Fragile X Syndrome

A handbook for families and professionals
FRAGILE X SYNDROME

A Handbook for Families and Professionals

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Fragile X syndrome is a hereditary condition which can cause learning problems in both males and females. It is the most common known cause of inherited mental impairment. The spectrum of intellectual involvement ranges from subtle learning difficulties and a normal IQ to severe developmental disability and autism. In addition to mental impairment, fragile X syndrome is associated with a group of physical and behavioral characteristics as well as speech and language delays.

Fragile X syndrome can be passed on in a family by individuals with no signs of the condition. In some families, it is a condition which has been occurring for decades, affecting numerous family members through the generations; while in others, it seems to have caused problems in only one person.

Regardless, the genetic implications of this diagnosis are far-reaching and can place a tremendous emotional burden on even distant relatives.
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INTRODUCTION

A person may have mental impairment or learning disabilities for many reasons. But did you know that almost half the time, no cause for the disability can be found? Families may go on for years, seeing specialist after specialist, searching for an explanation. Many of these families eventually draw their own conclusions about why the problems occurred. Others just stop looking for answers.

In recent years, more and more people are learning about fragile X syndrome. Increasingly, children and adults with no known cause for their mental impairment are being tested for this common genetic condition. As a result, many families with fragile X syndrome are being correctly diagnosed. Whether this is the answer they had been seeking for years, or whether this news comes about unexpectedly, fragile X syndrome is not the diagnosis most families had hoped to find. Learning about the implications of the fragile X diagnosis can be a slow and often painful process. With time, support, and understanding however, many people are able to cope and move forward.

When Tommy was almost three, his pediatrician suggested that he have a special type of blood test called a fragile X DNA study. His parents knew that Tommy was a very active little boy who sometimes had behavior problems. They were concerned because Tommy had not yet started to talk like other children his age and were eager to rule out any specific kind of problem. When their son’s blood test showed him to have fragile X syndrome, they could not believe it. It took them a long time before they could even talk about the possibility that their cute little boy might have serious learning problems.

Jean was a shy, withdrawn 12 year-old when her parents first found out about fragile X syndrome. For most of her school years, Jean needed extra tutoring in math just to keep up with her classmates. When Jean’s blood test was positive for fragile X syndrome, her parents’ first reaction was relief at finally solving the mystery of their daughter’s learning problems. But these feelings were mixed with worry when they thought about the possibility of more severe mental impairment in future generations.

Alice first learned of the possibility that she could have a child with fragile X syndrome when she received a letter from her cousin, Mary. Through Mary’s letter, she learned that two uncles who she’d never met had just been diagnosed with fragile X syndrome. As she began to read through the complicated descriptions of genes and chromosomes, carrier males and females, Alice became increasingly confused and frustrated. She wished that she had never opened the letter. Fragile X syndrome was not something she wanted to learn about, and she was angry with her cousin, with her uncles, and with life in general for burdening her future plans. It was three months before Alice was able to show the letter to her husband and siblings.
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Common Features of Fragile X Syndrome

**Physical**
- large ears
- long, narrow face
- prominent forehead
- prominent, square chin
- large testicles
- high palate (roof of mouth)
- hand calluses
- mitral valve prolapse
  (a leaky heart valve)
- seizures
- eye problems

**Non-Physical**
- developmental delay
- mental retardation
- learning disabilities
- hyperactivity
- autistic-like features:
  - hand biting
  - hand flapping
  - poor eye contact
- shyness, social anxiety
- mental health issues
- talkativeness
- rapid, repetitive speech
- difficulty adjusting to change

MEDICAL TALK

There is no way around it—learning about fragile X syndrome is like learning a new language. It takes time and patience to familiarize yourself with terms like X-linked and DNA. More than a quick glance is necessary to make sense out of charts and diagrams, X’s, and Y’s. Understanding how the condition is passed from generation to generation can also be difficult. The following information is intended as a general guide to understanding fragile X syndrome. Specific details about your family’s situation should be discussed with a genetic counselor. To find a genetic counselor in your area, ask for a referral from your doctor.

**Physical, Behavioral and Intellectual Characteristics**

A syndrome is simply a grouping of unusual physical, behavioral and/or intellectual features which occur together in a single person. In the case of fragile X syndrome, the common characteristics associated with this condition can be quite subtle, especially in young children.

As you can see from the photographs in this booklet, and as many families will tell you, children and adults with fragile X syndrome are often not very different in appearance from other people. In fact, when a baby is born with the condition, parents and doctors usually have no idea that anything is wrong. Generally, it is only as a child grows older and may be slow in walking or talking (developmentally delayed) that parents and others become concerned.

Still, certain physical characteristics are associated with fragile X syndrome in both males and females. The ears of people with the disorder are often large, and their faces may have a long and narrow shape, with a prominent square chin. The facial features tend to be more noticeable in adults than children, and in males more often than females. Macroorchidism, which simply means large testicles, is found in most adult men with the syndrome, and may sometimes be present in younger boys.

If fragile X syndrome only caused long faces and large ears, there would be very little reason for concern. Mental impairment, however, is common, especially among males. Children are often slow in developing speech. When they do talk, their speech is often repetitive and difficult to understand. Unusual behaviors, including hyperactivity, a short attention span, and autistic-like features, such as poor eye contact and hypersensitivity to the environment, also concern parents. Other common characteristics of fragile X syndrome are listed in the table above. It is important to remember that every individual with fragile X syndrome is unique. Therefore, people with the condition may have just a few or many of the features described.
**Medical Talk**

There is no way around it—learning about fragile X syndrome is like learning a new language. It takes time and patience to familiarize yourself with terms like *X-linked* and *DNA*. More than a quick glance is necessary to make sense out of charts and diagrams, X’s, and Y’s. Understanding how the condition is passed from generation to generation can also be difficult. The following information is intended as a general guide to understanding fragile X syndrome. Specific details about your family’s situation should be discussed with a genetic counselor. To find a genetic counselor in your area, ask for a referral from your doctor.

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THE BASICS OF HEREDITY

Fragile X syndrome can be passed on in families by people of either sex who have no obvious signs of the condition. To understand how this happens, you will first need to know about genes and chromosomes and human inheritance.

Every person’s body is made up of thousands of tiny structures called cells. Each cell comes with a full set of “instructions” which tell the cell what to do and how to make our bodies work. These instructions are called genes, and they are made from a chemical called DNA.

Genes usually come in pairs, and they determine everything about our bodies. For example, certain genes in our eye cells determine eye color, while other genes in our blood cells determine blood type.

Inside each cell, thousands of genes are packed together to form larger structures called chromosomes. Although we cannot see genes, we are able to visualize chromosomes using a microscope. Most people have 46 chromosomes (23 pairs) which are numbered from 1 to 22. We call the 23rd pair the sex chromosomes because they determine a person’s sex (male or female). In females, both sex chromosomes are similar and are called “X” chromosomes. Males have one “X” and one “Y” chromosome.

In the illustrations on the opposite page, the chromosomes from a man and a woman have been lined up to show their 23 pairs.
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GENES AND INHERITANCE

Genes are often called the units of heredity because the information they contain is passed from one generation to the next. Genes generally come in pairs, one from each parent; the exceptions are genes of the X (or Y) chromosome in males where there is only a single copy. In this way, our bodies work with a combination of instructions inherited from both our parents. Parents have no control over which genes get passed to their children.

In May 1991, the gene responsible for fragile X syndrome was identified. This gene is called FMR-1, and it plays an important role in normal brain development in all people. Every person has at least one FMR-1 gene. Women have two X chromosomes, so they have two copies of the FMR-1 gene. Men have only one X chromosome and have just one copy of the FMR-1 gene. Fragile X syndrome is caused by a complex change (called a mutation) in the FMR-1 gene that occurs over many generations. In people affected by fragile X syndrome, a mutation keeps the FMR-1 gene from functioning properly.

Although nearly all males with a fragile X mutation have learning and/or behavioral problems, a few appear to be unaffected. Girls and women who have a fragile X mutation are often unaffected because they have a second X chromosome which is working properly. However, some of these females have learning and/or mental health issues.

Fragile X syndrome is called an X-linked disorder because the FMR-1 gene is located on an X chromosome. X-linked conditions are inherited in a special way. A woman who carries the gene for an X-linked condition has a 50-50 chance of passing it to either a son or daughter. However, a man with the same X-linked gene passes it to all of his daughters (who are then carriers), and to none of his sons. The illustrations on the following pages explain why.

Four Different Conceptions Possible
Unlike other body cells, a woman’s egg cells and a man’s sperm cells each contain a total of 23 chromosomes (instead of the usual 46), representing only one member of each chromosome pair. In a female carrier, this means that half her eggs will have an X chromosome with the fragile X mutation, and the rest of her eggs will have an X chromosome without the fragile X mutation. Depending on which of her eggs gets fertilized, there is a 50-50 chance that the fragile X mutation will be present at conception.

Two Different Conceptions Possible
In a man who has a fragile X mutation, half his sperm cells contain an X chromosome, but the rest of his sperm have a Y chromosome. If one of his Y-containing sperm is involved in fertilization, the result will be a male (because of the Y), who is free of his father’s fragile X mutation. If an X-containing sperm fertilizes an egg, the result will be a female who carries the fragile X mutation on the X chromosome she received from her father. In other words, although all daughters of carrier males will have their father’s mutation, a father cannot pass the fragile X gene to his son.
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In May 1991, the gene responsible for fragile X syndrome was identified. This gene is called *FMR-I*, and it plays an important role in normal brain development in all people. Every person has at least one *FMR-I* gene. Women have two X chromosomes, so they have two copies of the *FMR-I* gene. Men have only one X chromosome and have just one copy of the *FMR-I* gene. Fragile X syndrome is caused by a complex change (called a mutation) in the *FMR-I* gene that occurs over many generations. In people affected by fragile X syndrome, a mutation keeps the *FMR-I* gene from functioning properly.

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By using direct DNA analysis, a specific piece of DNA within the FMR-1 gene can be studied. This piece of DNA contains repeated copies of the code CGG, which varies in length from one person to another. What distinguishes people who have a fragile X mutation from those who don’t is the number of times this CGG code is repeated, as well as the gene’s methylation status. Methylation is the process that controls whether the FMR-1 gene is turned on or off. An FMR-1 gene that is unmethylated is turned on and produces a protein (FMRP) which is crucial for normal development. If the gene is methylated, it is turned off and does not produce FMRP.

In people who do not have a fragile X mutation, the repeat number is usually less than 50 and the region is unmethylated. Most unaffected carriers of the fragile X mutation have pieces of DNA which are between 50 and 200 CGG repeats in size. This size segment is called a premutation, and again, the region is unmethylated. Premutations are unstable and may expand in size when passed from mother to child. If the gene expands to the size of a full mutation (greater than 200 CGG repeats, sometimes exceeding 1000 repeats), the gene becomes methylated (turned off) and does not work properly. Once the gene turns off, FMRP is no longer made. It is the loss of FMRP that causes the clinical features of fragile X syndrome. Boys with the full mutation usually have more features of fragile X syndrome than do girls because they only have one X chromosome, whereas females have two. Virtually all males with a full mutation, and most females with a full mutation, have some degree of mental impairment.

Research has shown that a minority of carriers of the premutation (50 to 200 CGG repeats) may also experience effects. Most common in females is premature menopause, also referred to as premature ovarian failure. Other effects such as learning problems, depression, obsessive-compulsive

continued
**DIRECT DNA ANALYSIS**

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The direct DNA test counts the number of repeats and checks the methylation status of the FMR-1 gene. In people who do not have a fragile X mutation, the repeat number is usually less than 50 and the region is unmethylated. Most unaffected carriers of the fragile X mutation have pieces of DNA which are between 50 and 200 CGG repeats in size. This size segment is called a premutation, and again, the region is unmethylated. Premutations are unstable and may expand in size when passed from mother to child. If the gene expands to the size of a full mutation (greater than 200 CGG repeats, sometimes exceeding 1000 repeats), the gene becomes methylated (turned off) and does not work properly. Once the gene turns off, FMRP is no longer made. It is the loss of FMRP that causes the clinical features of fragile X syndrome. Boys with the full mutation usually have more features of fragile X syndrome than do girls because they only have one X chromosome, whereas females have two. Virtually all males with a full mutation, and most females with a full mutation, have some degree of mental impairment.

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**DIAGNOSTIC TESTING**

**Chromosome Analysis and DNA Linkage Studies**

In the past, the laboratory test most frequently used to identify people with fragile X syndrome was *cytogenetic analysis*, more commonly referred to as *chromosome analysis*. Although routine chromosome analysis detects many causes of mental retardation, including Down syndrome, only a specialized chromosome study, which looks specifically for the fragile X chromosome, can identify people affected by fragile X syndrome. Chromosome testing, however, misses a significant number of carriers who have the fragile X mutation but who are intellectually normal.

In the late 1980’s and early 1990’s, more accurate tests called DNA linkage studies were done to identify intellectually normal carriers. These studies, which required analyzing blood samples from multiple family members, were quite costly and time-consuming. Although results from DNA linkage studies could be as high as 99% accurate in some families, determination of carrier status by direct DNA methods, as described on the following page, is now considered much more reliable. If you or your family had testing done using either chromosome analysis or DNA linkage, you should talk with your doctor or a genetic counselor about the direct DNA test.

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**Direct DNA Analysis**

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Research has shown that a minority of carriers of the premutation (50 to 200 CGG repeats) may also experience effects. Most common in females is premature menopause, also referred to as premature ovarian failure. Other effects such as learning problems, depression, obsessive-compulsive
disorder, and Parkinson-like tremors (particularly among males in later life) may also result from having the fragile X premutation. As new information is still emerging, contact the National Fragile X Foundation for the latest research regarding carriers.

A small amount of blood is necessary to examine a person’s DNA. By using a picture called a blot, the length of the repeated CGG section can be visualized. By checking the number of CGG repeats a person has, it is possible to identify male and female carriers, and to diagnose people who may have intellectual impairment caused by fragile X syndrome. The direct DNA test can also detect the fragile X mutation in a baby before it is born.

Direct DNA Analysis for the Fragile X Mutation

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*CGG Repeats and how the premutation differs from the full mutation*

Prenatal Diagnosis

Prenatal diagnosis (testing for the fragile X mutation in a baby before it is born) is available to any person shown to be a carrier of a fragile X mutation. Prenatal fragile X testing is usually performed on the developing baby using one of two methods: either *chorionic villus sampling* (CVS), performed at approximately 10 weeks of pregnancy, or *amniocentesis*, performed between 16–20 weeks of pregnancy. All couples considering prenatal diagnosis should meet with a genetic counselor before becoming pregnant in order to discuss the most current prenatal techniques, their limitations and benefits.

**Interventions**

At this time there is no cure for fragile X syndrome. Treatment and intervention, however, are available. Treatment is primarily provided through various forms of therapy, including special education, speech and language therapy, and occupational therapy. Certain medications may be helpful in managing the hyperactivity, poor attention span and other behavioral or emotional problems of children with fragile X syndrome. In order to create and provide the best educational, therapeutic, or vocational program, it is important to assess a person’s overall development. Learning strengths and weaknesses, specific behavioral problems, and medical needs must be evaluated on an individual basis. This evaluation is recommended for both children and adults.

**Education**

In the U.S., children whose development is affected by fragile X syndrome are eligible for special education services. The Individuals with Disabilities Education Act (IDEA), a federal law, mandates a free, appropriate public education in the least restrictive environment (that is, as much as possible with non-disabled children) for all children with special needs. IDEA requires a multidisciplinary evaluation for any child who may be eligible for special education services. This means that a variety of professionals and the parents of the child assess the child’s strengths and needs and determine appropriate intervention. Intervention varies, based upon the child’s age and individual needs. Settings range from home-based programs for infants to a variety of school-based classrooms. Every child eligible for special education has his or her own Individualized Family Service Plan (IFSP), for younger children, or Individualized Educational Plan (IEP), for school age children. There are some particular areas that should be addressed in planning for the education of a child with fragile X syndrome. The development of cognitive, speech and language, behavioral, sensory-motor, and academic areas can be addressed in developing the educational plan for a child affected by fragile X.

All states have programs to evaluate and provide educational services to children with special needs, although the types of programs available differ from state to state. To identify educational resources in your area, a good place to begin is to contact the principal at your local elementary school.
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<tr>
<td>Full mutation</td>
<td>&gt;200</td>
<td>Completely methylated</td>
<td>~50% affected</td>
<td>All affected</td>
</tr>
</tbody>
</table>

CGG Repeats and how the premutation differs from the full mutation

Prenatal Diagnosis

Prenatal diagnosis (testing for the fragile X mutation in a baby before it is born) is available to any person shown to be a carrier of a fragile X mutation. Prenatal fragile X testing is usually performed on the developing baby using one of two methods: either chorionic villus sampling (CVS), performed at approximately 10 weeks of pregnancy, or amniocentesis, performed between 16–20 weeks of pregnancy. All couples considering prenatal diagnosis should meet with a genetic counselor before becoming pregnant in order to discuss the most current prenatal techniques, their limitations and benefits.

INTERVENTIONS

At this time there is no cure for fragile X syndrome. Treatment and intervention, however, are available. Treatment is primarily provided through various forms of therapy, including special education, speech and language therapy, and occupational therapy. Certain medications may be helpful in managing the hyperactivity, poor attention span and other behavioral or emotional problems of children with fragile X syndrome. In order to create and provide the best educational, therapeutic, or vocational program, it is important to assess a person’s overall development. Learning strengths and weaknesses, specific behavioral problems, and medical needs must be evaluated on an individual basis. This evaluation is recommended for both children and adults.

Education

In the U.S., children whose development is affected by fragile X syndrome are eligible for special education services. The Individuals with Disabilities Education Act (IDEA), a federal law, mandates a free, appropriate public education in the least restrictive environment (that is, as much as possible with non-disabled children) for all children with special needs. IDEA requires a multidisciplinary evaluation for any child who may be eligible for special education services. This means that a variety of professionals and the parents of the child assess the child’s strengths and needs and determine appropriate intervention. Intervention varies, based upon the child's age and individual needs. Settings range from home-based programs for infants to a variety of school-based classrooms. Every child eligible for special education has his or her own Individualized Family Service Plan (IFSP), for younger children, or Individualized Educational Plan (IEP), for school age children. There are some particular areas that should be addressed in planning for the education of a child with fragile X syndrome. The development of cognitive, speech and language, behavioral, sensory-motor, and academic areas can be addressed in developing the educational plan for a child affected by fragile X.

All states have programs to evaluate and provide educational services to children with special needs, although the types of programs available differ from state to state. To identify educational resources in your area, a good place to begin is to contact the principal at your local elementary school.
Finding out that a child has a serious learning problem can be a terribly sad experience for parents. When the cause of the problem is hereditary, the news can be especially difficult to accept. For many parents, learning about fragile X syndrome causes a grief reaction, a mourning for the loss of hopes and expectations which are part of every family. This grieving, with all its feelings of anger, depression, and intense sadness, is certainly not unique to fragile X syndrome. It is a normal and natural reaction whenever a person experiences a loss, whether it be the death of a person or the giving up of ideals and expectations.

Even parents who learn about the diagnosis after many years are often surprised by the intensity of their grief reaction. They may feel that something is wrong with them for becoming upset and depressed after they had coped very well with their child's disability for years. This “opening of old wounds” can be a painful and confusing experience for many families, particularly for those who think it is an abnormal reaction. Although painful, this mourning is in fact a healthy way of dealing with bad news, and a necessary step in accepting a genetic diagnosis.

Even parents of a fragile X mutation may have feelings of lowered self-esteem. Upon hearing that they are carriers, many people state that they feel “defective” or “imperfect”. This reaction is common among carriers of other genetic conditions as well. In some genetic conditions, both parents of an affected child are carriers. Emotions may be just as intense but are shared equally by both partners. In fragile X syndrome, only one partner is a carrier, and he or she alone must shoulder the burden of “carrier guilt”.

Despite this, carriers of a fragile X mutation may have feelings of lowered self-esteem. Upon hearing that they are carriers, many people state that they feel “defective” or “imperfect”. This reaction is common among carriers of other genetic conditions as well. In some genetic conditions, both parents of an affected child are carriers. Emotions may be just as intense but are shared equally by both partners. In fragile X syndrome, only one partner is a carrier, and he or she alone must shoulder the burden of “carrier guilt”.

Seeking support from family, friends, and even a professional can be especially helpful in coping with these intense feelings. Often, talking with another parent who can identify with what you are going through is most helpful. For family and support services in your area, contact the National Fragile X Foundation or your local genetic counselor.
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Often the genetic implications of fragile X syndrome reach family members who are not expecting the information. The first reaction of a sister, for example, who learns she may be a carrier of a fragile X mutation, is commonly one of denial or anger. Rather than feeling grateful, the relative may resent this information, wishing she could return to a time when she did not worry about such matters.

The word “carrier” itself is an unfortunate term. The events that surround the passing on of genes are played out even before a baby is conceived, with no voluntary control on the part of the parents. We are all carriers of some genetic condition, since every person has several genes which have the potential to cause serious genetic disease in his or her children. Usually, the only time we find out about these genes is after the birth of a child with a hereditary condition. In other words, people with a fragile X mutation may not have any greater number of harmful genes than do other people, but because of the diagnosis of a relative, they just happen to know that one of them is a fragile X mutation.

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FAMILIES SPEAK OUT

What families are saying about their experiences with fragile X syndrome:

“Not knowing the cause of a child’s mental impairment can cause more destruction in a family than knowing it, facing it, and finally accepting it, thereby giving each member of the family more freedom to love each other and less time to blame each other.”

“I was extremely upset to find out that my son has fragile X syndrome after 30 years of not knowing. I am blaming myself, and I’m finding it hard to deal with.”

“It’s easy to have lots of self-pity and anger with the situations that life deals. However, they accomplish nothing. It’s better to move on with some sense of humor, love, and courage because these are the things that make us strong.”

“My son has a great imagination. Sometimes he talks to himself and answers in another voice. He imitates comedians, listens to the news, weather, sports, and watches cooking shows. He is very observant—he knows a lot more than he can bring out.”

“The frustrating thing about Mike is that, although he is mentally retarded, he seems to be average or even above average in some areas. For instance, he has an incredible memory—for baseball statistics, for places he’s been, for people he’s met. If only we could find a way for him to use those talents to make up for the areas he’s weak in.”

“I was shocked and dismayed but also relieved to know why my son had learning disabilities. It relieved a guilt that maybe I had contributed to his problem by being exposed to something during pregnancy.”

“Last Christmas I discovered I was the fragile X carrier in our large family. The bottom dropped out of my world. Now I thank God for the knowledge—my children and grandchildren have options.”

“The hardest thing to accept about fragile X syndrome is that it is a genetic defect and cannot be entirely eliminated from future generations.”

“There is so much I could share and things I have learned over the years. I would love to have the support of talking to others who understand.”

“We had accepted our son’s mental retardation long before we found out about fragile X syndrome. He is a gentle, loving, and caring young man. I only ask that I live one day longer than he does—then I’ll know where he is. That will be my peace of mind.”

“As parents, it’s hard to accept that there is something wrong which can’t be fixed by us.”

“I feel angry because fragile X syndrome never showed up in any part of the family—aunts, uncles, or cousins. Why me?”

“Every case is different and people will deal with it depending on their capabilities.”

“Accept fragile X for what it is, and get help as soon as you can.”
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THE NATIONAL FRAGILE X FOUNDATION

The National Fragile X Foundation unites the fragile X community to enrich lives through educational and emotional support, promote public and professional awareness, and advance research toward improved treatments and a cure for fragile X syndrome.