

Definition: **fragile X syndrome** from *The Penguin Dictionary of Psychology*

A genetic disorder caused by a mutation on the X chromosome. Symptoms include mental retardation, low muscle tone and elongated face often with large ears. Males have large testicles. Females often are subclinical, primarily because of the protection provided by the other, unaffected X chromosome. The syndrome often has a variety of behavioural characteristics including stereotyped actions, shyness and poor social development to the point where they may reach the diagnostic criteria for autism (see AUTISTIC SPECTRUM DISORDER).

Summary Article: **Fragile X Syndrome**

From *The Encyclopedia of Neuropsychological Disorders*

## DESCRIPTION

Fragile X syndrome is a genetic disorder, marked by cognitive, behavioral, emotional, and physical symptoms. It is the most common form of inherited mental retardation and affects 1 in 4,000 males and 1 in 8,000 females (Schwarte, 2008).

## NEUROPATHOLOGY/PATHOPHYSIOLOGY

Fragile X syndrome results from a repetition of the CGG trinucleotide sequence on the long arm of the X chromosome at location Xq27.3, first identified as a single gene disorder in 1991 (Hall, Burns, Lightbody, & Reiss, 2008). The CGG repetition inactivates the *FMR1* gene, which leads to a decline in production of the fragile X mental retardation protein (FMRP) and prevents the expression of FMRP, which is necessary for normal neuronal development and healthy brain functioning (Huber, 2007; Schwarte, 2008). FMRP functions to regulate various proteins necessary for synaptic development, neuronal maturation, and plasticity (Gothelf et al., 2008; Hall et al., 2008). In fragile X syndrome, the dendritic spines of neurons appear to be longer than in normal controls and are not fully developed (Huber, 2007).

At the Xq27.3 locus, anywhere from 6–50 CGG repeats are considered normal. Individuals with 50–200 repeats are considered premutation carriers, as they may have partial inactivation of the *FMR1* gene, and often show some clinical features of fragile X, although presentation and degree of deficit varies. fragile X syndrome is considered to be present in individuals with greater than 200 CGG repeats, which represents full mutation of the *FMR1* gene.

Recent work has examined the neuroanatomical sequelae associated with fragile X. Gothelf et al. (2008) compared neuroanatomical features in children with fragile X syndrome to age- and sex-matched controls. The investigators found significantly increased size of the caudate nucleus and decreased size of the posterior cerebellar vermis, amygdala, and superior temporal gyrus in those affected with fragile X syndrome.

## NEUROPSYCHOLOGICAL/CLINICAL PRESENTATION

The symptoms of fragile X syndrome include moderate to severe mental retardation, attention deficits, and developmental delays (Huber, 2007). The clinical presentation varies greatly among individuals, as fragile X is a disorder with incomplete penetrance, meaning even those with full mutation

can remain asymptomatic (Snustad & Simmons, 2003). Although severity of symptoms is somewhat dependent upon the number of CGG repeats, clinical presentation can be vastly different in individuals with the same number of repeats and even in affected individuals within the same family.

Because the syndrome is linked to the X-chromosome, males and females are impacted differently. Males tend to be more severely affected given their possession of only a single X-chromosome, while females with the disorder often have one unaffected X-chromosome, enabling them to potentially maintain some FMRP production, leading to less severe symptoms. Certain neuroanatomical phenotypes may also be associated with more severe cognitive deficits (Gothelf et al., 2008).

Males with fragile X syndrome often have moderate-to-severe mental retardation, with an average full-scale IQ of 40 (Schwarte, 2008). The cognitive profile of females with fragile X is much more variable and can range from normal to moderately impaired intelligence, but often females have low average intelligence. It is also believed that IQ tends to decline over time, but there is debate about whether such decline is due to loss of higher-order abilities, lack of development, or slower learning in affected individuals (Hall et al., 2008; Schwarte, 2008). Persons with the syndrome also typically have better verbal than visuospatial processing abilities. Executive dysfunction, specifically deficits in working memory, is often associated with the syndrome, as is difficulty performing arithmetic (Hall et al., 2008; Schwarte, 2008).

There is a high rate of comorbidity between fragile X syndrome and autism spectrum disorders. Autistic behaviors, such as stereotypies, gaze avoidance, self-injurious behaviors, and social and communication deficits are often apparent in individuals with fragile X syndrome (Schwarte, 2008). In males with fragile X syndrome, 60–90% show autistic features, while in females the rate varies from 25–80% (Gothelf et al., 2008). Further, 15–25% of individuals with fragile X syndrome are believed to meet the diagnostic criteria for autism (Schwarte, 2008). Persons with a comorbid autism diagnosis often have more severe deficits and are associated with poorer functional outcomes, including lower cognitive, language, social, and adaptive development (Fisch et al., 2007).

## **DIAGNOSIS**

Because fragile X syndrome is a genetic disorder, family history plays an important role in suspecting a diagnosis and initiating further testing. Diagnosis of fragile X syndrome is often difficult because of the wide variability of symptoms (Snustad & Simmons, 2003). The diagnosis and severity of symptoms is based on the number of CGG repeats and can be tested with molecular genetic techniques. Clinically, the first symptoms of the syndrome are often developmental delays. On average, boys with fragile X syndrome sit unassisted at 10 months, and walk and talk at around 20 months (Schwarte, 2008).

Because developmental delays are common in many childhood disorders, without additional suspect of fragile X in the family, children often go misdiagnosed or undiagnosed until much later. The average age of diagnosis of fragile X syndrome is 8 years (Schwarte, 2008).

Fragile X also has characteristic physical symptoms that have diagnostic value, including elongated face, large ears, prominent jaw, macrocephaly, macroorchidism, flat feet, high-arched palate, and joints that are hyperextensive (Schwarte, 2008). However, the physical symptoms of the disorder are not usually apparent at birth or early childhood and do not typically develop until much later, often not until adolescence.

## **TREATMENT**

Because the clinical features of fragile X syndrome are so individualized, treatment must be dependent upon the unique set of physical, cognitive, behavioral, and/or emotional problems. Multidisciplinary approaches are often necessary to address all problem areas. Primary medical doctors are important in the care of persons with fragile X syndrome in order to monitor the presence of common co-occurring medical conditions, such as problems associated with loose connective tissue and seizure disorders (Schwarte, 2008). The efficacy and side effects of medications need to be closely monitored in this population. Behavioral modification plans and medication management are an important component of treatment when behavioral symptoms are present. In children with speech and language difficulties, often a speech-language pathologist will be a part of the treatment team to lessen some of the communication barriers that may be present. Also, to increase likelihood of optimum development, individualized education plans are necessary to help identify strengths and weaknesses and facilitate learning to the individual's greatest capacity.

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