FMR1 Gene

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Fragile X mental retardation 1

genes

1. Normal Function

The *FMR1* gene provides instructions for making a protein called FMRP. This protein is present in many tissues, including the brain, testes, and ovaries. In the brain, it may play a role in the development of connections between nerve cells (synapses), where cell-to-cell communication occurs. The synapses can change and adapt over time in response to experience (a characteristic called synaptic plasticity). FMRP may help regulate synaptic plasticity, which is important for learning and memory. The protein's role in the testes and ovaries is not well understood.Researchers believe that FMRP acts as a shuttle within cells by transporting molecules called messenger RNA (mRNA), which serve as the genetic blueprint for making proteins. FMRP likely carries mRNA molecules from the nucleus to areas of the cell where proteins are assembled. FMRP also helps control when the instructions in these mRNA molecules are used to build proteins, some of which may be important for functioning of the nerves, testes, or ovaries.One region of the *FMR1* gene contains a particular DNA segment known as a CGG trinucleotide repeat, so called because this segment of three DNA building blocks (nucleotides) is repeated multiple times within the gene. In most people, the number of CGG repeats ranges from fewer than 10 to about 40. This CGG repeat segment is typically interrupted several times by a different three-base sequence, AGG. Having AGG scattered among the CGG triplets appears to help stabilize the long repeated segment.

2. Health Conditions Related to Genetic Changes

2.1 Fragile X-Associated Primary Ovarian Insufficiency

A trinucleotide repeat expansion in the *FMR1* gene increases a woman's risk of developing a condition called fragile X-associated primary ovarian insufficiency (FXPOI). In this condition, the CGG trinucleotide repeat in the *FMR1* gene is repeated about 55 to 200 times, which is referred to as a premutation. Women who develop FXPOI may experience irregular menstrual cycles, an inability to have children (infertility), early menopause, and elevated levels of a hormone known as follicle stimulating hormone (FSH). About 16 to 20 percent of women with a premutation have FXPOI, which leads to abnormal menstrual cycles and elevated FSH levels before age 40 and often causes infertility.

For unknown reasons, the premutation leads to the overproduction of abnormal *FMR1* mRNA that contains the repeat expansion. Researchers believe that the abnormal mRNA causes the signs and symptoms of FXPOI. It is thought that the mRNA attaches (binds) to other proteins and keeps them from performing their functions. In addition, the repeats make producing protein from the blueprint more difficult, and consequently, some people with the *FMR1* gene premutation have lower than normal amounts of FMRP. As a result, they may have mild versions of the physical features seen in fragile X syndrome (described above), such as prominent ears, and may experience emotional problems such as anxiety or depression.

2.2 Fragile X-Associated Tremor/Ataxia Syndrome

Men, and some women, with an *FMR1* gene premutation are at increased risk of developing a disorder known as fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is characterized by progressive problems with movement (ataxia), tremor, memory loss, reduced sensation in the lower extremities (peripheral neuropathy), and mental and behavioral changes. The disorder usually develops late in life and worsens over time.

As in FXPOI (described above), the premutation causes overproduction of abnormal *FMR1* mRNA containing the expanded repeat region, and researchers believe that this abnormal mRNA causes FXTAS. The abnormal mRNA has been found in clumps of proteins and mRNA (intranuclear inclusions) that are found in brain and nerve cells in people with FXTAS. Some researchers speculate that the proteins found in the inclusions cannot perform their normal functions, which could lead to the signs and symptoms of FXTAS. Another hypothesis is that the inclusions could cause the death of nerve cells important for movement and mental function. However, the exact role the inclusions play in the development of the disorder is unknown.

2.3 Fragile X Syndrome

Almost all cases of fragile X syndrome are caused by an expansion of the CGG trinucleotide repeat in the *FMR1* gene. In these cases, CGG is abnormally repeated more than 200 times, which makes this region of the gene unstable. As a result, the *FMR1* gene is turned off (silenced) and makes very little or no protein. A loss or shortage of FMRP disrupts normal functions of nerve cells and, consequently, the nervous system, causing severe learning problems, intellectual disability, and the other features of fragile X syndrome. About one-third of males with an *FMR1* gene mutation and the characteristic signs of fragile X syndrome also have features of autism spectrum disorders that affect communication and social interaction.

Fewer than 1 percent of all cases of fragile X syndrome are caused by other changes in the *FMR1* gene. Mutations may delete part or all of the gene or change one of the building blocks (amino acids) used to make FMRP. These genetic changes alter the 3-dimensional shape of the protein or prevent any protein from being produced. The abnormal or missing protein disrupts nervous system functions, leading to the signs and symptoms of fragile X syndrome.

2.4 Other Disorders

The *FMR1* gene premutation (55 to 200 CGG repeats) is associated with a variety of neurological problems grouped as fragile X-associated neuropsychiatric disorders (FXAND). Children with a premutation can have learning disabilities, attention-deficit/hyperactivity disorder (ADHD), intellectual disability, or developmental disorders that affect communication and social interaction (such as autism spectrum disorder). Some adults with a premutation have emotional or psychiatric problems, such as depression, anxiety, obsessive compulsive disorder, extreme tiredness (fatigue), chronic pain, or difficulty sleeping (insomnia). It is estimated that approximately half of people with a premutation have one or more of these problems. The neuropsychiatric abnormalities are thought to be caused by an abundance of abnormal *FMR1* mRNA that impairs the function of other proteins.

3. Other Names for This Gene

- FMR1_HUMAN
- FMRP
- FRAXA
- Protein FMR-1

References

1. Bretherick KL, Fluker MR, Robinson WP. FMR1 repeat sizes in the gray zone and high end of the normal range are associated with premature ovarian failure. HumGenet. 2005 Aug;117(4):376-82.
2. Hagerman R, Hagerman P. Advances in clinical and molecular understanding ofthe FMR1 premutation and fragile X-associated tremor/ataxia syndrome. LancetNeurol. 2013 Aug;12(8):786-98. doi: 10.1016/S1474-4422(13)70125-X. Review.
3. Hagerman RJ, Berry-Kravis E, Hazlett HC, Bailey DB Jr, Moine H, Kooy RF,Tassone F, Gantois I, Sonenberg N, Mandel JL, Hagerman PJ. Fragile X syndrome.Nat Rev Dis Primers. 2017 Sep 29;3:17065. doi: 10.1038/nrdp.2017.65. Review.
4. Hagerman RJ, Protic D, Rajaratnam A, Salcedo-Arellano MJ, Aydin EY, Schneider A. Fragile X-Associated Neuropsychiatric Disorders (FXAND). Front Psychiatry.2018 Nov 13;9:564. doi: 10.3389/fpsyt.2018.00564.
5. Hessl D, Wang JM, Schneider A, Koldewyn K, Le L, Iwahashi C, Cheung K, TassoneF, Hagerman PJ, Rivera SM. Decreased fragile X mental retardation proteinexpression underlies amygdala dysfunction in carriers of the fragile Xpremutation. Biol Psychiatry. 2011 Nov 1;70(9):859-65. doi:10.1016/j.biopsych.2011.05.033.

6. Hunsaker MR, Greco CM, Spath MA, Smits AP, Navarro CS, Tassone F, Kros JM,Severijnen LA, Berry-Kravis EM, Berman RF, Hagerman PJ, Willemsen R, Hagerman RJ,Hukema RK. Widespread non-central nervous system organ pathology in fragile Xpremutation carriers with fragile X-associated tremor/ataxia syndrome and CGGknock-in mice. Acta Neuropathol. 2011 Oct;122(4):467-79. doi:10.1007/s00401-011-0860-9.
7. Hunter JE, Berry-Kravis E, Hipp H, Todd PK. FMR1 Disorders. 1998 Jun 16[updated 2019 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): Universityof Washington, Seattle; 1993-2020. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1384/
8. Jacquemont S, Hagerman RJ, Leehey MA, Hall DA, Levine RA, Brunberg JA, ZhangL, Jardini T, Gane LW, Harris SW, Herman K, Grigsby J, Greco CM, Berry-Kravis E, Tassone F, Hagerman PJ. Penetrance of the fragile X-associated tremor/ataxiasyndrome in a premutation carrier population. JAMA. 2004 Jan 28;291(4):460-9.
9. Kim K, Hessl D, Randol JL, Espinal GM, Schneider A, Protic D, Aydin EY,Hagerman RJ, Hagerman PJ. Association between IQ and FMR1 protein (FMRP) acrossthe spectrum of CGG repeat expansions. PLoS One. 2019 Dec 31;14(12):e0226811.doi: 10.1371/journal.pone.0226811.
10. Li Y, Jin P. RNA-mediated neurodegeneration in fragile X-associatedtremor/ataxia syndrome. Brain Res. 2012 Jun 26;1462:112-7. doi:10.1016/j.brainres.2012.02.057.
11. Ma L, Herren AW, Espinal G, Randol J, McLaughlin B, Martinez-Cerdeño V, PessahIN, Hagerman RJ, Hagerman PJ. Composition of the Intranuclear Inclusions ofFragile X-associated Tremor/Ataxia Syndrome. Acta Neuropathol Commun. 2019 Sep3;7(1):143. doi: 10.1186/s40478-019-0796-1.
12. Tassone F, Beilina A, Carosi C, Albertosi S, Bagni C, Li L, Glover K, Bentley D, Hagerman PJ. Elevated FMR1 mRNA in premutation carriers is due to increasedtranscription. RNA. 2007 Apr;13(4):555-62.
13. Todd PK, Oh SY, Krans A, He F, Sellier C, Frazer M, Renoux AJ, Chen KC,Scaglione KM, Basrur V, Elenitoba-Johnson K, Vonsattel JP, Louis ED, Sutton MA,Taylor JP, Mills RE, Charlet-Berguerand N, Paulson HL. CGG repeat-associatedtranslation mediates neurodegeneration in fragile X tremor ataxia syndrome.Neuron. 2013 May 8;78(3):440-55. doi: 10.1016/j.neuron.2013.03.026.
14. Wang JY, Hessl D, Hagerman RJ, Simon TJ, Tassone F, Ferrer E, Rivera SM.Abnormal trajectories in cerebellum and brainstem volumes in carriers of thefragile X premutation. Neurobiol Aging. 2017 Jul;55:11-19. doi:10.1016/j.neurobiolaging.2017.03.018.
15. Wheeler A, Raspa M, Hagerman R, Mailick M, Riley C. Implications of the FMR1Premutation for Children, Adolescents, Adults, and Their Families. Pediatrics.2017 Jun;139(Suppl 3):S172-S182.

doi: 10.1542/peds.2016-1159D. Review.

16. Wittenberger MD, Hagerman RJ, Sherman SL, McConkie-Rosell A, Welt CK, RebarRW, Corrigan EC, Simpson JL, Nelson LM. The FMR1 premutation and reproduction.Fertil Steril. 2007 Mar;87(3):456-65.