What is Fragile X syndrome?

Fragile X syndrome (also called Fragile X) is the most common inherited form of mental retardation.* It results from a change, or mutation, in a single gene, which can be passed from one generation to the next. Fragile X appears in families of every ethnic group and income level.

Symptoms of Fragile X syndrome occur because the mutated gene cannot produce enough of a protein that is needed by the body's cells, especially cells in the brain, to develop and function normally. The amount and usability of this protein, in part, determine how severe the effects of Fragile X are.

The most noticeable and consistent effect of Fragile X is on intelligence. More than 80 percent of males with Fragile X have an IQ (intelligence quotient) of 75 or less.[1] The effect of Fragile X on intelligence is more variable in females. Some females have mental impairment, some have learning disabilities, and some have a normal IQ.

People with Fragile X syndrome also share certain medical problems as well as many common physical characteristics,[2] such as large ears and a long face. In addition, having Fragile X is often associated with problems with sensation, emotion, and behavior.

The National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health (NIH), is a major sponsor of research on Fragile X syndrome. Since 1991, when researchers funded by the NICHD discovered the gene that causes Fragile X, scientists have learned a great deal about that gene's structure and functions. The NICHD continues to support clinicians and scientists around the world who are working to find effective behavioral or other therapies, medical treatments, and prevention strategies for Fragile X.

* The NICHD recognizes that there is a debate about the use of the term "mental retardation," and that self-advocacy groups and professional associations are currently discussing alternative terms. Until a consensus is reached, and with the goal of addressing health-related issues faced by people with what has been traditionally known as "mental retardation," this booklet uses that term to describe some features related to Fragile X syndrome. For more information, please see the *Additional Resources* section of this booklet.

What causes Fragile X syndrome?

The underlying cause of Fragile X is a change in a single gene, the **Fragile X Mental Retardation 1 (*FMR1*) gene,** which is found on the X chromosome. (See the *Human cells 101* section for more information about the X chromosome.) But how does this change cause Fragile X?

Genes contain the information used by other parts of a cell to make proteins. Proteins are the body's building blocks. Each protein performs a specific job. They make up the structure of your organs and tissues and are needed for all of your body's chemical functions.

Each gene contains information for making at least one protein. If this information is changed, then the cell may not be able to make that protein, or it may not be able to make a form of the protein that the body can use. Fragile X occurs because the *FMR1* gene is unable to make normal amounts of usable **Fragile X Mental Retardation Protein,** or **FMRP.**

The amount of FMRP in the body is one factor that determines how severe the effects of having Fragile X are. A person with nearly normal levels of FMRP usually has mild or no symptoms, while a person with very little or no normal FMRP has more severe symptoms.

Scientists are still studying the role of FMRP in the body. One current research study revealed that certain cell processes brain cells use to communicate with one another occur in excess in mice that have little or no FMRP; that is, the brain cells may communicate too much or may communicate inappropriately. Researchers believe that FMRP may regulate the amount of communication between cells and keep it under control. Scientists are hopeful that they can identify a similar function for FMRP in humans.

Causes of Mental Retardation

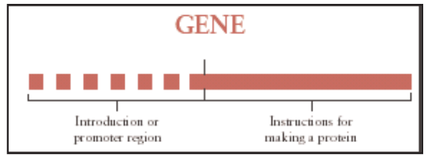
Mental retardation is associated with more than 500 conditions. Some of the most commonly known genetic causes among these are:

- Down syndrome, due to an error in the number of chromosomes
- Fragile X, due to a repeat in the genetic code that leads to a lack of production of a certain protein
- PKU (phenylketonuria), due to an error in a single gene that makes a defective enzyme

Other causes of mental retardation that can occur during pregnancy include the mother's excessive use of alcohol, exposure to poisons in the environment, and diseases such as rubella.

What keeps the FMR1 gene from producing FMRP in Fragile X syndrome?

The information for making a protein has two parts: the introduction, and the instructions for the protein itself. Scientists call the introduction "**the promoter region**" of the gene because of its role in starting the protein-building process. (For a more complete description of how proteins are made and the parts of a cell involved in making a protein, see the *Human cells 101* section.)



The promoter region of the *FMR1* gene contains **repeats** of a specific sequence (cytosine-guanine-guanine or CGG—see the *Human cells 101* section for specific information about the CGG sequence) that, when normal, controls the activity level of the gene in building FMRP.

The number of repeated sequences in the promoter region varies from person to person. Most people who do not have Fragile X have between six and 40 CGG repeats,[3] with the average being about 30 repeats in the promoter region.[4]

However, in a mutated *FMR1* gene, the promoter may have hundreds of repeated sequences.

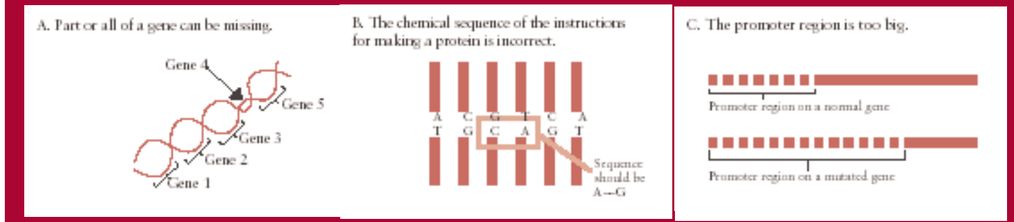
- A gene with 55 to 200 repeats is generally considered a **"premutation."***
- A gene with more than about 200 repeats is called a **"full mutation."**

* The number of repeats and their effects are still being studied. At the time this booklet was printed, the numbers included here were the most commonly cited for premutation in the published scientific literature: *Fragile X Syndrome Handbook* (2002) National Fragile X Foundation; American College of Medical Genetics Statement: Technical Standards and Guidelines for Fragile X (2001); Rousseau et al. (1996) *American Journal of Human Genetics* 59(Suppl):A188-1069. However, some research categorizes the premutation differently. For instance, in Crawford et al., 61 to 200 repeats is a premutation, while 41 to 60 repeats is an intermediate mutation (*Genetics in Medicine* 2001; 3:359-371). The American Academy of Pediatrics Policy Statement. *Health Supervision for Children with Fragile X Syndrome* uses 50 to 200 repeats for premutation (*Pediatrics* 1996; 98(2): 297-300). Tassone et al. (*American Journal of Medical Genetics* 2000; 97[3]:195-203) use large premutation (100 to 200 repeats) and small premutation (55 to 100 repeats). You may encounter differences in the number of repeats for a premutation depending on your source.

The larger number of repeats (more than 200) inactivates the gene. This inactivation process is called **methylation.** When the gene is inactivated, the cell may make little or none of the needed FMRP.

What goes wrong in a mutated gene?

A number of things can go wrong in a gene that can result in a mutation. The mutation affects the gene's ability to make the needed amount of protein or to make enough usable protein. Some of these mutations include:



In the case of Fragile X, usually the *FMR1* gene is present, and its chemical sequence is correct, so neither A nor B apply. However, a mutated *FMR1* gene includes repeats of a specific sequence in its promoter region, which creates a mutation like the one shown in situation C.

One interesting aspect of Fragile X is that, even with a full mutation gene, the body may be able to make some FMRP. Three things affect how much FMRP is produced:

- **The number of CGG repeats.** People with a full mutation (200 or more repeats) usually have many of the more severe symptoms associated with Fragile X. In contrast, people with a premutation gene may have few, if any, symptoms and may not even know they carry a mutated gene. Researchers are still trying to sort out any, patterns or trends in the symptoms of people with a premutation gene.

- **Being mosaic.** Not every cell in the body is exactly the same. In Fragile X, this means that some cells may have 200 or more repeats in the *FMR1* promoter, while other cells, premutation cells, may have fewer than 200 repeats. This is called being **"mosaic,"** meaning either that the mutation is in some of the cells, but not all of them, or that it is not in all of the cells to the same degree. The premutation cells may be able to make FMRP. Similarly, methylation may not happen at all, or to the same degree, in every cell. If enough cells produce FMRP, the symptoms of Fragile X will be milder than if none of the cells produce FMRP.

- **Being female.** Because females have two X chromosomes, females with Fragile X have one normal *FMR1* gene and one mutated *FMR1* gene in most of their cells. But, only one X chromosome is active in each cell, and only the genes on the active chromosome are used to build proteins. The cell seems to randomly choose which chromosome is used. In some cells, then, the X chromosome that contains the normal *FMR1* gene is active, and the cell uses it to make FMRP. As a result, even females with a full mutation are often able to make some of the needed protein. For this reason, the symptoms of Fragile X usually affect females less often and less seriously than males.

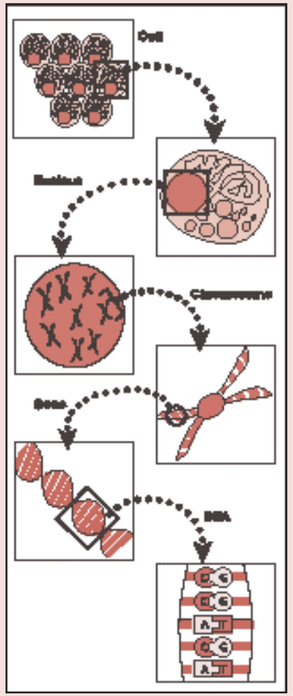
Human cells 101

More than 100 trillion **cells** make up the human body. Most of these cells contain all the genes and other information needed to "build" a human being. Much of this genetic information is found in the **nucleus** of the cell, a "control center" that keeps all the material together in one place.

The nucleus stores its genetic material in packages called **chromosomes.** Most people have 46 chromosomes in each cell—23 from their mother and 23 from their father. After fertilization, the two sets of chromosomes match up to form 23 pairs. The chromosomes in the 23rd pair are called the sex chromosomes, X and Y; they determine a person's sex. Males usually have one Y chromosome and one X chromosome; females usually have two X chromosomes.

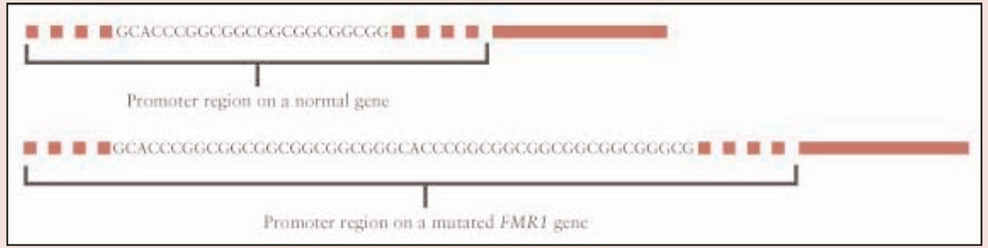
Each chromosome is made up of genes. **Genes** contain the information used by other parts of the cell to make proteins, the body's building blocks. Proteins make up the structure of your organs and tissues; they are also needed for your body's chemical functions. Each protein performs a specific job in different types of cells, and the information for making at least one protein is contained in a single gene.

Genes are made up of various lengths of **DNA,** which contains four chemicals: **adenine (A), guanine (G), cytosine (C),** and **thymine (T).** These chemicals line up like beads on a necklace to form strands of code. They also pair up with each other to form the double strands that are characteristic of DNA.



The gene's chemical code for a protein has two parts: the introduction area **(promoter),** and the instructions for creating the protein. The instructions for making the protein are inside the cell's nucleus, but the parts that actually make the protein are outside the nucleus. To send the instructions to the protein-producing areas of the cell, the gene "reads" the chemical code and rewrites it into a new form (called messenger RNA). The new form is then sent out of the cell's nucleus to make proteins. But, if either the original code or the new form of the code is incorrect or has missing parts, the cell can't make the correct protein. Without the protein, the body may not develop or function normally.

This is what happens in Fragile X. The *FMR1* gene contains too many repeats of one specific sequence, CGG, which is an important part of the promoter region for making FMRP (see the figure below).



The number of CGG repeats affects how the code is read and rewritten into its new form. So when the new form of the code gets to the protein-making areas of the cell, the cell has trouble using it to make FMRP, the protein that is abnormal, missing, or in low amounts in people with Fragile X. The cell either can't use the code, and so makes no FMRP, or tries to use the code and makes abnormal or unusable FMRP.

How many people are affected by Fragile X syndrome?

Currently, researchers don't know exactly how many people have either the full mutation or the premutation form of the *FMR1* gene. Even though researchers can estimate the number of people affected by Fragile X, these estimates can be very different.*

A summary of existing research[5] conducted by the Centers for Disease Control and Prevention in 2001 estimated that approximately one in 3,500 to 8,900 males is affected by the full mutation of the *FMR1* gene, and that one in 1,000 males has the premutation form of the *FMR1* gene. This study also estimated that one in 250 to 500 females in the general population has the premutation. Another study[6] estimated that one in 4,000 females is affected by the full mutation.

Although these estimates are useful in trying to understand the impact of Fragile X on various communities, keep in mind that these numbers are only the best estimates based on the available information. Many factors can affect the completeness and/or accuracy of the available information, which means that the number of people affected by Fragile X could actually be different. The important thing to remember is that, when you consider the individuals affected by full mutation and premutation forms of the *FMR1* gene, their families, and their communities, this condition impacts hundreds of thousands of people.

* The number of people affected by a full mutation or a premutation of the *FMR1* gene is still being studied. At the time this booklet was printed, few population-based studies had been done to determine exactly how many people were affected by Fragile X. The estimates included here from Crawford, Acuña, and Sherman differ from other estimates, including those provided by many of the national organizations dedicated to Fragile X (Bailey & Nelson, The Nature and Consequences of Fragile X Syndrome, *Mental Retardation and Developmental Disabilities Research Reviews*, 1:238-244, 1995; Prevalence of Fragile X Revisited and Revised, *The National Fragile X Foundation Quarterly;* Winter, 2002). For more information, please consult the specific articles or the national organizations listed in the *Where can I go for more information about Fragile X syndrome?* section of this booklet.

How is Fragile X syndrome inherited?

The gene for Fragile X is carried on the X chromosome. Because both males (XY) and females (XX) have at least one X chromosome, both can pass on the mutated gene to their children.

A father with the altered gene for Fragile X on his X chromosome will only pass that gene on to his daughters. He passes a Y chromosome on to his sons, which doesn't transmit the condition. Therefore, if the father has the altered gene on his X chromosome, but the mother's X chromosomes are normal, all of the couple's daughters would have the altered gene for Fragile X, while none of their sons would have the mutated gene (see **Diagram A**).

Current research indicates that a father can pass on the premutation form of the *FMR1* gene only to his daughters. In other words, if a daughter inherits the mutated *FMR1* gene from her father, she will get only the premutation from him, not the full mutation. Even if the father himself has a full mutation, it appears that sperm can carry only the premutation. Scientists don't understand how or why fathers can only pass on the milder form of Fragile X to their daughters. This remains an area of focused research.

Because mothers pass on only X chromosomes to their children, if the mother has the altered gene for Fragile X, she can pass that gene to either her sons or her daughters. If the mother has the mutated gene on one X chromosome and has one normal X chromosome, and the father has no genetic mutations, all the children have a 50-50 chance of inheriting the mutated gene (see **Diagram B**).

Diagram A

	Father	
	Y	$X^{fragile}$
Mother X	Boy XY	Girl $XX^{fragile}$
Mother X	Boy XY	Girl $XX^{fragile}$

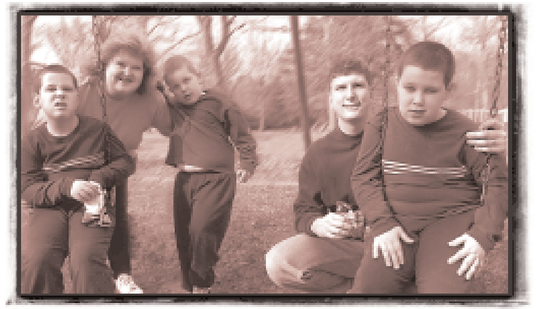
Diagram B

	Father	
	Y	X
Mother $X^{fragile}$	Boy $YX^{fragile}$	Girl $XX^{fragile}$
Mother X	Boy XY	Girl XX

The odds noted here apply to each child the parents have. Having one child who receives an X chromosome with the *FMR1* mutation does not increase or decrease the chances of having another child with the mutated *FMR1* gene. Nor do these odds influence the severity of the symptoms. Having one child with mild symptoms does not mean that the other children will have severe symptoms, and having a child with severe symptoms does not mean that other children will have mild symptoms.

A premutation gene is less stable than a full mutation. In some cases, the mutated gene may expand from the premutation to the full mutation as it is passed on from mother to child. The chances of expansion depend on the number of repeats in the promoter of the premutation gene; the higher the number of repeats, the more likely it is that the gene will expand. These chances also increase with each generation. Children of a mother who has the premutation, then, may have no genetic mutation, the premutation, or the full mutation.

Further, because an altered *FMR1* gene can be passed on without symptoms, many people are unaware that they have it. As a result, a premutation form of the *FMR1* gene can be silently passed through a family for generations, with no one ever showing any symptoms. However, with each generation, it becomes more likely that the premutation gene will expand its number of repeats to become a full mutation gene, which would also increase the number of and seriousness of symptoms.



What are the signs and symptoms of Fragile X syndrome?

Not everyone with Fragile X has the same signs and symptoms, or to the same degree. Even affected children in the same family can have different signs and symptoms. These differences often make Fragile X hard to diagnose. However, because everyone with Fragile X has too little FMRP, they do share a pattern of certain physical, social, mental, and sensory characteristics. Although most of the Fragile X research to date has focused on children, adults with Fragile X also have most of these signs and symptoms.

In general, the signs and symptoms of Fragile X fall into five categories:

- **Intelligence and learning**
- **Physical**
- **Social and emotional**
- **Speech and language**
- **Sensory**

Now consider each category in more detail.

What are the signs and symptoms?

Intelligence and learning

Many people with Fragile X have impaired intellectual functioning, which affects their ability to think, reason, and learn. In most cases, researchers use an intelligence test to measure intellectual functioning, resulting in an IQ (intelligence quotient) score. But this score reflects many things besides the ability to think. Attention disorders, hyperactivity, anxiety, and language processing problems can interfere with test-taking skills and learning. Because many people with Fragile X have these problems, a person with Fragile X may have more capabilities than his or her IQ score suggests.

Researchers consider people who score between 85 and 115 on an IQ test to have "average" intelligence.[7] On the whole, less than 20 percent of males with Fragile X have an IQ in this range.[2] At the same time, few people with Fragile X are severely or profoundly impaired, with IQs below 40 or 25, respectively.[8] In general, those with a full mutation tend to have an IQ somewhere in between 40 and 85, which is considered mild to moderate mental impairment.

Females tend to be less seriously affected by Fragile X than males. Even among females who have full-mutation *FMR1* genes, only about one-third have an IQ in the mental retardation range.[6] Females with Fragile X are more likely to have relatively normal cognitive development, or they may show a learning disability where their academic achievement in some areas is lower than their overall ability to learn. For example, a female with a learning disability in math might score several grades below her grade level in math, even though her IQ is within the normal range.

Many factors influence intelligence, and, like most individuals, people with Fragile X have areas of both strength and weakness. For example, people with Fragile X tend to have good memories for pictures and visual patterns. This ability helps them to learn to recognize letters and words. They are also generally able to follow instructions that are presented as pictures. Their main weaknesses are in thinking about abstract ideas, organizing information, planning ahead, and solving problems.

No matter what their IQ or areas of intelligence, all children and adults with Fragile X are capable of learning. Most children will progress in school and develop basic academic skills. Many adults can learn to take care of themselves and work at a job. People with Fragile X may need more time to learn, special teaching methods, or a specially tailored environment (see the *Suggestions for working with individuals with Fragile X* box), but they usually can and do make steady progress.

Suggestions for working with individuals with Fragile X

- Know the learning style of the individual.
- Develop a consistent daily schedule or routine.
- Use visual signs (pictures, sign language, logos, words) and concrete examples or materials to present ideas, concepts, steps, etc.
- Prepare the individual for any changes in routine by explaining them ahead of time, possibly using visual signs.
- Include functional goals with academic goals; for instance, teaching the individual the names of different pieces of clothing as well as how to dress him/herself.
- Provide opportunities for the child to be active and move around.
- Use computers and interactive educational software.
- Provide a quiet place where the child can retreat and regroup.

What are the signs and symptoms?

Physical

Many infants and young children with Fragile X have no distinctive physical features. Some children have very soft, velvety skin, a broad forehead, or a slightly larger head than other children their age.

However, when these children enter puberty, usually around age 11, they may begin to develop certain features that are typical of teens and adults with Fragile X, such as a longer face or jaw and larger, more noticeable ears. Most do not grow as tall as their peers, or as tall as one might expect them to grow, based on the height of their family members.

Other physical changes also come with puberty for those who have Fragile X. Many males develop enlarged testicles, a condition called macro-orchidism (pronounced mack-roe-ORK-id-izm). With this condition, the testicles may grow to twice their normal size. This condition is not due to hormonal imbalance and does not affect sexual development.

One job of FMRP may be to help the body maintain its connective tissues. Connective tissues support the body, inside and out. Many people with Fragile X have loose, flexible joints. They may have flat feet and be able to extend joints like the thumb, knee, and elbow further than normal. Weak connective tissue can predispose a person to certain medical conditions, such as hernia and frequent middle ear infections. Weak connective tissue can also affect the valves and vessels of the heart, so that blood in the heart may not flow smoothly, which creates a heart murmur (called mitral valve prolapse, pronounced my-trell valv proh lapss). Although it involves the heart, this condition is usually not life threatening, but it is a good idea for a person with a heart murmur to be monitored by a health care professional on a regular basis.

Late in life, some males who have a premutation may develop hand tremors[10] and problems with walking.

How does Fragile X affect the brain?

Understanding how Fragile X affects the brain and learning what role FMRP plays in normal brain development and function are areas of active research. For instance, some evidence suggests that FMRP is involved in forming pathways in the brain.

Normally, brain cells called **neurons** have special areas that grow toward each other to form connections. These connections, called "synapses," are arranged in neural pathways. Thoughts, sounds, and memories are recorded and stored in these pathways. However, not every experience recorded in these neural pathways is useful or needs to be kept throughout life. So, as part of normal development, the brain "prunes" itself. Like pruning the branches of a tree, removing unneeded or ineffective pathways in the brain strengthens other pathways and makes room for new growth and new learning.

FMRP may somehow influence the pruning process in the brain. People without enough FMRP may have may have too many neural pathways or many connections that don't work well. This situation would explain some of the symptoms of Fragile X, such as an extreme sensitivity to new sights, sounds, smells, and touches.

Using mice and fruit flies that no longer have a working gene to make FMRP, scientists are working to understand how the absence of this protein affects the brain. Recent research is trying to determine whether a certain process that runs out of control in mice with little or no FMRP leads to the behavioral and learning problems typical in people with Fragile X. Such animal studies may reveal exactly how FMRP functions in the brain and suggest ways to correct situations caused by a lack of the protein.

Fragile X affects females in some different ways. About 16 percent[11] to 19 percent[12] of females who have a premutation gene experience premature ovarian failure (POF), meaning their ovarian function stops before normal menopause, sometimes well before the age of 40. Some may experience POF as early as their mid-twenties. POF affects a woman's ability to get pregnant. It is important, then, for women to know whether or not they have a premutation gene, and to have this knowledge early enough, so that they can consider their options for having a family. In contrast, POF occurs in only 1 percent of women who have two normal *FMR1* genes,[13] and the average age of menopause for women who

are not affected by Fragile X is 51. Women who have a full mutation gene do not lose ovarian function as early as women with a premutation gene, but they still tend to begin menopause earlier than women who are not affected by Fragile X. Scientists do not know why the effect is milder in women who have a full mutation form of the gene than in women with a premutation form of the gene.

What are the signs and symptoms?

Social and emotional

Most children with Fragile X—especially boys—feel a great deal of social anxiety; that is, they aren't completely comfortable in new situations, meeting new people, or doing new things. Their level of anxiety can be so high that they may avoid social situations. When these children do seek contact with others, they are often extremely nervous or uncomfortable. Their anxiety may show up as a lack of eye contact and/or fast, choppy speech. Although all children feel some degree of social anxiety, this discomfort usually doesn't keep them from being social, as it may for children with Fragile X.

In addition to being anxious, males with Fragile X tend to be easily upset. They are easily overwhelmed with sights and sounds (see the *What are the signs and symptoms of Fragile X?—Sensory* section of this booklet for more information), and can become very distressed in a busy store or restaurant. Unexpected changes in routine, like entering a new class or classroom, can also upset them. Some children respond by becoming extremely rigid or tense, while others whine or cry. At times, their reactions can spill over into tantrums or repetitive actions, such as rocking back and forth and biting themselves. In adolescence, changes, such as rising hormone levels, may make these outbursts more extreme. In one study of teenage males with Fragile X, about one-third showed angry, aggressive behavior.[8] Such behavior can get them into trouble at school. Providing medication and a calm environment can help keep such behaviors from getting worse. (See the *Are there treatments for Fragile X?* section for more information.)

In addition, males with Fragile X tend to experience much longer periods of anxiety than their peers. Like other males, their heart rate and other signs of nervousness increase when they do challenging tasks, but many males with Fragile X stay highly anxious for much longer time frame. So, in addition to having a level of anxiety that is often higher than their peers, males with Fragile X also take longer to calm down than other males do.

Females with Fragile X may have social problems, too, but theirs tend to be milder. A female with Fragile X may feel uneasy around strangers or have trouble making friends, but these females don't tend to be aggressive as adolescents.

What are the signs and symptoms?

Speech and language

Language difficulties in children who have Fragile X range from mild stuttering to more severe problems with basic language skills. Basic language skills include the ability to pronounce words clearly, to speak and write using words and grammar correctly, and to communicate in meaningful ways.

Females with Fragile X rarely have severe problems with speech or language. In fact, many have vocabulary and grammar skills that are appropriate for their age, which can help them learn to read and write. However, their social anxiety and shyness may get in the way of communication. Some females with Fragile X speak in a rambling, disorganized way or often get off the subject. Most males with Fragile X have more serious problems expressing themselves. These difficulties typically include problems speaking clearly and other problems with language that can be moderate to severe. In terms of speech, males with Fragile X often have problems coordinating the structures, vocal processes (such as pitch, loudness, and tone), and movements needed for clear speech. They often have difficulty receiving and processing spoken information, such as following spoken directions, storing words and concepts for future use, and creating their own meaningful responses to questions or comments.

Males with Fragile X may stutter or leave sounds out of their words. Many repeat themselves, restart the same sentence many times, or ask the same question again and again. Some may talk too fast, mumble, or speak in a loud, high voice. Some of these difficulties may be due to sensory overload or social anxiety, rather than a problem with the parts of the brain that control speech and language.

Perhaps most importantly, males with Fragile X usually have difficulty using speech and language in social contexts. They often seem unaware of conversational "clues," such as facial expressions, tone of voice, and body language. As a result, they may speak out of turn, fail to answer a question, or turn away because they aren't sure what to do. Unlike males with other developmental disorders, like autism, males with Fragile X seem to be very interested in communicating, but may experience sensory overload or social overload when they try to hold a conversation.

For some children, language problems are more severe. Many children with Fragile X begin talking later than expected. Most begin using words around age four, but some may not talk until age of six or eight.[6] Most talk eventually, but some may remain nonverbal throughout life. For these nonverbal children, a wide variety of picture-based and computer-based devices may help them to communicate, which could also reduce behavior difficulties that result from not being able to talk. Pictures, sign language, and generic gestures can also be helpful for all children with Fragile X, before they start talking.

What are the signs and symptoms?

Sensory

Many children with Fragile X are sensitive to certain sensations. They may become frantic at the sound of a loud noise or may be easily distracted by slight sounds in the room. They may be bothered by the texture of their clothes against their skin, or they may be unable to focus on the parts of their environment that are important, such as the sound of the teacher's voice. Infants with Fragile X may have problems drinking from a bottle, perhaps because the feel of the nipple upsets them. Some children try to avoid being touched, and even a brief tickle or hug may be overwhelming. Even though many of these symptoms are often life-long, most people affected by Fragile X, with the proper intervention, can find ways to handle or avoid the discomfort. (See the *Are there treatments for Fragile X syndrome?* section for more information.)

Children with Fragile X may also have problems with balance. A sense of balance helps keep the body upright and stable. Problems with balance, coordination, and connective tissue can cause difficulties for children with Fragile X as they learn to sit, stand, and walk, or later, to ride a bike. Even so, most children with Fragile X learn to do these tasks.

Disorders commonly associated or sharing features with Fragile X

Autism. Most males and about one-third of females with Fragile X show some autism-like behaviors, such as flapping hands, biting themselves, repetitious actions, and walking on toes.[14] About 33 percent of children with Fragile X show enough of these behaviors to receive a formal diagnosis of autism.[15] However, among people diagnosed with autism first, only about 4 percent are found to have an X chromosome with the *FMR1* gene mutation.

Attention Deficit Disorder (ADD)/Attention Deficit Hyperactivity Disorder (ADHD). Between 80 and 90 percent of males, and 35 to 47 percent of females with Fragile X have an attention disorder.[16,17] They are unable to focus their attention and stay with a task. They may be disorganized. Some are hyperactive and seem to be constantly in motion.

Connective Tissue Problems. Due to weak connective tissue, people with Fragile X have a higher risk of dislocating their joints and developing hernias and ear infections than those who aren't affected by Fragile X. About half of adults with Fragile X have a heart murmur caused by mitral valve prolapse,[17] which is usually not life threatening.

Seizures. About 20 percent[6] of children with Fragile X also experience seizures. In most cases, seizures are successfully treated with medication and disappear by adolescence.

Premature Ovarian Failure (POF). POF occurs when a woman's ovaries stop working properly and she is under the age of 40. As mentioned earlier in this booklet, about 16 to 19 percent of females who carry a premutation gene for Fragile X experience POF, some as early as age 20.[10,11] Women with a full mutation gene for Fragile X are less likely to have POF, but do tend to go through menopause earlier than women who do not carry a mutated gene.