Fragile X syndrome and Autism: Genetics of both Conditions

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Fragile X syndrome is the leading hereditary cause of mental retardation and second to Down syndrome as a specific genetic cause. Both males and females can be affected with this genetic condition. However, the frequency of Fragile X is higher in males, and they tend to be more severely affected. Current estimates are that about one male in every 2,000 to 4,000 will inherit the fragile X mutation and be affected.
A significant association of Fragile X with autism has been noted. Fragile X has been found to be the most common genetic disorder identified among groups of autistic persons. Current testing results show that approximately 4% of autistic individuals will be found to have fragile X upon testing. Likewise approximately 20% of fragile X males are considered to have autism. The overlapping of these two conditions points to the likelyhood of a common final pathway.

Approximately 1/700 males will be born as a Fragile X premutation carrier. They carry the Fragile X mutation in an unexpressed form. Some of them (~20% over age 50 years) develop a progressive ataxia/tremor/dementia syndrome. Approximately one female in every 300 inherits the fragile X premutation. Carrier males and females are at high risk to pass on the fragile X mutation and to have affected offspring.

Due to its prevalence, it is important for health care professionals to learn about and become familial with the Fragile X syndrome and its relationship to autism. It is important for clinicians to be able to recognize the features of both conditions, to be able to know when to request genetic testing, and be know how to interperet the results of this genetic testing. This information is important for health care professionals who may have contact with autistic individuals at risk of having the fragile X syndrome or of being carriers.

In comparison to some other genetic and chromosomal syndromes, males with fragile X syndrome often do not have very specific or recognizable features; hence, they are frequently quite normal in appearance and are not identified as having the syndrome. Some males with fragile X syndrome show characteristic facial features that can be recognized. These may include a long, narrow face, narrow inter-eye distance, highly arched palate of the mouth, and enlarged ear size. There may be prominent thumbs, hand calluses, hyper-extensibility of the joints, and flat feet. Enlarged testicular volume, also known as macroorchidism, is commonly present and is particularly noticeable after puberty. In childhood, recurrent otitis media is present is about 60 percent of affected boys. This often requires the insertion of one or more sets of polyethylene tubes in the tympanic membranes to present the resulting conductive hearing loss and resultant language and articulation deficits. Flat feet are common which can usually be treated with orthopedic shoes. Approximately 10 percent of affected males develop seizures which usually can be controlled with standard anticonvulsant therapy.

Adult males with fragile X syndrome have a variable degree of mental impairment. On IQ testing, a range of 20 to 50 is common, with an average of around 35. Some younger boys with fragile X have IQs that fall within the borderline to normal range (70-85), but these scores often show a decline as the boys grow older. Most boys with the syndrome have speech delay and language problems, including rapid repetitive speech, cluttering of speech, and articulation difficulties. Poor fine motor coordination, hypotonia, and gross motor delays are common. Many boys have difficulty processing sensory information and blocking out competing sensory stimulation. Behavioral problems in males with fragile X frequently include attention deficit hyperactivity disorder, impulsivity, poor eye contact, shyness, and high levels of anxiety. The anxiety of making eye contact leads to a characteristic eye gaze aversion when shaking hands particularly with strangers. Individuals with fragile X syndrome often possess a very engaging personality and have excellent imitative skills, a good imagination, and a delightful sense of humor. Males with the syndrome often display hand-flapping and hand-biting with resulting callus formation. Some males may become aggressive and for a few it is a daily problem. They are frequently are tactilely defensive. Boys with fragile X often have difficulty adapting to changes in their routine. The majority of fragile X males have some autistic-like features. Approximately 10 percent are disgnosed with autism. Fragile X syndrome is the most common genetic syndrome associated with autism, and it may provide a clue about the nature of brain malfunction in autism. Neuroimaging studies have suggested common areas of central vermis cerebellar hypoplasia exist in the two conditions.

Females who are carriers of fragile X syndrome are usually perfectly normal. However, about 33 percent may have a mild disability in some specific area of learning or schoolwork. About 10 percent may have mild retardation. Occasionally, an affected female will have more severe to profound retardation. Physically distinct features are not commonly recognized in female carriers, but in some instances, they do resemble those seen in males with fragile X. Females who have the syndrome appear to have specific weaknesses in mathematics; motor and speech and language problems are also commonly seen. Females affected by fragile X syndrome tend to have behavioral problems that include shyness and timidity, social withdrawal, depression, and attention deficit hyperactivity disorder.

Fragile X syndrome is caused by a defect in the gene FMR1 (fragile X mental retardation type 1). The common form of thissyndrome is due to a mutated expansion of a CGG triplet repeat in the gene. In most normal individuals, this CGG triplet is repeated approximately 10 to 55 times. In the DNA of people who are carriers of fragile X, this triplet expands to 56 to 200 repetitions (referred to as a premutation), and in people affected by the syndrome, the CGG triplet is usually repeated more than 200 times (referred to as a full mutation).

Women who carry a fragile X premutation are usually completely unaffected by the syndrome, but when they pass on their chromosome to their offspring, it usually undergoes an expansion. The risk of the premutation expanding to a full mutation is related to the premutation size, with a risk of about 30 percent for the size of 56 to 69 repeats, of about 80 percent for 70 to 79 repeats, 90 percent for 80 to 89 and nearly 100 percent for 90 or more repeats. Twenty to 40 percent of males who have a full fragile X premutation present also have cells that show a premutation. These males are referred to as mosaics and appear to be less severely affected by the syndrome. Women can also be mosaics, but less than 10 percent of women who are affected by the syndrome appear to be mosaic.

The fragile X gene is located near the end of the long arm of the X chromosome at band Xq28.3. When cells from an affected individual are grown under special conditions (i.e., low folic acid), the end of the chromosome appears to stretch or break; hence, the name fragile X. When the FMR1 gene has the full mutation present, it usually does not function to synthesize any of the fragile X protein (FMRP). It is the lack of FMRP that is the cause of the syndrome. The fragile X chromosome is inherited in an X-linked manner. If a woman is a carrier of the mutated gene, her sons are at risk of being affected by fragile X, while her daughters may be carriers. With each pregnancy, there is a 50 percent chance that the fragile X chromosome will be passed on. If a son receives the chromosome, he will have a risk of about 80 percent of being affected, and if a daughter receives the chromosome, she will have about a 30 percent risk of being affected.

Males can inherit the premutation as well. If they do, they are considered carriers and are called non-penetrant males. These males do not show the fragile X chromosome in their blood; likewise, they usually do not have mental impairment or physical signs of the syndrome. They pass on their X chromosome to all of their daughters and to none of their sons. Daughters of non-penetrant males do not inherit the a full mutation. Hence, all daughters of males who are non-penetrant are carriers, and none of their sons are carriers.

Recently, a new syndrome related to male carriers has been identified. A number of male carriers of the fragile X premutation, all over 50 years of age, have been found that are affected by a multisystem, progressive neurological disorder. The two main clinical features of this new syndrome include cerebellar ataxia and/or intention tremor. Other documented symptoms include short-term memory loss, executive function deficits, cognitive decline, Parkinsonism, peripheral neuropathy, lower limb proximal muscle weakness, and autonomic dysfunction. MRI studies show symmetrical regions of increased T2 signal intensity in the middle cerebellar peduncles and adjacent cerebellar white matter. Molecular findings include elevated mRNA and low-normal or mildly decreased FMRP levels. The clinical presentation of these patients, coupled with a specific MRI lesion and neuropathological findings, provides a delineation of this fragile X premutation-associated tremor/ataxia syndrome and distinguish it from other movement disorders.

DNA testing for diagnosing fragile X syndrome include two complementary DNA tests. The first is by PCR which can accurately determine the number of triplet repeats. The second is a genomic Southern blot which provides useful information about whether the gene is methylated and turned off or not. The DNA testing can identify both carriers and affected individuals, and can be used for prenatal diagnosis. Prenatal diagnosis involves either chorionic villus sampling (CVS), which is done at about 10 weeks of pregnancy, or amniocentesis, done at around 16 weeks. Cells from the fetus are obtained by either of these procedures and are tested for the presence of the fragile X mutation by DNA analysis. The results of ongoing studies have shown that the prenatal DNA test is highly reliable.

Currently, no cure and no specific therapy are available for the fragile X syndrome. The specific function of the missing FMR protein is unknown, although it is known to be an RNA binding protein, may regulate the translation of a limited subset of mRNAs, and appears to be important for normal brain development. Some treatments including speech and language therapy, occupational therapy, certain medications, behavioral management techniques, educational strategies and inclusion programs have proven to be very beneficial and can lead to marked improvements.

Bibliography

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