

Fragile X Syndrome

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Abstract

Fragile X syndrome is the most frequent cause of inherited mental retardation. It is caused by a dynamic mutation i.e. the progressive expansion of polymeric (CGG)_n trinucleotide repeats located in the non coding region at the 5' end of the FMR1 gene at Xq 27.3. It is an X linked disorder; the manifestations are seen in all of carrier males and in 35% of carrier females. This type of mode of inheritance is described as X linked semidominant or X linked dominant with decreased penetrance. The clinical features other than mental retardation include subtle dysmorphism, behavioral abnormalities and macroorchidism in postpubertal males. The phenotype being subtle, clinical diagnosis may be difficult especially in young children. Hence, all cases of mental retardation without obvious cause should be tested for fragile X syndrome, it is often the only way to identify fragile X syndrome cases. The parents and relatives of such a case need to be offered genetic counseling to prevent the recurrence of fragile X syndrome in the family. The cytogenetic and molecular diagnostic tests are available; the latter replacing the formers over the years. Polymerase chain reaction based tests are used for screening and Southern blot hybridization is the diagnostic test for detections of mutation and premutation. Prenatal diagnosis is possible by carrying out Southern blot hybridization on samples of chorionic villi or amniotic fluid. The complexities due to premutation and variable severity of manifestations in carrier females need to be understood while counseling families with fragile X syndrome.

Key words

Fragile X syndrome, mutations, premutations, X linked semidominant, mental retardation, trinucleotide repeat disorder, dynamic mutation, genetic counseling.

History

The increased incidence of males in mentally retarded populations as compared to the females was noted for a long time⁽¹⁾. In 1943, Martin and Bell⁽²⁾ described a family of sex linked mental retardation without dysmorphic features. In 1969, Lubs⁽³⁾ observed a marker X chromosome in a family with mentally retarded

males. They and their mother expressed a constriction at the end of the long arm of the X chromosome. This 'fragile site' on X chromosome gave the name fragile X syndrome to the disorder. The causative gene for fragile X syndrome is *FMR-1* (for Fragile site Mental Retardation-1).and was identified in 1991, by Fu et al⁽⁴⁾.

Etiology

The chromosomal abnormality; namely Fragile site on Xq27.3 is used as a diagnostic marker for fragile X syndrome. But the disorder is not a chromosomal disorder. It is caused by mutation in *FMR-1* gene on X chromosome at Xq27.3. Fragile X syndrome belongs to a group of disorders caused by expansion of triplet repeats. Expansion of trinucleotide repeats has been identified as a common mechanism of hereditary neurodegenerative diseases including spinal and bulbar muscular atrophy ([Kennedy disease](#)), [Huntington's disease](#), [dentatorubral-pallidoluysian atrophy](#) (DRPLA), [Machado-Joseph disease](#) (MJD), fragile X syndrome, [myotonic dystrophy](#) and [Friedreich's ataxia](#). Almost all cases of fragile X syndrome are caused by expansion of CGG repeats in the 5' untranslated region of the *FMR-1* gene⁽¹⁾.

Normal individuals have 6 to 50 CGG repeats at this site. These repeat are stably transmitted from generation to generation. In individuals with fragile X syndrome the number of repeats is increased to more than 200. When the number is more than 200, the *FMR-1* gene gets methylated and becomes nonfunctional. The individuals with CGG repeat number between 50 and 200 are known as premutation carriers. Carriers of premutation do not have mental retardation and male premutation carriers are known as Normal Transmitting Males (NTM).

The allele with CGG repeat number of more than 200 is known as a full mutation. All males with full mutation are mentally retarded. About half of females with full mutation have mental subnormality or some mild phenotypic features of fragile X syndrome.

A small group of cases of fragile X syndrome are reported due to intragenic deletion or point mutation in the *FMR-1* gene^(5, 6).

Prevalence of fragile X syndrome

Fragile X mental retardation has been detected in all populations and ethnic groups. Most of the studies give prevalence of Fragile X syndrome as 0.5 to 3% of mentally retarded males of unknown etiology⁽⁷⁾. The higher prevalence up to 11% have also been reported; possibly due to strict selection criteria. In general population, the prevalence of fragile X syndrome is found to be around in 1 in 4000 males⁽⁸⁾ For females, recent large studies have established prevalence of premutation carriers as 1/260 in general population⁽⁹⁾.

Clinical features

Phenotype in males

The most prominent feature and significant problem of fragile X syndrome is mental retardation. The associated dysmorphic features are subtle making the clinical diagnosis difficult.

The face is long with prominent mandible and large ears. The phenotype is subtle in young children⁽¹⁰⁾ and evolves with age. Macroorchidism (testicular size more than 30 ml) is an important feature in postpubertal males. However, it is not present in all fragile X syndrome males nor it is specific for fragile X syndrome. Hyperextensibility of finger joints, pectus excavatum, mitral valve prolapse, strabismus and epilepsy are other possibly seen features⁽¹⁹⁾.

Behavioral Phenotype

Mental retardation in fragile X syndrome males varies from mild to profound with most affected males being moderate to severely retarded⁽¹¹⁾. A number of behavioral characteristics associated with fragile X syndrome have been described. They include hyperactivity, short attention span, stereotypic behavior (hand flapping, hand rubbing, preservative speech, echolalia), poor eye contact, tactile defensiveness and anxiety related to social contact. Many of these features suggest the possibility of autism.

Manifestations in females

About half of the females with full mutation show some manifestation of fragile X syndrome⁽¹²⁾. But females are usually less severely affected than males.

Manifestation in Premutation carriers

Premutation carriers were supposed to be asymptomatic carriers and always clinically normal. Recently a syndrome of tremor, ataxia and cognitive decline is reported in premutation carriers. The penetrance of this syndrome increases with age and 75% of premutation carrier beyond 80 years have intentional tremors and gait ataxia^(13,14). Twenty eight percent of females with premutation experience premature ovarian failure⁽¹⁵⁾.

Diagnosis

Due to lack of clinical diagnostic criteria, simple scoring systems have been developed to select individuals for fragile X syndrome testing⁽¹⁶⁾. But these scoring systems are mostly useful for population based studies. As the diagnosis of each case is very important for the family, every child with unexplained mental retardation should be tested for fragile X syndrome.

There are two methods for diagnosis. One is based on chromosomal study to demonstrate fragile X chromosome under special folic acid deficient culture conditions. The cytogenetic tests (based on demonstration of fragile X chromosome) can be false negative (due to inappropriate culture condition) or false positive (due to fragile X E site near the fragile X A site of fragile X syndrome). The molecular (DNA) tests are of two types. The screening tests are

polymerase chain reaction (PCR) based and easy. The cases selected by PCR based test need to be confirmed by Southern blot hybridization. Southern blot hybridization detects mutation as well as pre mutation in males and females.

Some fragile X syndrome males have full mutation in some cells of the body and premutation in some cells of the body. Such male are known as mosaics and may have less severe intellectual handicap⁽⁹⁻¹⁸⁾. Mosaics for methylation are also known⁽¹⁸⁾

A diagnostic test based on use of antibody to FMR protein (product of *FMR-1* gene) to detect presence or absence of FMR protein in lymphocytes or hair root cells is also possible⁽¹⁷⁾. This test can be used to diagnose affected males; but is not useful to detect premutation carrier and female carrier of full mutation.

Management

At present there is no cure for fragile X syndrome. A wide variety of measures are used to take care of their special educational needs and to make the affected individuals independent and integrate in the society as much as possible. Pharmacological agents like antidepressants, anticonvulsants are used whenever indicated. The families should be cautioned regarding claims of utility of megavitamins or alternate forms of therapy for cure of mental retardation.

Genetics of Fragile X syndrome

Presence of premutation and variable expression in female carrier make genetic counseling for fragile X syndrome difficult. It is essential to understand the complexities of genetic aspects of fragile X syndrome before counseling a family and a carrier of fragile X syndrome. The premutation carriers have CGG repeats varying from 50 to 200 in number. The premutation alleles with such intermediate number of repeats are unstable. When transmitted from one generation to the next generation through a female, the number of repeats increases. If the number of repeats becomes more than 200, the premutation is said to have got converted to full mutation. The chance that a premutation will get converted to full mutation increases as the number of repeats in the premutation allele increases⁽¹⁹⁾. The increase in the size of repeats occurs only when the premutation is transmitted by a female. When the male transmits the premutation to the next generation, the number of repeats does not increase and thus, there is no risk of fragile X syndrome in the offsprings of a premutation carrier male (also known as normal transmitting male - NTM). Thus, NTM is more likely to have affected grandsons than affected brother. This fact was observed long before the mutation and

premutation were identified and was known as 'Sherman Paradox'.

Genetic Counseling

Associated mental retardation and high risk of recurrence makes genetic counseling essential for the families with fragile X syndrome. With the availability of molecular tests, carrier detection and prenatal diagnosis is possible. The most important step is the diagnosis of the affected case. All mentally retarded children need to be investigated for fragile X syndrome. The mother of an individual with fragile X syndrome is an obligate carrier. She may have full mutation or premutation. The chance that she will pass on the X chromosome with mutation (or premutation as the case may be) to her sons or daughters is 50%. So the chance that her offsprings will not inherit the X chromosome with mutation (and will not be affected) is 50%. If the mother is a carrier of full mutations, she will transmit it to 50% of her sons who will be affected. She will also transmit the mutation to 50% of her daughters, but there is no way to predict whether the daughter with full mutation will have clinical manifestation and if yes, what will be the severity of mental handicap. This is because the severity of the manifestations varies greatly in the females with full mutation; possibly depending on the X inactivation pattern.

If the mother is a carrier of premutation, the chance that her offsprings will inherit the normal X chromosome is 50%. The rest 50% will inherit the other chromosome. But whether the premutation will get changed to full mutation will depend on the number of repeats in the premutation allele of the mother. If the number of repeats in the mother is between 55 and 59, the risk of premutation getting converted to full mutation is 5.4%. The risk increases with increasing number of repeats and becomes almost 100% when the number of repeats in the premutation allele is more than 100⁽¹⁸⁾. If the number of repeats in the mother is between 60 and 80; the risk of the premutation getting converted to the full mutation varies from 19% to 50%. For the repeat numbers between 80 and 100; the risk varies from 73 to 87%.

The daughters of a carrier woman and female relatives on the maternal side (sisters, sisters' daughters) need to be tested for carrier detection. An attempt should be made to educate the family to discuss issue with their relatives about the necessity of carrier detection and genetic counseling to prevent recurrence of mentally handicapped children in the family⁽¹⁹⁾.

Prenatal diagnosis

Carrier females need to be provided genetic counseling and offered prenatal diagnosis. The reliable prenatal diagnosis is done by Southern blot analysis in the DNA sample obtained from

chorionic villi or amniotic fluid. Birth of an affected child can be avoided by terminating pregnancy if the fetus is found to carry a full mutation.

It should be clear to the family and the counselor that the phenotype and intelligence of a female fetus with full mutation can not be predicted by any prenatal tests and about 50% female carrier of full mutation are phenotypically normal. Fragile X mental retardation being one of the leading causes of mental retardation, screening of general population for identification of carrier females and offering them prenatal diagnosis for prevention of birth of mentally handicapped child has also been tried and found feasible⁽²⁰⁾.

Fragile X-associated tremor/ataxia syndrome (FXTAS), a neurodegenerative disorder, was described recently among male carriers of expanded alleles (55-200 CGG repeats; premutation range) of the fragile X mental retardation 1 (*FMR1*) gene. Major features of the syndrome include intention tremor, gait ataxia, and parkinsonism in men over 50 years of age. This disorder is believed to be relatively common, possibly affecting 1 in 3,000 men over the age of 50 years in the general population. This raises the possibility that some patients presenting with essential tremor (ET) may harbor expanded *FMR1* alleles. Nowadays, with the finding that carrier males are at risk for fragile-X-associated tremor/ataxia syndrome (FXTAS), screening has become less evident, since it may lead to unwanted presymptomatic diagnosis for this disorder⁽²¹⁾.

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