

AGG Interruptions and Fragile X Inheritance

CGG repeats are the magic number that indicates full mutations or premutations, and that's usually it. We envision a long tract of CGGCGGCGGCGG over and over again, as the genetic counselor or doctor described. Here, we look at "AGG interruptions" and their relation to these DNA patterns.

An Overview of the Importance of AGG Interruptions

First, a quick genetics review.

DNA is a strand of chemicals, called nucleotides. The nucleotides that make up DNA are adenine, thymine, cytosine, and guanine (abbreviated as A, T, C and G). So a CGG repeat is a triplet of cytosine-guanine-guanine. The pattern of nucleotides — such as ATCGATCG — makes up a gene that instructs the cell on how to make or regulate proteins.

In the 1990s, after the discovery of the *FMR1* gene and the CGG repeat expansion that causes Fragile X syndrome, Fragile X experts began talking about a different DNA pattern called an AGG interruption, which occurs between about every nine or 10 CGGs.

In the normal or typical Fragile X gene (5–45 repeats), you might have a 30-CGG-repeat pattern that has 10 CGGs – 1 AGG – 10 CGGs – 1 AGG – 10 CGGs. These AGG "interruptions" act as a sort of anchor, keeping the 30-repeat *FMR1* gene stable, like fence posts every 10 feet in a long fence.

As DNA samples were being studied by Fragile X researchers, they found that while some individuals had AGG interruptions every 9–10 CGG repeats, some lost them as the repeats got bigger. So a person who has 60 CGG repeats might have 10 CGGs – 1 AGG – 10 CGGs – 1 AGG – 40 CGGs.

This led to two questions regarding the presence or pattern of AGG interruptions: Do the number or placement of AGG interruptions affect the stability of the FMR1 gene? And why do some premutations expand and some not?

A study by Dr. Sarah Nolin at Institute of Basic Research in New York, Dr. Elizabeth Berry-Kravis at Rush Medical Center in Chicago, and Asuragen Inc. in Austin, Texas, looked at how AGG interruptions affect the stability of the premutation, and how to develop and use the technology that would identify these AGG interruptions in Fragile X testing.

The study found that if there were 33 or fewer CGGs in a row beyond the last AGG, then the premutation usually didn't expand. But when there were 39 or more CGGs in a row after the last AGG, without any AGG interruptions, then the premutation was usually unstable (expanding by one or more CGG repeats). This helps us understand why some premutations with, for example, 62 CGG repeats, appear stable over generations, whereas some with the same number of 62 repeats expand over subsequent generations. It's because the one with a long tract (>39 repeats) of CGG repeats without an AGG "anchor" is more likely to expand than one with properly interspersed AGG interruptions.

The technology that was developed to identify the presence and placement of the AGG interruptions is exciting. Asuragen, in cooperation with the UC Davis MIND Institute, has developed a unique type of PC test called AmplideX. It can identify the AGG interruptions in both males and females and in both normal and expanded

FMR1 genes. Since this study, additional work has been done to create the Xpansion Interpreter test.

For scientific reasons, labs have had a hard time finding AGG interruptions, especially in women. This new technology overcomes these hurdles. Variations on a genetic testing method called polymerase chain reaction, or PCR, reveal the number and location of AGG interruptions. Three different PCR studies done together show very different patterns of the CGG repeat region when AGG interruptions are present. Specially trained experts in a laboratory can review all three studies to solve the problem of where the AGG interruptions are located.

If you are interested in your options for obtaining AGG interruption testing, speak with your genetic counselor or provider.

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Why it Matters

There are a number of reasons why this issue of AGG interruptions is important.

If you or a family member have a premutation that hasn't expanded to a full mutation, this technology may give you more accurate risk figures for that premutation to expand.

It is possible that the number of AGG interruptions may contribute to or affect the risk for FXPOI or FXTAS. The risk for FXPOI is about 20%–25% in female premutation carriers and the risk for FXTAS is about 30%–40% in male and 5%–8% in female carriers. At this point we don't have good predictors of who may develop these two conditions. It is possible that this technology identifying AGG interruptions may lead us to better predict the group at highest (and lowest) risk for these Fragile X-associated disorders.

There is a very real possibility that you may more often hear, "I have 65 repeats with three AGG interruptions, ya-hoo!"

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