Perspective

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Diagnosis Requires Genetic Testing to Determine Syndrome Dominant Inheritance

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Description

Fragile X Syndrome (FXS) is a genetic disorder characterized by mild-to-moderate intellectual disability. The average IQ in males with FXS is under 55, while about two thirds of affected females are intellectually disabled. Physical features may include a long and narrow face, large ears, flexible fingers, and large testicles. About a third of those affected have features of autism such as problems with social interactions and delayed speech. Hyperactivity is common, and seizures occur in about 10%.Males are usually more affected than females.

Genetic Testing

This disorder and finding of Fragile X syndrome has an X-linked dominant inheritance. It is typically caused by an expansion of the CGG triplet repeat within the FMR1 fragile X messenger ribonucleoprotein gene on the X chromosome. This results in silencing (methylation) of this part of the gene and a deficiency of the resultant protein, which is required for the normal development of connections between neurons. Diagnosis requires genetic testing to determine the number of CGG repeats in the FMR1 gene. Normally, there are between 5 and 40 repeats; fragile X syndrome occurs with more than 200. A permutation is said to be present when the gene has between 55 and 200 repeats; women with a permutation have an increased risk of having an affected child. Testing for permutation carriers may allow for genetic counselling. There is no cure. Early intervention is recommended, as it provides the most opportunity for developing a full range of skills. These interventions may include special education, speech therapy, physical therapy, or behavioral therapy. Medications may be used to treat associated seizures, mood problems, aggressive behavior, or ADHD. Fragile X syndrome is estimated to occur in 1.4 per 10,000 males and 0.9 per 10,000 females.

Most young children do not show any physical signs of FXS. It is not until puberty that physical features of FXS begin to develop. Aside from intellectual disability, prominent characteristics of the syndrome may include an elongated face, large or protruding ears, flat feet, larger testes macroorchidism, and low muscle tone. Recurrent otitis media middle ear infection and sinusitis is common during early childhood. Speech may be cluttered or nervous. Behavioural characteristics may include stereotypic movements and atypical social development, particularly shyness, limited eye contact, memory problems, and difficulty with face encoding. Some individuals with fragile X syndrome also meet the diagnostic criteria for autism.

Macroorchidism

Males with a full mutation display virtually complete penetrance and will therefore almost always display symptoms of FXS, while females with a full mutation generally display a penetrance of about 50% as a result of having a second, normal X chromosome. Females with FXS may have symptoms ranging from mild to severe, although they are generally less affected than males. Most young children do not show any physical signs of FXS.

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Although individuals with FXS have difficulties in forming friendships, those with FXS and ASD characteristically also have difficulties with reciprocal conversation with their peers. Social withdrawal behaviours, including avoidance and indifference, appear to be the best predictors of ASD in FXS, with avoidance appearing to be correlated more with social anxiety while indifference was more strongly correlated to ASD. When both autism and FXS are present, a greater language deficit and lower IQ is observed as compared to children with only FXS. FXS is characterized by social anxiety, including poor eye contact, gaze aversion, prolonged time to commence social interaction, and challenges forming peer relationships.

Social anxiety is one of the most common features associated with FXS, with up to 75% of males in one series characterized as having excessive shyness and 50% having panic attacks. Social anxiety in individuals with FXS is related to challenges with face encoding, the ability to recognize a face that one has seen before.

It appears that individuals with FXS are interested in social interaction and display greater empathy than groups with other causes of intellectual disability, but display anxiety and withdrawal when placed in unfamiliar situations with unfamiliar people. This may range from mild social withdrawal, which is predominantly associated with shyness, to severe social withdrawal, which may be associated with co-existing autism spectrum disorder. Females with FXS frequently display shyness, social anxiety and social avoidance or withdrawal. In addition, permutation in females has been found to be associated with social anxiety.