full mutation, their one and only copy of the FMR1 gene does not work, and they have fragile X syndrome. Females can also have fragile X syndrome, however they usually have milder intellectual disability. Because females have two copies of the FMR1 gene, if they have one copy of a methylated full mutation, their other FMR1 gene is

usually working. This allows for some FMR1 protein to be made. This is why only about half of females with a full mutation have fragile X syndrome and why they usually have less severe intellectual disability than do males.

The number of FMR1 CGG repeats that an individual has falls into one of four categories (see table below).

Category of FMR1 CGG repeat size	Number of FMR1 CGG repeats
Normal	5-44
Intermediate	45-54
Premutation	55-200
Full mutation	Over 200

Individuals with 45 to 54 CGG repeats (i.e., the intermediate range) are not at risk of having a child with fragile X syndrome. However, the number of CGG repeats that are passed on by a female with CGG repeats in this range may increase slightly in the next generation (e.g., a mother with 50 CGG repeats may have a child with 55 CGG repeats). Premutation carriers are individuals who have between 55 and 200 CGG repeats. 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). Thus, female premutation carriers are at risk of having a child with fragile X syndrome.

Most premutation carriers do not have intellectual disability, but some may have mood disorders such as anxiety or depression. Premutation carriers are at risk for a condition called fragile X-associated tremor/ataxia syndrome (see trait profile)and female premutation carriers are also at risk for a condition called fragile X-associated primary ovarian insufficiency (see trait profile).

Risk to family members

Mothers of individuals with fragile X syndrome are either carriers of a premutation (i.e., 55-200 CGG repeats) or full mutation (i.e., over 200 CGG repeats). Female premutation carriers have a 50% chance of passing on their abnormal FMR1 gene copy with every pregnancy, and are at risk of having a child with fragile X syndrome. However, the chance of a premutation in a mother expanding to a full mutation in her child corresponds to the number of CGG repeats in her premutation (i.e., the higher the number, the higher the risk). Females with a full mutation (i.e., over 200 CGG repeats) have a 50% chance in every pregnancy of having a male with fragile X syndrome.

Male 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 do not have fragile X syndrome. Males with fragile X syndrome generally do not reproduce.

Special considerations

None

Resources

National Fragile X Foundation
http://www.fragilex.org
FRAXA Research Foundation
http://www.fraxa.org
Genetics Home Reference: Fragile X syndrome
http://ghr.nlm.nih.gov/condition/fragile-x-syndrome
Medical Home Portal: Fragile X syndrome
http://www.medicalhomeportal.org/diagnoses-and-conditions/fragile-x-syndrome/description

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