

## Genotype-Phenotype Correlates in Fragile X Syndrome

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### Abstract

Fragile X syndrome is a genetic disorder that affects both males and females but males are more severely affected than females. It is characterized by intellectual and learning disabilities, behavioral and or psychiatric comorbidities, mildly dysplastic connective tissue, and large testes. Fragile X cases have more than 200 repeats of the trinucleotide CGG at a fragile locus of the X chromosome (Xq27.3) which affords the basis of the molecular diagnosis of the syndrome. Although there is no current curative treatment of Fragile X syndrome, there are many available therapeutic modalities that can be used to control its manifestations and improve the quality of life of its sufferers. Lastly but by no means least, it is well documented that the earlier the diagnosis and implementation of early intervention and individualized rehabilitation programs, the better the prognosis.

**Keywords:** Fragile X syndrome; CGG repeats; Intellectual disability; Autism spectrum disorder; Attention deficit hyperactivity disorder; FMR1 gene; FMRP

### Introduction

A mother came to my office asking for my opinion about the condition of her 3-year-old male kid and my advices regarding the best way of dealing with him. He was born at term after uneventful pregnancy and the perinatal period passed without complications. He has two male cousins from the maternal side experiencing learning disabilities and poor scholastic achievement. He was breast fed and weaned at 18 months; by that time she started to notice that he prefers to be left alone and becomes agitated if she leaves him with other family members. At 24 months of age, she was really worried because of the delay in acquisition of normal motor and linguistic milestones and evident poor social reciprocity and joint attention. She sought medical advice but her primary care physician told her not to worry and reassured her that he will grow out of it. After examining the child, I decided to do some investigations that settled my provisional diagnosis of Fragile X syndrome with Autism Spectrum Disorder (ASD).

### What is meant by fragile X syndrome [Fra(X)]?

Fragile X syndrome is a genetic disorder that affects both males and females but males are more severely affected compared to females. It is characterized by intellectual and learning disabilities, behavioral and or psychiatric comorbidities, mildly dysplastic connective tissue, and large testes. It occurs in about one in 4000 males and one in 8000 females [1-3].

### Historical overview

Martin and Bell [4] reported the first documented pedigree of sex linked mental retardation (intellectual disability). Later in 1969, Lubs [5] revealed a fragile site on the long arm of the X chromosome in males and some females of the same family. Then, non

endocrinological macro-orchidism has been linked to the disorder in the affected males of some families [6,7]. Then Sutherland [8] showed that the fragile site documentation was only possible in specific cell culture medium.

### What is behind the occurrence of fragile X syndrome?

**Fra (X) genotype:** Fragile X is an X linked disorder in which there is a marker on the X chromosome which represents a fragile site (non-stainable gap at the locus Xq27.3). Within this locus, there is an area which contains a variable number of repeats of the trinucleotide CGG. Such area affords the basis of molecular diagnosis of the disorder as normal human beings have from 6–40 CGG repeats but Fragile X sufferers have more than 200 of such repeats. On the other hand, premutation carriers whether males or females were found to have between 55 and 200 CGG repeats [9,10].

The molecular mechanism of Fra X syndrome has been explored thoroughly and showed that the abnormal expansion of CGG repeats silences the FMR1 gene; a gene that is responsible for synthesis of a protein called FMRP. Furthermore, it has been documented that such gene silencing is associated with increased levels of FMR1 messenger ribonucleic acid (m RNA) in addition to the reduced levels of FMRP; a protein which controls the production of other vital proteins and shares in synapses development. Synapses are specialized connections between neurons and are crucial for relaying nerve impulses. In cases of deficient FMRP, disruption of nervous system functions occurs with the development of fragile X syndrome manifestations including neurodevelopmental impairment and psychopathology [3,11,12].

It is worthy to mention that premutation carriers classically have none of fragile X manifestations but they can have affected offspring; however, some of them might have reduced amount of FMRP with the subsequent development of milder versions of the physical manifestations of the syndrome and emotional problems including anxiety or depression, learning disabilities, psychosis, and autistic like behavior [13,14]. Furthermore, permutation increases the risk of fragile X associated primary ovarian insufficiency (FXPOI) [15] and fragile X associated tremor/ataxia syndrome (FXTAS) [16].

**Inheritance:** Fragile X syndrome is an X-linked dominant disorder which means that one copy of the mutant gene in each cell is sufficient for the disorder to manifest itself. A mutation in one of the two copies of the X chromosome in females and in the only copy of it in males is sufficient to result in the development of the syndrome. In female carriers, FMR1 gene permutation can expand to more than 200 CGG repeats in the gamete cells that develop into ova which results in increased risk of having an affected offspring while this does not happen in males with the permutation. Males pass the permutation only to their daughters as Y chromosomes do not have FMR1 gene [3,17].

### What are the types of abnormalities that are frequently recorded among fragile X syndrome sufferers?

**Fra (X) phenotype:** Manifestations of fragile X syndrome are mainly cognitive, behavioral, and craniofacial. In male sufferers, peri-pubertal increase in testicular size is a characteristic feature of the syndrome [1-3,17].

Cognitively, the sufferers had different degrees of intellectual disability ranging from mild to profound. Sometimes, borderline normal range of IQ with learning disabilities is encountered among sufferers especially females while most males have mild to moderate degrees of intellectual disability. Delayed speech and language development is usually apparent in affected toddlers by the age of 2. When developed, speech may be cluttered in affected males with mild intellectual disability while those with severer degrees of ID may show short bursts of repetitive speech [18-20].

Behaviorally, sufferers may have DSM5 diagnostic criteria of anxiety especially social anxiety and panic attacks with much less frequency of obsessive compulsive disorder (OCD). On the other hand, mood disorders are rare and if any they are usually transient and stressors related and may manifest as fluctuating mood, irritability, self-injury, and aggressive behavior [21]. Attention Deficit Hyperactivity Disorder (ADHD) is encountered in most male cases and 30% of Fra X females. Inattentiveness is usually life-long while hyperactivity and impulsivity improve with age [22]. On the other hand, concurrent Autism Spectrum Disorder occurs in 15-60% of Fra X cases and because of such high prevalence, screening for FMR1 mutation is highly recommended in autistic children. Interestingly, psychosis and catatonia have been reported in permutation carriers where multiple genetic and environmental hits resulted in intensified involvement and significant clinical expression [21,23,24].

Neurologically, seizures are encountered in about 15% of affected males and 5% of affected females [25]. Hypotonia with hyperextensibility of fingers are occasional abnormalities [3,26].

Craniofacially, sufferers show macrocephaly in early childhood. Other abnormalities include thickening of nasal bridge down to the nasal tip, large ears with softening of its cartilage, the irides may be pale blue with epicanthal folds, dental crowding, and prognathism which usually becomes apparent at puberty [1-3,27].

Occasionally, nystagmus, squint, myopia, mild cutis laxa, torticollis, pectus excavatum, kyphoscoliosis, flat feet, submucosal cleft palate, prolapse of mitral valve, and aortic dilatation may be encountered. Also, recurrent sinusitis and otitis media are commonly encountered during early childhood [3,18,27].

### Management of Fragile X Syndrome

Molecular diagnosis of the syndrome can be done using polymerase chain reaction (PCR) to detect the expanded CGG repeats in the FMR1 gene [28,29]. Todorov et al. [30] reported fragile X mosaicism in a male by using PCR and methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA). They claimed that such combined analysis is a perfect means for diagnosis of fragile X syndrome as it assesses the CGG expansion and the CpG methylation status, and could detect the copy number changes along fragile X mental retardation genes (FMR1, FMR2). So, it is considered as an applicable way for neonatal screening as it excludes premutations.

Visual and hearing assessment is recommended to detect any associated sensory impairment. Cardiac problems are to be excluded using echocardiography and ECG. EEG is indicated in fragile X sufferers with seizures while neuroimaging is considered in those with ataxia or suspected structural brain abnormalities [18,31].

Therapeutic interventions for fragile X syndrome sufferers are conducted by multidisciplinary teams although there is no specific treatment for it. Early intervention is pivotal to improve the outcomes of management. Special education, occupational therapy, sensory integration, and anticipatory management to avoid excessive excitation will help to control behavior problems. Behavior therapy with parental training is very valuable in improving the concomitant behavioral disorders. Any associated visual or hearing deficits and or cardiac problems must be dealt with in the usual manner [31,32].

Pharmacotherapy is resorted to aiming at ameliorating the comorbid psychiatric manifestation in cases suffering from Fragile X. Psychostimulants are indicated to control those suffering from ADHD while antidepressants as selective serotonin reuptake inhibitors (SSRIs) are used to target any associated anxiety or mood disorders. On the other hand, antipsychotics as Risperdal may be utilized to target significant self-injurious, violent, and or aberrant behavior. Anticonvulsants are indicated in fragile X cases suffering from seizures. Metabotropic glutamate receptors (mGluR5) which are linked with synaptic plasticity may be targeted by drugs aiming at controlling core symptoms of the syndrome. Recently, lithium has been tried to improve behavior and verbal memory of the sufferers [18,32,33].

### Prognosis

Life expectancy in Fra (X) cases is claimed to be about 12 years less than the general population with similar causes of death [34]. There is slightly accelerated growth rate early in life that makes cerebral gigantism a potential differential diagnosis [3,6]. Motor milestones are delayed but with more or less a stable course with no deterioration. Macro-orchidism may be noticed before puberty but it becomes evident after it. Cluttered speech is characteristic in highly functioning fragile X sufferers. Psychological phenotype is characterized by hyperactivity, labile emotions, and different autistic features [1-3,18]. It is well documented that the earlier the diagnosis and implementation of early intervention and individualized rehabilitation programs, the better the prognosis. Also, higher IQs and absence of or well managed seizures and heart defects are associated with better prognosis.

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