Fragile X Syndrome

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HCQU Northwest

Fragile X Syndrome (FXS), also called Martin Bell Syndrome, is the most common heritable cause of cognitive disability. It is the second known chromosomal cause of cognitive disability (Down syndrome is first). It is the most common known cause of Autism or "Autistic-like behaviors", and is characterized by distinct physical and behavioral characteristics.

It is estimated to affect 1:5000 males and 1:8000 females and found in all races and socioeconomic groups. Sixty percent of males with FXS exhibit hand flapping or biting; 90% exhibit poor eye contact and 60% have autism. Females with FXS generally have higher IQ's than males and most exhibit shyness and social anxiety.

History

In the late 1800's there was an excess of males with Intellectual Disability noticed based on the US census data.

In 1943 a pedigree was published by Martin and Bell describing the syndrome.

In 1969 Lehrke's PHD Thesis argued for the presence of an x-linked intellectual disability gene.

In the 1970's, Sutherland showed culture medium lacking folic acid appearing to have a gap or break in the end of the long arm of the x chromosome.

In 1991, the mutation causing the FX syndrome was identified and the gene isolated.

Genetics

The Fragile X name comes from the broken appearance in the X chromosome where the FMR1 gene is found. It causes a mutation in the FMR1 gene. The mutation shuts off the production of the FMR1 protein, which is necessary in the development of neuron connections between nerve cells or synapses in the brain, therefore disrupting the relaying of nerve impulses. The CGG (cytosine, guanine and guanine) Trineuceotide repeat, a section of the DNA in the FMR1 gene, normally repeats in that order about 30 times.

In the Gray zone it repeats 45-55 times. These individuals do not have FXS; however, are somewhat more likely to have children with an increased number of CGG repeats.

In the Permutation the repeat is 55-200 times. These individuals have few to no symptoms of FXS. They may have subtle intellectual, behavioral or physical symptoms and are carriers but usually unaware.

In the full mutation the repeat is 200-800 times. All males will have significant symptoms. Fifty percent of females will have symptoms; however, the severity is decreased.

The more repeats, the more unstable the FMR1 gene is. Once the FMR1 gene changes to unstable (permutation) there is a high probability of mutating from generation to generation. In other words a family with no history of FXS, begins to have it appear in several offspring.

Females that carry the gene have a 50% chance of passing it to sons & daughters (she has 2 X chromosomes) . Males with the gene pass it to all daughters, who are now carriers & none of his sons because males pass the X chromo to daughters & Y to sons.

Approx. 1/250 females & 1/800 males carry the gene mutation.

Scientists have found that during early development of the fetus (before the end of the first trimester), RNA attaches itself to the FXS gene and appears to gum up the gene (only one needed), inactivating it and

(Continued on page 2)

Since 1969, Milestone Centers, Inc. has provided programs and services to people with developmental and behavior-

Genetics *(continued from Page 1)*

thus rendering it unable to produce a protein necessary for the transmission of signal between brain cells. [*http://weill.cornell.edu/news/pr/2014/02/scientists-uncover-trigger-for-most-common-form-of-intellectual-disability-and-autism-finding-may-ex.html*]

Researchers are using embryonic stem cells (that tested positive for FXS) to test an experimental drug that may be able to prevent this shut off. They suspect it may also be used for other nervous system genetic disorders (Huntingdon's disease, Amyotrophic Lateral Sclerosis (ALS), etc.)

Diagnosis

DIAGNOSIS of Fragile X is by DNA and karyotype testing.

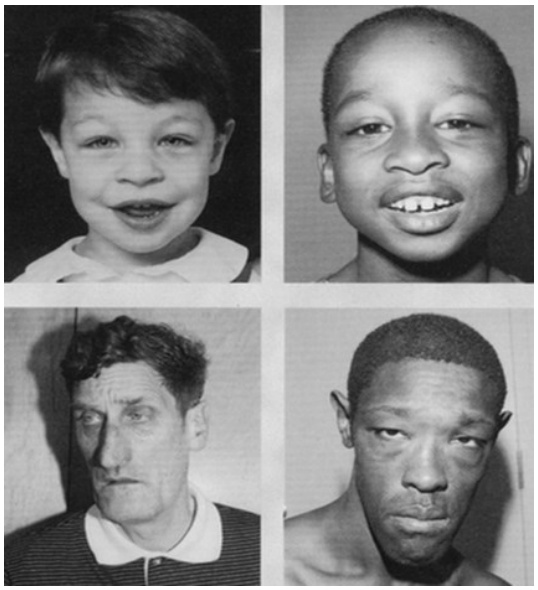
Testing for Fragile X is recommended for:

- Any person who has mental retardation of unknown cause, developmental delay, or learning disability
- Any person with autism or showing autism-like behaviors
- Any person with a relative who has Fragile X or mental retardation of unknown cause
- Anyone who was previously assessed for Fragile X using the chromosome test (see description on the next page)
- Women with premature ovarian failure (POF) or with a family history of POF

Phenotype

Physical Phenotype

Females either do not have the characteristics seen in males or they are milder. The reason is females have two X chromosomes (males have only one) and are able to produce enough of the FMR1 protein to fill most of the body's needs, but not all.



Characteristics that are often not present prior to puberty are a large head disproportional to the body size, and a long, narrow face with prominent ears as described in the picture at right:

Other facial features include a broad forehead, puffiness around the eyes, narrow palpebral fissures (slit between the eyes), epicanthal folds (covering over the inner corner of the eye).

Dental anomalies are a high arched palate or cleft palate.

Strabismus (lazy or crossed eye) is often present as well as refractive errors such as nearsighted and farsighted. Nystagmus (constant involuntary movement of the eyeball) is also seen.

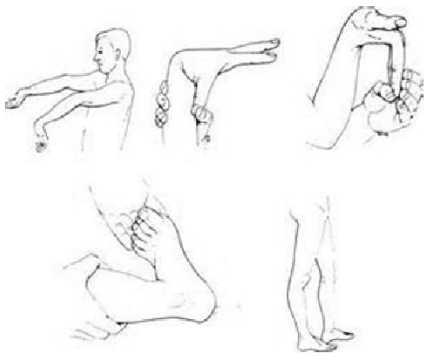
Chronic otitis media (ear infection) affects mostly males prior to puberty due to a floppy eustachian tube that does not drain the middle ear properly. Pressure Equalization Tube placement is needed in some instances.

Macroorchidism (abnormally large testes) is present in over 80% of males with FXS, but is also common in males with intellectual impairment without FXS. Some males with FXS will have macroorchidism prior to puberty; however, after puberty nearly all males will have testicles that are at least twice the volume of typical males. Adult males are often fertile and rare incidences of testicular tumors have been reported.

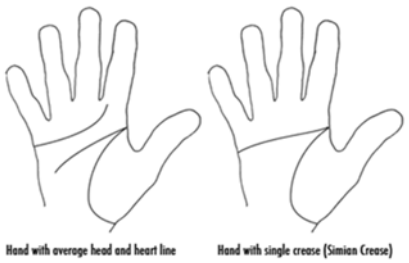
Orthopedic anomalies include pes planus (flat foot), pectus excavatum (funnel chest or sunken breast

Phenotype *(continued from page 2)*

bone), excessive joint laxity (double-jointedness), club foot and scoliosis. Skin Manifestations include soft smooth skin, wrinkled palms, single palmar crease, abnormal elastin and cutis verticis gyrate (thickening of the scalp with wrinkled appearance).



Excessive joint laxity



Single palmar crease

Cardiac Manifestations typically occur after adolescence and include: Mitral Valve prolapse, Mitral Valve Regurgitation, and mild dilation of the base of the aorta.

Hypertension and kidney dysfunction also can occur.

In 1984 FXS meant only one condition - FXS. Today it includes:

- Fragile X–associated tremor/ataxia syndrome (FXTAS)
- FragileX–associated primary ovarian insufficiency (FXPOI).

Fragile X-associated tremor / ataxia syndrome (FXTAS):

FXTAS is a neurodegenerative disorder that affects FX permutation carriers. It affects approximately 40% of males over 50 and 8% of females over the age of 40. Symptoms can include: action tremor (usually starts first), progressive cerebellar ataxia (balance impairment in sitting, standing and walking; also lack of coordination with hands and slurred speech), parkinsonism, cognitive decline, psychiatric disturbances and autonomic (involuntary body functions) and peripheral neuropathies.

The goal is to reduce symptoms and slow progression. Referrals are needed to neurology, urology, rehabilitation, genetic counseling and social services.

Fragile X-Associated Primary Ovarian Insufficiency (FXPOI):

FXPOI refers to impaired ovarian function, sometimes referred to as premature menopause (cessation of menses before age 40). Approximately 20% of women that carry the FMR1 permutation will develop FXPOI. Approximately 5% of females can resume ovulation, menstrual cycles and achieve pregnancy without fertility treatments, however infertile women should be tested for FXS.

Neurologic Findings

Hypotonia (low muscle tone) is caused by disruption of the signals between nerves and muscles causing decreased muscle strength.

Seizures are common in approximately 20% of those with FXS. Seizures usually start after age three and rarely after age nine. Seizures are more common in males and most frequently are the Simple or Complex Partial type of seizure.

Sleep Apnea due to facial structure and hypotonia of the mouth is likely.

People with FXS tend to have shorter sleep duration and longer night waking episodes.

There is an increased incidence of SIDS (Sudden Infant Death Syndrome) in infants with FXS, so episodes of apnea, obstructed breathing or possible seizures require a detailed workup and close monitoring.

Behavioral Phenotype includes:

- Intellectual disability
- Learning disabilities
- Language impairment
- Neuropsychiatric disturbances

Intellectual Disabilities

Intellect ranges from mild to profound with majority testing in the moderate range from 35 to 40. Their verbal IQ's are often higher than their performance would indicate.

Learning Disabilities

Learning disabilities are common, especially in Mathematics; strengths include single-word vocabulary visual matching task, reading and spelling skills.

Language impairment

Speech and language are generally delayed, even with normal intellect. Receptive language is poor. They have difficulty with comprehension of language, both listening and understanding. Expressive language also lacks in communication of thoughts using spoken and written language (dysfluency).

They tend to talk in incomplete sentences, repeat words said by others (echolalia), involuntarily repeat rapidly their own words

(palilalia) and uncontrollabley repeat a particular word or phrase despite absence of stimulus (perseveration). They also exhibit poor fluency in conversation and poor topic maintenance, shifts in speech pitch, and memory deficits.

Neuropsychiatric Issues

ADHD – 80-90% of boys and up to 50% of females with FXS may be extra sensitive to sensory stimuli. Hyperactivity and inattention are seen, with inattention being more common. Disruptiveness and hyperactivity tend to decrease with age, but attention and concentration persist. ADHD is managed with medication and behavior intervention, including management of the learning environment.

Autism – In 2-6% of all children diagnosed with Autism, the cause is the FX gene mutation. Thirty-three percent of all children diagnosed with FXS also have some form of Autism.

Gaze aversion is very common in males over the age of nine years when greeting another person. Head and gaze aversion is common with recognition of someone. This is different however from gaze aversion associated with people with autism. This is a higher frequency of gaze aversion compared to people with Intellectual Disability without FXS.

Gaze aversion causes disruption in social interaction and interpersonal relations. Males with FXS generally are socially responsive as compared to females with FXS.

Stereotypy – hand flapping, however, is less common in females with FXS.

Self-Injurious Behavior – exhibited as hand biting and scratching and may be elicited by excitement or frustration.

Shyness or Social Anxiety – Commonly seen in females with both the full mutation and permutation. It affects males as well, but is often overshadowed by ADHD symptoms or level of intellectual disability.

Aggression – as high as 50% of adolescents and men with FXS have been reported to have problems with aggressive outbursts; however, this seems to diminish in middle to late life.

Psychosis is seen.

Treatments

Speech, language, physical and occupational therapies need to be started early to be effective.

Medications may be used to treat:

- Seizures and mood instability
- Attention deficit
- Hyper arousal sensory overstimulation
- Aggression and Intermittent Explosive Disorder
- OCD, Anxiety and Depression
- Sleep disturbances

SENSORY DIET

A sensory diet is an **occupational therapy intervention** strategy devised to attain and maintain appropriate arousal states throughout each day. A sensory diet consists of a **carefully planned program** of specific sensory-motor activities that is scheduled according to each individual's needs (Wilbarger & Wilbarger, 2002) and each family's schedule and resources. A sensory diet can help maintain an age appropriate level of attention for optimal function to reduce sensory defensiveness. Like a diet designed to meet an individual's nutritional needs, a sensory diet consists of specific elements designed to meet the individual's sensory integration needs. The sensory diet is based on the notion that controlled sensory input can affect one's functional abilities.

Martin (1991) states in Principles of Neuroscience:

> Sensory systems are not only our means for perceiving the external world, but are also essential to maintaining arousal, forming our body image and regulating movement.

http://www.fragilex.org/treatment-intervention/therapy/sensory-diet

Fragile X Syndrome Test

Name: _____ Role/Title: _____

Agency: _____ Date: _____

Please provide contact information (email address, fax number, or mailing address) where you would like your certificate to be sent:

_____

_____

You must submit your completed test, with at least a score of 80%, to receive **1 hour** of training credit for this course.

* To submit via fax, please fax the test and evaluation to 814-728-8887. Please fax only the test and evaluation, not the entire training packet.
* To submit via email, please send an email to HCQUNW@MilestonePA.org. Please put "Fragile X Syndome" on the subject line, and the numbers 1—10, along with your answers, in the body of the email, OR scan the test and evaluations pages and email as attachments.
* To submit via mail, send the test and evaluation pages to Milestone HCQU NW, 247 Hospital Drive, Warren PA 16365.

Knowledge Assessment:

1. Men who carry the gene that causes Fragile X pass it on to all their sons. True False
2. Sixty percent of males with FXS also have Autism. True False
3. Females generally do not have the physical characteristics commonly seen in males, or they are milder, because they have two X chromosomes. True False
4. The majority of people with FXS have IQs ranging from 50-75. True False
5. A sensory diet consists mainly of vegetables and protein True False

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EVALUATION OF TRAINING

Training Title: Fragile X Syndrome Date: _____

- ☐ Direct Support Professional
- ☐ Provider Administrator/Supervisor
- ☐ Program Specialist
- ☐ Provider Clinical Staff
- ☐ Consumer/Self-Advocate
- ☐ Family Member
- ☐ Support Coordinator
- ☐ Support Coordinator Supervisor
- ☐ PCH Staff/Administrator
- ☐ County MH/MR/IDD
- ☐ FLP/LSP
- ☐ Other (please list): _____

Please circle your PRIMARY reason for completing this home-study training:

☐ It's mandatory ☐ interested in subject matter ☐ need training hours ☐ convenience

Please circle the best response to each question.

5 = Strongly Agree 4 = Agree 3 = Undecided 2 = Disagree 1 = Strongly Disagree

1.	As a result of this training, I have increased my knowledge.	5	4	3	2	1
2.	I learned something I can use in my own situation.	5	4	3	2	1
3.	This training provided needed information.	5	4	3	2	1
4.	The training material was helpful and effective.	5	4	3	2	1
5.	Overall, I am satisfied with this training.	5	4	3	2	1
6.	I am glad I completed this training.	5	4	3	2	1

Suggestions for improvement: _____

Additional information I feel should have been included in this training: _____

I would like to see these topics/conditions developed into home-study trainings: _____