Early Check
Expanded health screening for your baby

Fragile X Syndrome Fact Sheet for Health Professionals

North Carolina is conducting a pilot study to screen newborns for fragile X syndrome (FXS).

To gather additional information about the technical aspects of screening for FXS in newborns, the National Institutes of Health has awarded a contract to:

- RTI International
- University of North Carolina at Chapel Hill (UNC-CH)
- Duke University
- Wake Forest School of Medicine
- North Carolina State Laboratory of Public Health

This project team will perform voluntary laboratory testing and provide follow-up for infants who screen positive for fragile X syndrome. Screening will be performed by the NC State Laboratory of Public Health on the dried blood spot retained after standard newborn screening.

About Fragile X syndrome

Frequency: Fragile X syndrome (FXS) is the most common genetic cause of intellectual disabilities in boys. Both males and females have FXS, but females are usually more mildly affected. The frequency of FXS is not precisely known, but approximately 1 in 3,600-4,000 males and 1 in 4,000-6,000 females are born with the condition. FXS affects people of all ethnicities and races.

Effects: FXS has a wide range of developmental, behavioral, and physical effects that vary in severity. Boys with FXS often have speech delays, and mild to moderate intellectual disability.

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- Behavioral characteristics can include inattention with or without hyperactivity, aggressive tendencies, and autism or autistic behaviors. Children who have autism may also have a higher incidence of seizures.
- Physical features can include connective tissue laxity that results in hyperextensible joints, flat feet, high arched palate, and ear infections. Characteristic elongated face, large ears, and macroorchidism may not be apparent until puberty.
- Females can experience the same developmental, behavioral, and physical effects of FXS as males, but these are more variable and typically milder in females. About one-third of females who has the full fragile X mutation has intellectual disability. Some females with the full mutation have no apparent features of the condition.

Cause: FXS is caused by a full mutation in the gene FMR1, which provides instructions for the Fragile X Mental Retardation Protein (FMRP) necessary for normal brain development. The full mutation silences the gene, reducing available FMRP.

Inheritance: The full mutation occurs when the gene becomes unstable due to a repeated DNA pattern of the trinucleotide CGG (cytosine-guanine-guanine).

- Most people have less than 45 CGG repeats, which is considered the normal range.

- 45-54 CGG repeats is called Gray Zone or Intermediate allele.
- Fragile X premutation associated with "carrier status" ranges from 55-200 CGG repeats. When passed from mother to child, premutations can expand to greater than 200 CGG repeats, which is the full mutation.
- For some women, AGG interruptions in the string of CGG repeats can stabilize the gene and decrease the risk of expansion from premutation to full mutation.

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- Most children with FXS inherit the mutation from their mother, who has the premutation or sometimes the full mutation. However, mutations are also transmitted from father to daughter on the X chromosome.

- The full mutation results in hypermethylation of *FMR1*, leading to a decrease in the production of the fragile X mental retardation protein (FMRP) and causing the features associated with fragile X syndrome.

Treatment: There is no cure or single treatment for fragile X syndrome; however, a variety of therapies, medications, and interventions can help children with FXS reach their full potential. Early intervention is recommended to give children with FXS the best possible start. Children with FXS can be cared for by their regular pediatrician, and many also benefit from specialized fragile X clinic visits.

Testing: Fragile X can be tested for on blood or saliva. Prenatal diagnosis and preimplantation genetic diagnosis are also available.

- Parents of children with fragile X syndrome (FXS) or fragile X premutation (FXPM) should consider testing.
- Testing should be considered for children, siblings, cousins, and more distant family members of people with FSX or FXPM, especially if they have problems with development, learning, or behavior. Knowing if a grandparent has FXPM can guide testing for other family members.
- Maternal grandfathers of children with fragile X should consider testing, especially if they have developed trembling hands, changes in personality or mood, or difficulty walking or thinking.
- Family members who are pregnant or considering pregnancy should speak with their doctor or a genetic counselor to learn more about this complex inheritance pattern, testing, and reproductive technologies.

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More information

- **American Academy of Pediatrics Health Supervision Guidelines for Fragile X Syndrome:** http://pediatrics.aappublications.org/content/127/5/994
- **National Fragile X Foundation**: https://fragilex.org/
- **CDC Fragile X Syndrome:** https://www.cdc.gov/ncbddd/fxs/index.html
- **Early Check Information for Healthcare Professionals:** https://www.earlycheck.org/Early%20Check%20Information%20for%20Health%20Care%20Providers.pdf

Fragile X Clinics

Greenwood Genetics Center South Carolina (various locations)	https://www.ggc.org/fragilex	(843) 664-2983
Duke University Medical Center Durham, NC	https://fragilex.org/duke-university-medical-center/	(919) 668-4468

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