Fragile X
For Healthcare Providers

This is a customized health care provider version of our website. Please visit the main website to find more comprehensive information for families and schools (www.negenetics.org).

Fragile X syndrome occurs in both males and females. It is caused by a change or mutation in the FMR1 gene located on the X chromosome. The FMR1 gene produces a protein important for normal brain development. Fragile X syndrome is caused by what is termed a trinucleotide repeat expansion (an increase in a CGG repetitive sequence) in the FMR1 gene. There is a range of normal number of CGG repeats (5-44 repeats), in which there is no known instability and will not lead to an expansion; an intermediate range (45-54 repeats) in which about 14% of the time can expand to premutation size; a premutation range (55-200 repeats) and a full mutation (>200 repeats). Intellectual disability may be found in up to 50% of females and virtually all males with a full mutation.

NOTE: This document only reviews the features found in males and females with a full mutation.

Physical characteristics and/or symptoms

*Note: not all people with Fragile X will have all of these features.*

**MALES** - The clinical findings in males with a full mutation may include the following:

- Intellectual disability (IQ may range from 22-65).

- Behavioral differences *may* include:
  - Autism spectrum disorder
  - Hyperactivity
  - Shyness
  - Gaze aversion
  - Hand flapping
  - Hand biting
  - Temper tantrums
• Specific facial appearance and physical findings which may include:
  o Large head
  o Long face
  o Large forehead and chin
  o Ears that stick out
  o High arched palate or sometimes cleft palate

• Macroorchidism - not apparent until after puberty

• Joint hypermobility

• Cardiac findings include mitral valve prolapse and aortic root dilatation.

• Strabismus

• Other findings may include:
  o Hypotonia
  o Reflux
  o Recurrent otitis media
  o High blood pressure
  o Seizures.

**FEMALES** - Clinical finding in females who have a full mutation:

• Females may have some of the same physical features as males.

• Mild intellectual disability in up to 50% of females (IQ may range from 74-91).

• Other learning difficulties or subtle cognitive features, such as difficulty with math

• Behavioral differences **may** include the following:
  o Social anxiety
  o Selective mutism
  o Excessive shyness
  o Poor eye contact
  o Hyperactivity, and/or impulsive behavior.

**Recommended Routine Surveillance**

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[www.negenetics.org](http://www.negenetics.org)
• Assessment of feeding/eating, digestive problems (including constipation and gastroesophageal reflux)
• Surveillance for cardiac abnormalities
• Assessment for hypertension
• Ophthalmologic evaluation
• Monitor recurrent otitis media
• Evaluate hypotonia and/or connective tissue findings
• Monitor for seizures

Emergency Protocols

There are no specific emergency protocols for this particular condition as it is not typically associated with episodes of sudden and serious medical decompensation.

• Emergencies should be handled as with any child.
• If seizures are present, the following seizure action plan may be useful:
  https://www.epilepsy.com/learn/managing-your-epilepsy/seizure-action-plans

Specialists Who May Be Involved

Follow up is need on a case-by-case basis. A multidisciplinary team approach to best meet the child’s individual needs is recommended.

• Cardiologist
  o Screening for mitral valve prolapse
  o Aortic root dilatation

• Developmental specialist
  o Speech therapy
  o Physical therapy
  o Occupational therapy
  o Autism spectrum disorder /autistic signs

• Gastroenterologist
  o Gastroesophageal reflex
  o Constipation

• Geneticist /Genetic Counselor:
  o Diagnosis
  o Coordination of care
  o Genetic risk for family

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Clinical trials

- Neurology
  - Monitor seizures

- Ophthalmologist
  - Strabismus

- Orthopedists
  - Gait ataxia
  - Joint laxity
  - Pes planus
  - Hypotonia

- Ophthalmologist
  - Strabismus

Sample Forms

- Sample paragraph to be used for Letters of Medical Necessity or Letters to the school:

  My patient __________________ has been diagnosed with Fragile X. This condition is characterized by hypotonia, autism, behavioral differences, and developmental delays/intellectual disability. Medical complications with Fragile may seizures and gastrointestinal symptoms. Because of these, ______ needs the following accommodations.

Seven Important Aspects of School Life

“Fragile X at a Glance” will help you talk with parents and schools about:

- Medical / Dietary Needs
- Education Supports
- Behavior & Sensory Supports
- Physical Activity, Trips, Events
- School Absences & Fatigue
- Emergency Planning
- Transitions
Resources

Fragile X Syndrome: Diagnosis, Treatment and Research
This book published in 2002 by John Hopkins University Press is a good resource. It was edited by Randi Jenssen Hagerman, M.D. and Paul J. Hagerman, M.D., Ph.D.

National Center for Biotechnology Information (NCBI) Bookshelf – Fragile X
http://www.ncbi.nlm.nih.gov/books/NBK22189/

American Academy of Pediatrics (AAP) – Health Supervision Guidelines
http://pediatrics.aappublications.org/content/127/5/994.full.pdf%20html

FMR1 Disorders
https://www.ncbi.nlm.nih.gov/books/NBK1384/

AAP: Fragile X Syndrome: Resources for Pediatric Clinicians

National Fragile X Foundation – Find a Clinic
https://fragilex.org/our-research/fragile-x-clinics/