

## Is there a cure for Fragile X syndrome?

Although research continues and knowledge about Fragile X and its characteristics grows, there is no cure for Fragile X at this time.

## Are there treatments for Fragile X syndrome?

Currently there is no definitive, single treatment for Fragile X. However, there are a variety of ways to help minimize the symptoms of the condition. Children with Fragile X who receive appropriate **education, behavioral or physical therapy, and medication** have the best chance of using their individual capabilities and skills. Even those with significant mental retardation can learn to master many self-help skills.

One important factor in developing a child's long-term potential is **early intervention**. The sooner a child begins to get help, the more opportunity for learning. Because a young child's brain is still forming, early intervention gives children the best start possible and the best chance of developing their full potential. Even so, no matter when a person is diagnosed with Fragile X, it's never too late to benefit from treatment.



## Are there treatments?

### Educational options

Most children with Fragile X, including those with severe mental retardation, are guaranteed free, appropriate public education under federal law. Public Law 105-17: The Individuals with Disabilities Education Act—IDEA (1997) makes it possible for children with disabilities to get free educational services and educational devices to help them learn as much as they can. Each child is entitled to these services from age three through high school, or until age 21, whichever comes first. Also, every state operates an early intervention program for children from birth to age three; children with Fragile X should qualify for these services. The law also states that children must be taught in the least restrictive environment, appropriate for that individual child. This statement does not mean that each child will be placed in a regular classroom, but instead, that the best combination of one-to-one tutoring, small group work, and regular classroom work will be arranged.

Because not all children or adolescents with Fragile X have mental impairment or special needs, a medical diagnosis of Fragile X does not guarantee access to special education services. The child must have certain cognitive or learning deficits. Parents can contact a local school principal or special education coordinator to learn how to have their child examined to see if he or she qualifies for services under the IDEA.

If a child qualifies for special services, a team of people, including the child's parents or caregivers, teachers, school psychologist, and other child development specialists, will work together to design an **Individualized Education Plan (IEP)** for the child. The IEP includes specific learning goals for that child, based on his or her needs and capabilities. The team also decides how best to carry out the IEP, such as making choices about classroom placement for the child, determining any devices or special assistance the child needs, and identifying the developmental specialists who will work with the child.

A child with Fragile X should be evaluated and re-evaluated on a regular basis by his or her special services team. In this way, the team can determine how the child is doing and whether any changes are needed in his or her treatment (for instance, changes to the IEP, changes in classroom placement, or changes in other services) to ensure the child is getting the best possible care.

In general, there are three classroom placement options for a child with Fragile X, based on his or her specific abilities and needs:

- **Full inclusion in a regular classroom.** The child spends the full day in the regular classroom rather than just among children with special needs. This situation is sometimes called “mainstreaming.” Specialists work with the child in the classroom, with other students present. There may be an aide assigned to help the child with certain kinds of tasks.
- **Inclusion with “pull-out” services.** In this type of placement, the child spends most of the day in the regular classroom. However, for part of the day, he or

she attends small-group classes with one or more developmental specialists, such as a speech-language therapist or a physical therapist. This arrangement gives the child exposure to children who do not have special needs, as well as more individual attention to his or her areas of special needs.

- **Full-time, special education classroom.** Some children with Fragile X may do better in a smaller special education class than in a regular classroom. Special education classrooms usually have fewer children and offer more individualized attention from the teacher. Such programs may be offered at the school or in central locations that serve a larger area. Regional special education centers often have facilities and equipment designed for children with special needs. For some children, a special school for children with similar disabilities may be the best option.

Placement decisions should be based on each child’s needs and abilities. In most cases, these decisions require a balance of various priorities to maximize the chances for the best possible outcome for the child.

## Are there treatments?

### Therapeutic options

A variety of professionals can help individuals with Fragile X and their families deal with symptoms of the disorder. Such assistance is usually most effective when provided by health care professionals experienced with Fragile X.

- **Speech-language therapists** can help people with Fragile X to improve their pronunciation of words and sentences, slow down speech, and use language more effectively. They may set up social or problem-solving situations to help a child practice using language in meaningful ways. For the minority of children who fail to develop functional speech, this type of specialist may work with other specialists to design and teach nonverbal ways of communication. For example, some children may prefer to use small picture cards arranged on a key ring to express themselves; or they may learn to use a hand-held computer that is programmed to “say” words and phrases when a single key is pressed.



- **Occupational therapists** help find ways to adjust tasks and conditions to match a person’s needs and abilities. For example, this type of therapist might teach parents to swaddle or massage their baby who has Fragile X to calm him or her. Or the therapist might find a specially designed computer mouse and keyboard or a pencil that is easier for a child with poor motor control to grip. At the high school level, an occupational therapist can help a teenager with Fragile X identify a job, career, or skill that matches his or her interests and individual capabilities.<sup>17</sup>



- **Physical therapists** design activities and exercises to build motor control and to improve posture and balance. They can teach parents ways to exercise their baby's muscles. At school, a physical therapist may help a child who is easily over-stimulated or who avoids body contact to participate in sports and games with other children.
- **Behavioral therapists** try to identify why a child acts in negative ways and then seek ways to prevent these distressing situations, and to teach the child to cope with the distress. This type of specialist also works with parents and teachers to find useful responses to desirable and undesirable behavior. During puberty, rising and changing hormone levels can cause adolescents to become more aggressive. A behavioral therapist can help a teenager recognize his or her intense emotions and teach healthy ways to calm down.



The services of these specialists may be available to pre-school and school-aged children, as well as to teens, through the local public school system. In a school setting, several specialists often work together to assess each child's particular strengths and weaknesses, and to plan a program that is specially tailored to meet the child's needs. These services are often free. More intense and individualized help is available through private clinics, but the family usually has to pay for private services, although some health insurance plans may help cover the cost.

## Are there treatments?

### Medication options

Currently, there is no medication that can cure Fragile X. Further, the Food and Drug Administration (FDA) has not approved any drugs specifically for the treatment of Fragile X or its causes. But, in many cases, medications<sup>18</sup> have been used to treat many of the symptoms associated with Fragile X, as shown in the table on the next page. **Please note that the NICHD does not endorse or support the use of any of these medications in treating symptoms of Fragile X syndrome, or for other conditions for which the medications are not FDA approved.**

Medication is most effective when paired with therapy designed to teach new coping skills or behavior. Not every medication helps every child with behavioral symptoms related to Fragile X. Doctors usually prescribe these kinds of medications on a trial basis, to see if they help. If so, the doctor may need to adjust the dose to meet the needs of each child.



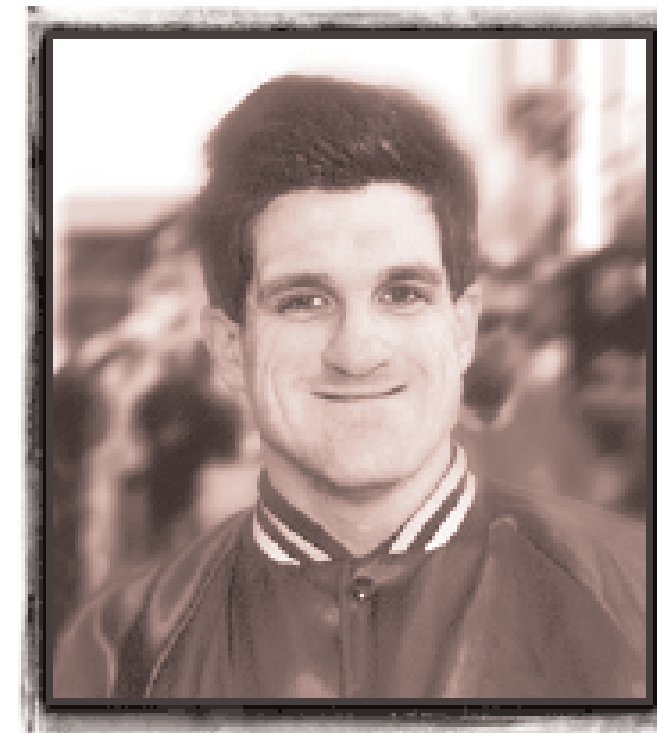
*This chart is meant for reference ONLY and should not take the place of your health care provider's advice. You should discuss any questions you may have about medication with your health care provider directly.*

Some of these medications have serious risks involved with their use; others may make symptoms worse at first or may take several weeks to become effective. Doctors may have to try different dosages or different combinations of medications to find the most effective plan. Families, caregivers, and doctors need to work together to ensure that a medication is working, and that a medication plan is safe.

Symptoms	Generic Medications (Brand names in parentheses)
Seizures Mood instability	<ul style="list-style-type: none"> <li>Carbamazepine (Tegretol)</li> <li>Valproic acid or divalproex (Depakote)</li> <li>Lithium carbonate</li> <li>Gabapentin (Neurontin)</li> <li>Lamotrigine (Lamictal)</li> <li>Topiramate (Topomax), tiagabine (Gabitril), and vigabatrin (Sabril)</li> <li>Phenobarbital and primidone (Mysoline)</li> <li>Phenytoin (Dilantin)</li> </ul>
Attention deficit (With or without hyperactivity)	<ul style="list-style-type: none"> <li>Methylphenidate (Ritalin, Concerta) and dexamethamphetamine (Adderall, Dexedrine)</li> <li>L-acetylcarnitine</li> <li>Venlafaxine (Effexor) and nefazodone (Serzone)</li> <li>Amantadine (Symmetrel)</li> <li>Folic acid</li> </ul>
Hyperarousal Sensory over-stimulation (Often occurs with ADD/ADHD)	<ul style="list-style-type: none"> <li>Clonidine (Catapres TTS patches)</li> <li>Guanfacine (Tenex)</li> </ul>
Aggression Intermittent explosive disorder Obsessive-compulsive disorder (Often occurs with anxiety and/or depression)	<ul style="list-style-type: none"> <li>Fluoxetine (Prozac)</li> <li>Sertraline (Zoloft) and citalopram (Celexa)</li> <li>Paroxetine (Paxil)</li> <li>Fluvoxamine (Luvox)</li> <li>Risperidone (Risperdal)</li> <li>Quetiapine (Seroquel)</li> <li>Olanzapine (Zyprexa)</li> </ul>
Sleep disturbances	<ul style="list-style-type: none"> <li>Trazadone</li> <li>Melatonin</li> </ul>

## What are the options for adults who have Fragile X syndrome?

IDEA requires transition plans for moving from one phase of life to another, and the move from teenager to young adult to adult is no exception. The special services team, which can include family, teachers, a school psychologist, and other developmental specialists, makes the transition plan based on the individual's needs, interests, and skills. These plans may include vocational assessment and training, additional education, supported employment, and community participation. IDEA requires that the plan be in place by the time the individual is 16 years old. The plan will also consider the individual's level of independence to determine what type of living arrangements he or she might benefit from in the future.



As the teenager with Fragile X gets closer to finishing high school, or to his or her 21st birthday, the structure of his or her day may change to include work/study programs, job-related behavior training, and independent living classes. With the proper treatment and training, a young person with Fragile X may be able to live on his or her own, hold a job, and be an active member of his or her community.

## What should I do if I find out someone in my family has Fragile X syndrome?

If someone in your family, a child or an adult, is diagnosed with Fragile X, you may also want to be tested to see if you have a mutated *FMR1* gene. It is now possible to test for Fragile X in people of any age, as well as before birth. These tests are simple and accurate.

At present, testing for Fragile X is not done routinely. The tests are often done to help diagnose a child who is developmentally delayed or shows signs of autism or mental retardation.<sup>19</sup> Couples who have one or more relatives with mental retardation of unknown cause may also want to be evaluated before deciding to have a child.

Health care professionals may also recommend an evaluation for Fragile X in a person with one of the following traits:<sup>20</sup>

- Any person who has mental retardation of unknown cause, developmental delay, or learning disability
- Any person with autism or showing autistic-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



## Tests commonly used to diagnose Fragile X

A number of tests are used to diagnose Fragile X. Each test has its limitations, so in many cases more than one test may be used. The most accurate tests are DNA tests.

- **DNA molecular tests** count the number of CGG repeats in the promoter region of the *FMR1* gene and check to see if the gene is methylated (inactive). These tests are used most often to diagnose Fragile X. The two main DNA tests include:
  - **Southern Blot** studies how quickly DNA pieces move through a liquid or gel when exposed to electricity. Although good at finding large numbers of repeats and determining methylation, this process is rather slow.
  - **Polymerase Chain Reaction (PCR)** multiplies the amount of DNA being tested so it can be analyzed more quickly. Although it can miss some large repeat mutations, this test is much faster to perform and is very good at detecting small and medium-sized repeat segments.

- **Chromosome test** looks for the “broken” area of a chromosome using a microscope. Because this test is older, costly, and often inaccurate, it is recommended that another type of test be used to diagnose Fragile X. The DNA test is needed to confirm the diagnosis.
- **Protein test** measures the amount of FMRP produced by living cells. This test is useful for screening large groups of people for Fragile X. In the future, this test may be helpful in evaluating how severe an *FMR1* mutation is. The DNA test is needed to confirm the diagnosis.

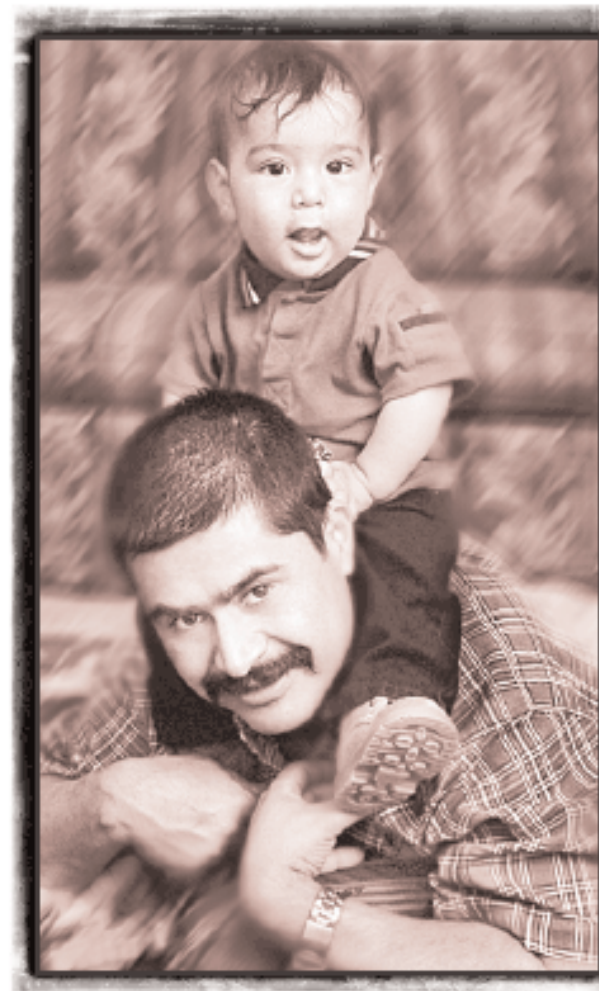




### *Prenatal testing for families who are at risk*

A pregnant woman who has characteristics that place her at risk for Fragile X, such as features of Fragile X or a family history that suggests the presence of Fragile X, may want to have a prenatal test. During such a test, the doctor either takes a sample of amniotic fluid, a process called amniocentesis, or takes a sample of cells from the placenta, a process called chorionic villus sampling. Then the cells are sent to a lab, where they go through one of the methods used to diagnose Fragile X. Cells that contain a larger number of CGG repeats would be diagnosed as having Fragile X.

These tests can be done on many different types of body tissues. In most cases, a simple blood test provides the cells needed. But cells from hair roots and from inside the cheek can also be used. If you or one of your family members wants to be tested, talk to your health care provider. He or she will likely take a sample of your blood and send it to a lab. The results will come back in a number of weeks. For more information on tests for Fragile X and their features, please refer to the *Additional Resources* section of this booklet.



## What is being done to develop treatments or a cure for Fragile X syndrome?

Since the late 1960s, the NICHD has supported the research of scientists who are trying to understand Fragile X. The work of these scientists continues to increase knowledge about this disorder, but many questions still remain unanswered.

In 1991, researchers funded by the NICHD identified *FMR1* as the gene that, when mutated, causes Fragile X. Since that time, the NICHD has been a major source of funds for Fragile X research. In addition, a number of private, non-profit organizations, including the **FRAXA Research Foundation**, the **National Fragile X Foundation**, and the **Conquer Fragile X Foundation**, are also dedicated to continuing Fragile X research and to raising awareness of the disorder.

In the Children's Health Act of 2000, congress authorized the NICHD to create and maintain at least three research centers specifically for Fragile X research. In March 2003, the NICHD announced awards for the following Mental Retardation and Developmental Disabilities Research Centers to house the new Fragile X Research Centers: the University of North Carolina, in affiliation

with the University of Kansas; the University of Washington; and Baylor College of Medicine. The efforts of these new centers began in late spring 2003.

Also in 2000, the NICHD initiated, with financial collaboration from the FRAXA Research Foundation and the National Institute of Mental Health, a special research program to support noted scientists around the world in an effort to find treatments and a cure for Fragile X.

Some of these researchers are examining Fragile X at the molecular level. Some of the questions they are asking include:

- Why does the *FMR1* gene have an increased number of CGG repeats in the promoter region?
- What causes the increased methylation of the promoter region, which blocks the gene from producing FMRP?
- What is the role of FMRP in the brain?
- How does FMRP help other proteins, and what are the functions of those proteins?

The findings from such research may help to prevent or reverse mental retardation and other symptoms of Fragile X.

To advance the field of Fragile X research, scientists are also working to create models of how the human brain works. Some are creating computer programs that imitate the way the human brain learns and remembers. Other scientists modify genes in other animals, such as mice and fruit flies, to try new interventions or treatments. For instance, researchers can replace the *FMR1* gene in a normal mouse with a mutated human *FMR1* gene. Such "transgenic" animals are key to much of the current research. For example, one recent study is examining the effects of a certain substance in transgenic mice that don't produce FMRP. Researchers believe that this compound could help regulate brain processes that are impacted by a lack of FMRP. Using these mice, researchers can test this new intervention to ensure that it is safe and effective before the intervention is used with humans.





Can we prevent or cure Fragile X? Two decades ago, researchers might have said “No.” Now scientists are exploring several promising possibilities, including:

- **Gene repair, gene reactivation, and gene therapy.** Scientists may be able to induce certain brain chemicals to repair defective *FMR1* genes. Researchers also seek ways to prevent or reverse methylation, the process that interferes with the instructions for making FMRP and inactivates the *FMR1* gene. Still other scientists are trying to determine if it is possible to replace defective genes with stable, working copies of the *FMR1* gene. This type of gene research involves a number of challenges. First, it is important that researchers learn how many cells are needed to produce the right amount of protein. Too much of the protein may be as harmful as too little, so finding the right balance is crucial. Another difficulty lies in targeting only the defective *FMR1* genes for repair or reactivation, without affecting other healthy genes. Further, replacing genes, especially those involved in brain function, carries additional problems and risks. However, researchers continue to pursue these avenues.

NICHD-supported and other sponsored research is already underway to study the possibility of reversing methylation on the *FMR1* promoter sequence, prenatally. Success in this area may allow scientists to “reactivate” FMRP production before a child is born. Other gene research is also underway.

- **Protein replacement.** Scientists already make FMRP in the lab. At present, however, they are unable to get FMRP to the brain, partly because the FMRP molecule is too large to pass through the structures that protect the brain. Someday people with Fragile X may be able to take a pill or injection of FMRP to relieve many of the symptoms of Fragile X.
- **Protein substitute through medication.** Scientists may be able to use other substances to take the place of FMRP in certain brain processes. Using these substitutes, brain processes and other functions of FMRP may be able to occur normally. For example, new drugs may be able to regulate processes in the brain, like communication between neurons, that seem to be affected by low levels of FMRP.

While these research avenues are promising, none of them has progressed enough to provide immediate help to someone with Fragile X. Parents, families, and caregivers should work together with health care professionals, educators, and therapists to ensure that those affected by Fragile X receive the care that they need.

This is an exciting time in Fragile X research. Dr. James Watson, who received the Nobel Prize in Physiology or Medicine for the co-discovery of the double-helix structure of DNA, believes that science will be able to defeat the negative effects of Fragile X. He predicts, “Our wealth of research strategies and technologies may soon lead to new forms of therapy and medication. Someday we may be able to prevent the mental retardation and other symptoms of Fragile X.”

