

The ABCs—and Xs—of FXTAS Genetics

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Fragile X-associated tremor/ataxia syndrome (FXTAS) was first described in grandfathers of children with fragile X syndrome (FXS) in 2001 by Dr. Randi Hagerman and her group at the UC Davis M.I.N.D. Institute. These grandfathers, all over 50 years of age and carriers of the FMRI premutation, were generally healthy until the onset of FXTAS symptoms. We now know that FXTAS can also occur in females (also over 50 years of age), though the incidence is much lower and is usually accompanied by milder symptoms. Initially, most cases of FXTAS were identified in families with FXS, but now cases are often diagnosed in adult neurology clinics. That means some newly diagnosed families have never heard of Fragile X.

The symptoms and course of FXTAS are described in the adjoining article by Dr. Maureen Leehy. Here we review the genetics of FXS and FXTAS, and who is at risk for the latter.

FXTAS GENETICS

FXTAS is due to a change in the Fragile X gene (called the FMRI gene) on the X chromosome. Genes are the units of heredity that are responsible for making or regulating proteins in our bodies. They are found on chromosomes, of which most individuals have 46. Two of these chromosomes are sex chromosomes—two Xs in females and an X and Y in males. The gene is like a factory with different parts—the part involved in Fragile X is called the promoter. The promoter of the FMRI gene contains a specific pattern of DNA (the molecule that makes up your genes) called a CGG repeat. A normal FMRI gene contains about 5-45 CGG repeats. Individuals who have a Fragile X premutation (often called carriers) have about 55-200 CGG repeats, and those with a full mutation have over 200 CGG repeats, causing fragile X syndrome.

Individuals with 45-54 repeats are said to have a gene in the “intermediate” or “grey zone” range. These genes are stable in most families, though some families show instability (changes of one or more CGG repeats). There are no reports of grey zone genes leading to the birth of a child with FXS or to any of the symptoms associated with being a carrier such as FXTAS or ovarian dysfunction.

At this time it is estimated that symptoms of FXTAS occur in about 30-40 percent of males with a premutation and less than 5 percent of females with a premutation. Early studies suggest that the risk for FXTAS increases in men as they get older (this is called age-related penetrance). The risk in males from 50-59 years old with a premutation is approximately 17 percent; ages 60-70 approximately 38 percent; ages 70-80 years approximately 47 percent; and over 80, about 74 percent.

FEMALES AND THE FMRI GENE

In females with the premutation, the lower incidence and milder symptoms of FXTAS occur for a number of reasons. Since females have two X chromosomes, their other, presumably normal X chromosome provides some protection from the effects of the X with the premutation. Also, in each cell of the female body, one of the Xs is randomly activated (turned on) while the other is turned off. The activation ratio is the ratio of cells with the premutation X turned on to those with the normal X turned on. If you have a low activation ratio that means you have more of the premutation Xs turned on (and thus fewer of the normal Xs activated). This may account for those women who do get FXTAS, as they have less protection from their normal X chromosome.

Because the FMRI gene is on the X chromosome, it is inherited in a specific genetic pattern, called X-linked inheritance. The premutation can occur in both males and females, as they both have at least one X chromosome. (As mentioned above, females usually have two X chromosomes.) The premutation can potentially expand to a full mutation when passed from a mother to her offspring—both boys and girls. In boys the full mutation will cause fragile X syndrome. Because of their second, presumably normal X chromosome, girls with a full mutation can have anywhere from subtle or mild to significant features of FXS.

All women with a premutation (as well as those with a full mutation) are at some risk to have a child with FXS. A woman has a 50/50 chance of passing on her X with the premutation (which can expand to a full mutation) and a 50/50 chance of passing on her X with the normal FMRI gene. The risk for a premutation to expand to a full mutation is dependent on her number of CGG repeats—the higher the number, the greater the risk of expansion to a full mutation in her children. Females with a premutation also have increased incidence of early menopause, infertility and ovarian dysfunction, also known as premature ovarian failure (POF). Finally, as mentioned above, a small number of females with the premutation have developed FXTAS.

MALES AND THE FMRI GENE

A man with a premutation will pass it on to all of his daughters and none of his sons (he passes his Y chromosome on to his sons). The premutation tends to stay stable in sperm, therefore daughters of men with a premutation usually have repeat sizes somewhat similar to their fathers. All daughters of male premutation carriers are premutation

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