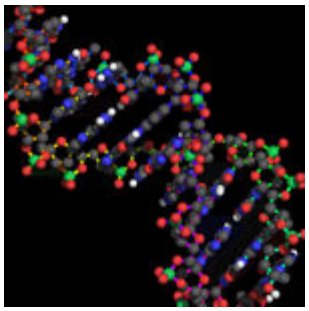
How Does the Premutation Differ From the Full Mutation?

Category	CGG repeats	Methylation of FMR1	Female	Male
Stable	6 to ~45	Unmethylated	Not affected	Not affected
Gray zone	~45 to ~55	Unmethylated	Not affected	Not affected
Premutation	~55 to ~200	Unmethylated	Usually not affected	Usually not affected
Full mutation	>200	Completely methylated	~50% affected	All affected

The major factor that determines the presence or absence of fragile X syndrome is the number of CGG repeats in the FMR1 (fragile X mental retardation) gene on the X chromosome. Typically, if the number of repeats is in excess of 200, it triggers the methylation of the CpG island, a regulatory region for the FMR1 gene. As a result, the production of FMRP (fragile X mental retardation protein) is shut off and the absence of FMRP results in fragile X syndrome.



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Most humans are in the stable category for the FMR1 gene. The most common number of repeats is 30. They do not have fragile X syndrome, and they almost always pass on a stable version to their children.

Individuals who have from about 45 to about 55 CGG repeats are in the gray zone. They do not have fragile X syndrome. While they usually pass on a stable version to their children, they are somewhat more likely than those in the stable category to have children with an increased number of CGG repeats.

People with about 55 to about 200 are in the premutation range. They generally have few or no symptoms of fragile X syndrome. However, recent studies have shown that some have subtle intellectual, behavioral, or physical symptoms.

People with more than 200 CGG repeats have the full mutation. All males with the full mutation will experience significant symptoms. Some females with the full mutation will have symptoms of fragile X but in general, the severity is decreased.

Finally, there are individuals who do not fall cleanly in any of these categories. Some people exhibit mosaicism; their cells vary as to the repeat size or degree of methylation. The impact of fragile X syndrome on these individuals depends on the percentage of cells that are affected and the tissues that are involved.

There are also exceptional individuals who have more than 200 CGG repeats but the FMR1 gene is not methylated. Their range of symptoms is broad, but they experience much milder characteristics of fragile X syndrome.

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