Fragile XE syndrome

Other Names: FRAXE intellectual disability, FRAXE syndrome

_Fragile XE syndrome is a rare genetic condition mainly characterized by mild intellectual disability and caused by mutations in the FMR2 gene on the X chromosome._

Characteristics of Fragile XE syndrome

Fragile XE syndrome is a rare genetic condition associated with mild intellectual disability in the absence of physical abnormalities. The incidence of Fragile XE syndrome is estimated at approximately 1 in 25,000 to 1 in 50,000 males. Developmental delays (i.e., delays in speech, language, motor, social, or thinking skills) are often seen in individuals with this condition. Affected individuals may also have behaviors commonly observed in children with autism (e.g., poor eye contact, repetitive use of language, hand-flapping), attention problems, and hyperactivity.

Diagnosis/Testing

Changes or mutations in a gene called FMR2 cause Fragile XE syndrome. This gene makes a protein called the fragile X mental retardation 2 protein (FMR2P) that plays an important role in normal brain development. The FMR2 gene contains a three-letter code, CCG, that is repeated over and again, and thus it is known as a “CCG repeat.” The number of CCG repeats can be different from one person to another. Individuals who do not have fragile X syndrome usually have between 6 CCG repeats (e.g., CCG-CCG-CCG-CCG-CCG-CCG) and 30 CCG repeats. However, individuals with Fragile XE syndrome usually have an abnormally high number of CCG repeats (i.e., over 200 CCG repeats). A large number of CCG repeats is known as an expanded CCG 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 XE syndrome typically have a methylated full mutation, so the FMR2 gene is turned off and does not make the FMR2P. Instead of a methylated full mutation, some individuals with Fragile XE syndrome have a missing piece (i.e., deletion) within the FMR2 gene.

Management/Surveillance

Management of Fragile XE syndrome often involves intensive educational and behavioral therapies. Treatment with certain medications may also help with the behavioral features seen in Fragile XE syndrome.

Mode of inheritance

Fragile XE syndrome is inherited in an X-linked pattern. Since the FMR2 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 FMR2 gene does not work, and they have Fragile XE syndrome. It is thought that most females with a methylated full mutation do not have features of the condition.

The number of FMR2 CCG repeats that an individual has falls into one of four categories (see table below).

<table>
<thead>
<tr>
<th>Category of FMR2 CCG repeat size</th>
<th>Number of FMR2 CCG repeats</th>
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<tbody>
<tr>
<td>[Table content]</td>
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<tr>
<td>Normal</td>
<td>6-30</td>
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<tr>
<td>----------------</td>
<td>------</td>
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<tr>
<td>Intermediate</td>
<td>31-60</td>
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<tr>
<td>Premutation</td>
<td>61-200</td>
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<tr>
<td>Full mutation</td>
<td>Over 200</td>
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</tbody>
</table>

Individuals with 31 to 60 CCG repeats (i.e., the intermediate range) are not at risk of having a child with Fragile XE syndrome. However, the number of CCG repeats that are passed on by a parent with CCG repeats in this range may increase slightly in the next generation (e.g., a mother with 45 CCG repeats may have a child with 50 CCG repeats).

Premutation carriers are individuals who have between 61 and 200 CCG repeats. Premutations are considered “unstable” when transmitted by a parent. This means that when a premutation is passed down from a parent to her child, the premutation may expand into a full mutation in the child (e.g., a mother with 80 CCG repeats may have a child who has over 200 CCG repeats). Thus, premutation carriers are at risk of having a child with Fragile XE syndrome.

**Risk to family members**

Female premutation carriers have a 50% chance of passing on their abnormal FMR2 gene copy with every pregnancy, and are at risk of having a child with Fragile XE syndrome. However, the chance of a premutation in a mother expanding to a full mutation in her child corresponds to the number of CCG repeats in her premutation (i.e., the higher the number, the higher the risk). Females with a full mutation (i.e., over 200 CCG repeats) have a 50% chance in every pregnancy of having a male with Fragile XE syndrome.

**Special considerations**

None

**Resources**

**References**


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Created by: Seema Jamal, MSc, LCGC