Fragile X Syndrome

Developed by the Staff of the Bresnahan-Halstead Center
School of Special Education
The University of Northern Colorado

Description

Fragile X syndrome, also called fra(X)syndrome, FRAXA syndrome, FXS, marker X syndrome, Martin-Bell syndrome, X-linked mental retardation and macroorchidism, is a genetic condition that causes a range of developmental problems including learning disabilities and cognitive impairment. Usually, males are more severely affected by this disorder than females.

Individuals who are affected usually have delayed development of speech and language by age two. Most males with Fragile X syndrome have mild to moderate intellectual disability, while about one-third of females who are affected are intellectually disabled. Children with Fragile X syndrome may also have anxiety and hyperactive behavior such as fidgeting or impulsive actions. They may have attention deficit disorder (ADD), which includes an impaired ability to maintain attention and difficulty focusing on specific tasks. About one-third of individuals with Fragile X syndrome have features of autism spectrum disorders that affect communication and social interaction. Seizures occur in about 15 percent of males and about five percent of females with Fragile X syndrome.

Most males and about half of females with Fragile X syndrome have characteristic physical features that become more apparent with age. These features include a long and narrow face, large ears, a prominent jaw and forehead, unusually flexible fingers, flat feet, and in males, enlarged testicles (macroorchidism) after puberty.

Cause

Mutations in the FMR1 gene cause Fragile X syndrome. The FMR1 gene provides instructions for making a protein called FMRP. This protein helps regulate the production of other proteins and plays a role in the development of synapses, which are specialized connections between nerve cells. Synapses are critical for relaying nerve impulses.

Nearly all cases of Fragile X syndrome are caused by a mutation in which a DNA segment, known as the CGG triplet repeat, is expanded within the FMR1 gene. Normally, this DNA segment is repeated from five to about 40 times. In people with Fragile X syndrome, however, the CGG segment is repeated more than 200 times. The abnormally expanded CGG segment turns off (silences) the FMR1 gene, which prevents the gene from producing FMRP. Loss or a shortage (deficiency) of this protein disrupts nervous system functions and leads to the signs and symptoms of Fragile X syndrome.

Males and females with 55 to 200 repeats of the CGG segment are said to have an FMR1 gene pre-mutation. Most people with a pre-mutation are intellectually normal. In some cases, however, individuals with a pre-mutation have lower than normal amounts of FMRP. As a result, they may have mild versions of the physical features seen in Fragile X syndrome (such as prominent ears) and may experience emotional problems such as anxiety or depression. Some children with a pre-mutation may have learning disabilities or autistic-like behavior. The pre-mutation is also associated with an increased risk of disorders called Fragile X-associated

primary ovarian insufficiency (FXPOI) and Fragile X associated tremor/ ataxia syndrome (FXTAS).

Inheritance Pattern

This condition is inherited in an X-linked dominant pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes. The inheritance is dominant if one copy of the altered gene in each cell is sufficient to cause the condition.

A mother who carries Fragile X has a 50% chance of passing the mutated gene to each of her children. Her children will either be carriers or they will have Fragile X syndrome. Carrier men will pass the pre-mutation to all their daughters but none of their sons. These daughters are carriers but they do not have Fragile X syndrome. The Fragile X pre-mutation can be passed recessively through generations in a family before a child is born with the syndrome.

Prevalence

The agreed upon prevalence of Fragile X syndrome in males is approximately 1 in 3,600 to 4,000 and in females is approximately 1 in 4,000 to 6,000. About 1 in 259 women carry Fragile X and could pass it to their children. About 1 in 800 men carry Fragile X; their daughters will also be carriers. Fragile X syndrome is the number one inherited cause of intellectual disabilities and the most common known cause of autism worldwide. Most people with Fragile X are not yet diagnosed. The reason it is lower in females is that, while all males with an FMR1 full mutation will have Fragile X syndrome, some females with an FMR1 full mutation will not have behavioral, cognitive or physical features of FXS.

Signs and Symptoms

General Signs and Symptoms:

- Intellectual disabilities, ranging from mild to severe
- Attention deficit and hyperactivity, especially in young children
- Anxiety and unstable mood
- Autistic behaviors, such as hand-flapping and not making eye contact
- Sensory integration problems, such as hypersensitivity to loud noises or bright lights
- Speech delay, with expressive language more severely affected than receptive language
- Seizures (epilepsy) affect about 25% of people with Fragile X syndrome

In Males:

- **Behavioral characteristics** can include ADD, ADHD, autism and autistic behaviors, social anxiety, hand-biting and/or flapping, poor eye contact, sensory disorders, and increased risk for aggression.
- **Intellectual disabilities** in Fragile X syndrome include a range from moderate learning

disabilities to more severe intellectual disabilities. The majority of males with Fragile X syndrome demonstrate significant intellectual disability.

- **Physical features** may include large ears, long face, soft skin, and large testicles in post-pubertal males. Connective tissue problems may include ear infections, flat feet, high arched palate, double-jointed fingers, and hyper-flexible joints. No one individual will have all the features of Fragile X syndrome, and some features, such as a long face and macroorchidism, are more common after puberty.
- **Disposition**: Generally, individuals with Fragile X syndrome are also very social and friendly, have excellent imitation skills, have a strong visual memory/long term memory, like to help others, are nice, thoughtful people, and have a wonderful sense of humor.

In Females:

- **Behavioral characteristics** seen in males can also be seen in females, though females often have milder intellectual disability and a milder presentation of the syndrome's behavioral and physical features.
- **Intellectual disabilities**: About one-third of females with Fragile X syndrome have a significant intellectual disability. Others may have moderate or mild learning disabilities, emotional/mental health issues, general anxiety, and/or social anxiety. A small percentage of females who have the full mutation of the FMR1 gene that causes Fragile X syndrome will have no apparent signs of the condition—intellectual, behavioral, or physical. These females are often identified only after another family member has been diagnosed.

Diagnosis

The FMR1 DNA Test (sometimes called the Fragile X DNA Test) is the standard for determining the presence of Fragile X. This test looks for an expanded mutation (called a triplet repeat) in the FMR1 gene. DNA testing detects more than 99% of individuals (both males and females) with Fragile X syndrome, as well as Fragile X carriers. There are three general circumstances in which Fragile X testing should be considered:

1. Clinical symptoms that suggest Fragile X Syndrome, FXTAS, or infertility/FXPOI.
2. A family history of Fragile X syndrome, FXTAS, intellectual or learning disabilities or autism of unknown cause, or infertility.
3. Family or personal history of a Fragile X genetics and inheritance (i.e., carrier).

Specific indications for testing include:

- Any male or female with intellectual disabilities, developmental delay, speech and language delay, autism or learning disabilities of unknown cause.
- Any female with infertility, elevated FSH levels, premature ovarian failure, primary ovarian insufficiency, or irregular menses.
- Any adult over 50 with features of FXTAS, including intention tremors, ataxia, memory loss, cognitive decline, or personality change, especially in combination with a positive family history of Fragile X.
- Any preconception or pregnant woman who expresses interest in or requests Fragile X carrier testing.

Prognosis

Life expectancy for people with Fragile X syndrome is generally normal. Many affected people participate in an active lifestyle and have good health. Some people are more prone to a number of medical problems, such as ear infections and/or seizures. Regular medical checkups and awareness of increased health risks may improve the outlook for people who are affected.

Treatment and Intervention

While there is currently no cure for Fragile X syndrome, there are many treatments and interventions that can improve the lives of individuals who are affected and their families. Given the proper education, therapy, and support, all persons with Fragile X syndrome can make progress. Most children with Fragile X syndrome qualify for special education services. Education can be complemented by a variety of therapies that will help the children become more independent in the transitions from childhood through adolescence and into adulthood. Supportive therapy for children who have Fragile X syndrome includes:

- Special education and anticipatory management including avoidance of excessive stimulation to decrease behavioral problems.
- Medication to manage behavioral issues, although no specific medication has been shown to be beneficial.
- Early intervention, special education and vocational training.
- Vision, hearing, connective tissue problems, and heart problems when present are treated in the usual manner

Research on FXS

The FRAXA Research Foundation (FRAXA) is the leading organization in FXS research. FRAXA's mission is to find effective treatments and ultimately a cure for Fragile X by accelerating the pace of research. As in building a highway, they aim to speed the flow of research, eliminating bottlenecks along the route.

In their early years, when little was known about the causes and effects of Fragile X, FRAXA funded basic research. Initially, the field was the province of molecular biologists and geneticists. Later, they began to recruit neuroscientists. Currently, Fragile X is a hot topic in neuroscience with thousands of scientists around the world are tackling topics related to Fragile X.

Recent Clinical Trails

ClinicalTrials.gov lists trials that are related to Fragile X syndrome. Click on the link to go to ClinicalTrials.gov to read descriptions of these studies. The National Fragile X Foundation provides a state by state list of clinical trials involving Fragile X-associated disorders. Click on National Fragile X Foundation to view the list.

In recent years, the FRAXA Research Foundation has also recruited and advised pharma industry partners who have invested tens of millions of dollars in Fragile X clinical trials of investigational drugs (companies like Neuropharm, Novartis, Roche, Seaside, Alcobra, and Neuren.) This is one way to bring new Fragile X treatments to market. But there is also a

growing list of available drugs that have shown promise in preclinical testing, but are still waiting for clinical trials. Because these drugs are already on the market, few companies have any motivation to fund trials. While trials designed to obtain FDA approval for new drugs or new indications are very expensive, trials of available drugs in Fragile X can be done on a smaller scale by clinical researchers for far less money. This is a great value, but the costs must be borne primarily by the Fragile X community.

At the same time, advances in technology have opened up new strategies. Drug repurposing is the application of approved drugs to treat new diseases. FRAXA have contracted with a leading company in this field, Healx, to conduct an in-depth study of biological changes caused by the Fragile X mutation and match those changes to the known effects of all available drugs, via sophisticated computer algorithms. This big data match-making approach to drug repurposing has the potential to reveal treatments for Fragile X that can be clinically useful right from the start. FRAXA is also funding efforts to fix Fragile X at the most basic level, by reactivating the silenced FMR1 gene. FRAXA is funding groundbreaking studies using the latest technologies like CRISPR, Xi, and iDRiP to restore the function of the Fragile X gene in boys and girls with the full mutation.

For more information on the types of research, clinical trials and current research grants on Fragile X syndrome please follow the link below:
https://www.fraxa.org/fragile-x-research/

Link to Scientific Articles:

https://www.ncbi.nlm.nih.gov/pubmed?term=%28Fragile+X+Syndrome%5BMAJR%5D%29+AND+%28fragile+X+syndrome%5BTI%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D

Resources and Links

Patient Support and Advocacy Resources

1. National Fragile X Foundation: https://fragilex.org
2. Fragile X Research Foundation: https://www.fraxa.org
3. National Organization for Rare Disorders: https://rarediseases.org/rare-diseases/fragile-x-syndrome
4. March of Dimes: https://www.marchofdimes.org/baby/fragile-x-syndrome.aspx

Educational Resources:

1. American College of Medical Genetics and Genomics Guideline (PDF): http://www.acmg.net/PDFLibrary/Fragile-X-Carrier-Testing.pdf
2. Emory University School of Medicine: Fragile X Syndrome (PDF): http://genetics.emory.edu/documents/resources/factsheet47.pdf
3. Emory University School of Medicine: Fragile X Pre-mutation—a Cause of Premature Ovarian failure (PDF): http://genetics.emory.edu/documents/resources/factsheet46.pdf
4. US National Library of Medicine: Encyclopedia: Fragile X Syndrome: https://medlineplus.gov/ency/article/001668.htm

5. Kennedy Krieger Institute: https://www.kennedykrieger.org/patient-care/conditions/fragile-x-syndrome
6. MalaCards: Fragile X Syndrome: https://www.malacards.org/card/fragile_x_syndrome
7. Boston Children's Hospital: http://www.childrenshospital.org/conditions-and-treatments/conditions/f/fragile-x-syndrome