FRAGILE X-ASSOCIATED DISORDERS (FXD)

A Handbook for Families, Health Care Providers, Counselors, and Educators

The National **Fragile X** Foundation

TABLE OF CONTENTS

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INTRODUCTION

Fragile X-associated Disorders (FXD) are a group of related genetic conditions that can affect family members in different ways. One of the conditions, fragile X syndrome (FXS), is the most well-known. FXS can affect both genders, though it occurs more frequently and tends to be more severe in males.

The other Fragile X-associated Disorders are fragile X-associated primary ovarian insufficiency (FXPOI), which affects women, and fragile X-associated tremor/ataxia syndrome (FXTAS), an adult onset neurological disorder that affects more males than females.

The changes in the Fragile X gene that cause FXD can be passed on in a family by individuals with no signs of a Fragile X condition. In some families, multiple family members can be affected over generations, while in others one of the conditions has been known to occur in only one individual.

The genetic and emotional aspects of an FXD diagnosis are often far-reaching and can affect the lives of many family members.

This handbook is for families, health care providers, counselors, educators, and all those wishing to learn about FXD. It describes all three conditions in detail, including features and symptoms, genetic information, testing, and currently available treatments.

—Handbook authors Liane J. Abrams, MS, CGC, NFXF Genetic Specialist, and Jayne Dixon Weber, NFXF Support Services Coordinator

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SECTION I

Genetics of Fragile X-Associated Disorders

Fragile what? Many people have never heard of Fragile X-associated Disorders before someone in the family is diagnosed with one. It is possible you have been concerned about your child's development for some time now and just received a diagnosis of FXS. Or maybe you have been unsuccessful in getting pregnant and found out you are a Fragile X "carrier." Maybe you have an older male relative who has tremors, memory loss or balance problems and you are starting to wonder about the cause. Let's look at the different Fragile X-associated Disorders:

- Fragile X syndrome (FXS): The most common inherited cause of intellectual disabilities, fragile X syndrome occurs in both genders. Girls generally have less severe symptoms. It can cause developmental and language delays, learning impairment, and behavioral and mental health issues. Individuals with FXS have a form of the Fragile X gene called a "full mutation."

- Fragile X-associated primary ovarian insufficiency (FXPOI): A cause of infertility, early menopause and other ovarian problems in women of reproductive age who are Fragile X carriers. Carriers have a form of the Fragile X gene called a "premutation."

- Fragile X-associated tremor/ataxia syndrome (FXTAS): An adult onset (over age 50) neurological condition that can cause balance and memory problems, tremors and other neurological and psychiatric symptoms in Fragile X carriers. It is more common in males than females. FXTAS is also caused by a Fragile X premutation.

In some families only one of these conditions may occur, while in others, all three conditions can occur in related family members.

CASE SCENARIO OF A FAMILY

Deborah and Tom have two children, Linda and Michael. Michael was a fussy baby and didn't walk until he was 20 months old. He is a sweet boy, but he often gets overwhelmed in group situations. His speech was also delayed, and when he was two and a half his pediatrician referred him to a genetics clinic. At the clinic he was tested for fragile X syndrome and was confirmed to have it. Deborah was then tested and found to be a Fragile X carrier.

At about the same time, Deborah's sister Janie was trying to start a family, but was having difficulty conceiving. She had just made an appointment with an infertility specialist when Deborah called with her news about being a carrier. Deborah told Janie that some Fragile X carriers have infertility, so Janie asked her doctor to test her. She then found out she is also a carrier.

In genetic counseling, the sisters learned that one of their parents must be a carrier. Not so coincidentally, their father had recently been diagnosed with Parkinson's disease. He also seemed to be increasingly forgetful. Then they read that these could be features of a neurological condition that occurs in some male (and less frequently, female) Fragile X carriers. Within a short time period, the family had gone from never having heard about FXD to quickly learning that multiple family members were directly affected. Even though they were facing many challenges, they were finally getting some answers to why they were having these different but related problems.

CELLS, CHROMOSOMES, GENES, AND DNA

The Fragile X gene can be passed on in families by and to people of either gender who have no obvious signs of FXD. To understand how this happens, we will review basic hereditary information.

Every person's body is made up of many millions of tiny structures called cells. Within each cell is the genetic information we inherit from our parents. The genetic information is contained in "genes," and the genes are found lined up on structures called chromosomes. The genes are made from long

strands of DNA (deoxyribonucleic acid). DNA is often called the "genetic code." The DNA molecules are symbolized by letters C, G, T and A. Each gene is made from a specific sequence of DNA molecules.

Chromosomes and genes are like strings of plastic beads. The whole strand of beads represents the chromosome, each bead might represent a gene, and the plastic from which the beads are made would be the DNA molecules.

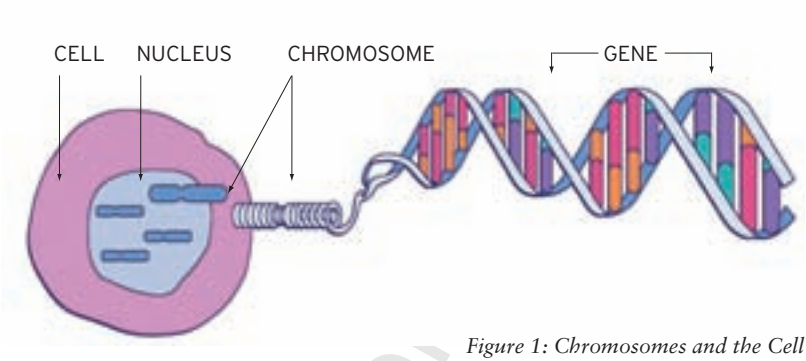

Figure 1: Chromosomes and the Cell

Genes, which usually occur in pairs, are the instructions that determine our growth, development, and many other characteristics. For example, certain genes determine eye and hair color, while others determine blood type.

Genes are often called the units of heredity because the information they contain is passed from one generation to the next. We all inherit one gene of each pair from our mother and the other gene in a pair from our father. In this way, our bodies work with a combination of instructions inherited from both our parents. Parents have no control over which genes they pass on to their children.

A given gene can occur in many alternative forms called alleles. For example, the gene for eye color has an allele for blue eyes, an allele for brown eyes, green eyes, etc. This is similar to the various types of apples that occur: each

type, such as Delicious, Pippin or Fuji, might be called an allele in the apple family. This concept of each allele as one form of a gene is important in understanding the genetics of FXD, because we all have different size Fragile X alleles.

Thousands of genes pack together to form chromosomes. Most people have 46 chromosomes (23 pairs). There are 44 "non-sex" chromosomes, numbered in pairs from 1-22, that are the same in males and females. 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. The Fragile X gene is on the "X" chromosome. The following diagrams illustrate chromosomes from a female and a male.

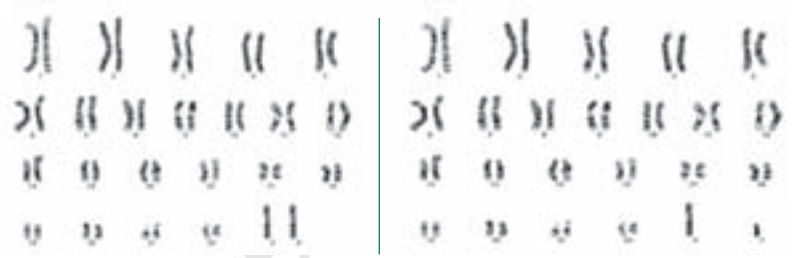

Figure 2: Female and Male Chromosomes

THE FRAGILE X GENE—FMR1

Fragile X got its name because under a microscope, a portion of the X chromosome from an individual with fragile X syndrome appears "broken" or "fragile." (Note the constricted or "pinched in" part of the chromosome on the bottom of the photograph in Figure 3 on the next page—it is thinner than the sections above or below it.) As researchers studied this area of the X chromosome in individuals with fragile X syndrome, they found it contained more than the normal amounts of DNA. Specifically, it turned out to have a large number of repetitions of DNA called a CGG repeat (see below). This expansion of DNA is what gives the Fragile X chromosome its unique appearance.

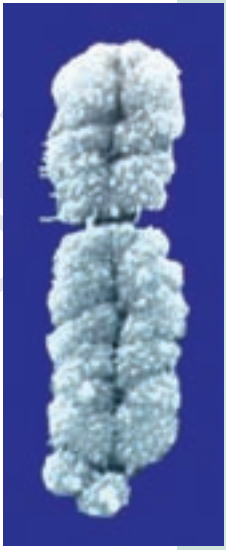

Figure 3: Fragile X Chromosome Under a Microscope

In May 1991, researchers identified the gene responsible for Fragile X. This gene, which is on the X chromosome, is called FMR1, which stands for "Fragile X Mental Retardation 1." (Note that most of the disability community no longer uses the term "mental retardation," instead referring to it as "intellectual disability," but that is what the gene was originally named in the scientific literature.) Every person has at least one copy of the FMR1 gene. Women have two X chromosomes, so they have two copies of the gene. Men have only one X chromosome, so they have just one copy of FMR1. The gene varies in length from one person to another. The variation occurs because there is a range of CGG repeat numbers from person to person. What distinguishes people who have a Fragile X mutation from those who don't is the number of times this CGG pattern is repeated.

Most of our genes either make a protein or regulate proteins made by other genes. The FMR1 gene is responsible for producing a protein that is important in brain development. This protein is called FMRP (Fragile X Mental Retardation Protein). Individuals with fragile X syndrome have a deficiency of this protein.

FMR1 GENE CATEGORIES

There are four general categories of FMR1 CGG repeats: normal, intermediate, premutation, full mutation.

1. ***Normal***
   - This allele has 5 to 45 CGG repeats.

2. ***Intermediate or "Gray Zone"***
   - 45 to 54 CGG repeats. This allele is common in the general population (approximately 1 in 50 individuals).
   - This allele is not associated with any known medical problems, and individuals in this range are not at known risk to have children with fragile X syndrome.

- In a small number of families these intermediate alleles change slightly in the next generation and may have the potential to lead to premutations (see below) in future generations.

3. ***Premutation***
   - 55 to 200 CGG repeats.*
   - Individuals with an FMR1 premutation are often referred to as "carriers." -As many as 1 in 130 women and 1 in 700 to 800 men are estimated to be carriers of the Fragile X mutation, according to current studies.
   - A premutation has the potential to be unstable and to expand to a full mutation when passed from mother to child, causing fragile X syndrome.
   - Many individuals with premutations have no symptoms and no known family history of Fragile X.
   - Females with a premutation are at risk for infertility/early menopause and other ovarian disorders (FXPOI).
   - Males (and to a lesser degree, females) with a premutation are at risk for the adult onset neurological disorder FXTAS.

4. ***Full mutation***
   - More than 200 CGG repeats.*
   - Approximately 1 in 4,000 individuals has a full mutation.
   - Leads to fragile X syndrome in males.
   - A full mutation can lead to fragile X syndrome in some females. Other females may have mild features (e.g. learning disabilities, anxiety, shyness) or no obvious features of FXS.
   - The full mutation causes the FMR1 gene to "turn off" and not work properly. This occurs by a process called methylation, which is like a switch that turns off the gene. (Normally the gene is "unmethylated" or switched on.) This means the gene does not produce any or enough FMRP, which is believed to be necessary for normal brain development. Current research is focusing on this protein and its function.

** Although laboratories report these very distinct genetic categories, there is clearly some clinical overlap between them. Some individuals with "large premutations" (over 150 CGG repeats) have distinct features of FXS, while others with small full mutations (200 to 250 CGG repeats) have milder features of FXS. We are therefore seeing a blurring of these categories as we learn more about the clinical aspects of Fragile X-associated Disorders.*

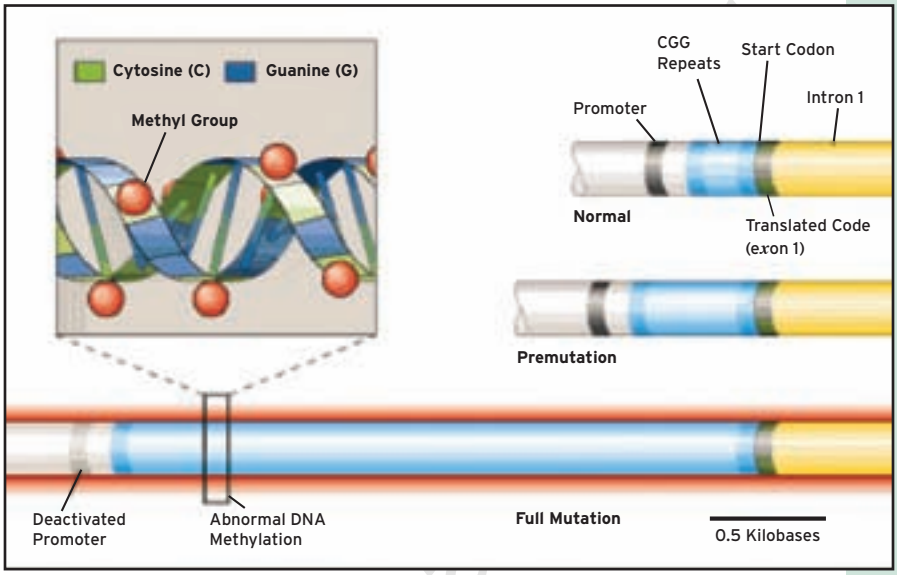

Figure 4: The FMR1 Gene and FMR1 Mutation Sizes

HOW FRAGILE X IS INHERITED

Fragile X is called an X-linked disorder because the FMR1 gene is located on the X chromosome. X-linked conditions are inherited in a special way. A woman who carries the gene that causes an X-linked condition has a 50-50 chance of passing it to a child, whether it is a son or daughter. This is because she has two X chromosomes, and she passes one or the other on in each pregnancy. 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. This is because he passes his only X chromosome to all his daughters and his Y chromosome to all his sons.

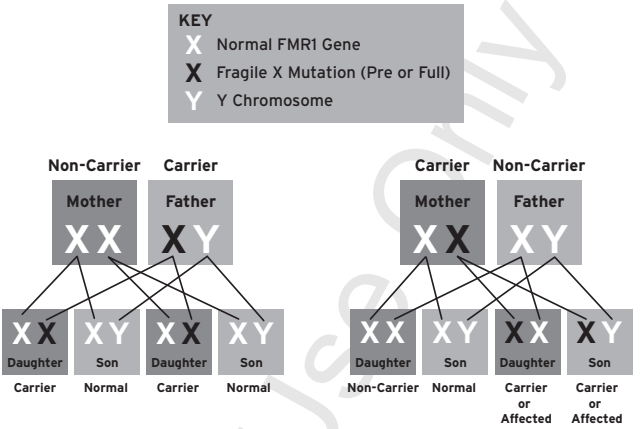

Figure 5: Fragile X Inheritance

Fragile X inheritance exhibits some particular trends. When a father passes the premutation to his daughters, the CGG count usually stays in the premutation range. If a mother passes her X with the premutation to her children, the CGG repeat number can stay in the same range or can increase into the full mutation range. The higher the mother's CGG repeat number the greater the chance for it to expand to a full mutation in the next generation. Females with an FMR1 premutation can inherit it from either parent, whereas males can inherit it only from their mothers.

SECTION 2

Clinical Symptoms

FRAGILE X SYNDROME

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

As you can see from the photographs in this handbook, and as many families will affirm, children and adults with fragile X syndrome are 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. Often, parents and others become concerned only when a baby is delayed in early developmental skills such as sitting up, walking or talking.

Still, certain physical and behavioral characteristics are associated with fragile X syndrome in both males and females (see chart below). Note, however, that facial features tend to be more noticeable as children get older (particularly in males). In addition to the features listed below, approximately one-third of boys with FXS have some degree of autistic-like behavior, typically referred to as an "autism spectrum disorder" (ASD).

Common Features of Fragile X Syndrome

PHYSICAL

- Large ears
- Long, narrow face
- Prominent forehead or chin
- Large testicles in teens/adults
- High palate (roof of mouth)
- Flat feet
- Seizures
- Crossed/lazy eyes
- Tendency for ear infections
- Hyperflexible joints, particularly of the hands and wrists

COGNITIVE/BEHAVIORAL

- Developmental delay
- Learning and intellectual disabilities
- Attention deficits and hyperactivity
- Hand-flapping and/or biting
- Poor eye contact
- Shyness, anxiety
- Behavior issues
- Speech/language delays
- Rapid, repetitive speech
- Difficulty with transitions
- Increased sensitivity to sounds, touch, crowds, certain foods and textures

SECTION 2

Clinical Symptoms

It is important to remember that every individual with FXS is unique. Therefore, people with FXS may exhibit a wide range of the features described on page 10.

A small number of individuals with FXS have what is called "mosaicism." This means they have a mixture of cells with different CGG repeat numbers and or/methylation status. For instance, a boy may have a mixture of both full mutation and premutation FMR1 alleles, and he may have some cells that are unmethylated and therefore produce some amount of FMRP. As seen with females, production of a small amount of FMRP may make a difference in a person's functional level.

FEMALES WITH A FULL MUTATION

The effects of a full mutation in females can range from quite minimal to significant developmental delays and intellectual deficits, though these deficits do not occur with the same frequency as in males. This is because females with a full mutation have a normal functioning FMR1 gene on their other X chromosome, which means they usually produce some FMRP. Their normal Fragile X gene may thus compensate for or "cover up" some effects of the full mutation.

However, in addition to the learning and developmental issues listed above, some of the symptoms reported in females with a full mutation include difficulty with math, reading maps and graphs, picking up "social cues," social anxiety, depression, and other mental health issues. Females with a full mutation are not at risk for FXPOI or at higher risk for infertility than the general population.

COMMON RESPONSES TO A DIAGNOSIS OF FXS

A diagnosis of fragile X syndrome in a child can—and generally does—cause a multitude of feelings in parents. Many parents experience sadness that the

hope of the typically developing child they expected has been lost, and their future is uncertain and unpredictable. By the time of the diagnosis, however, parents may feel relieved and ready to go forward, now that they have finally gotten an answer to why their child is not meeting developmental milestones.

Also, FXS is truly a family diagnosis. One child's diagnosis opens up the possibility that other individuals may be directly affected: grandparents or siblings might be carriers, aunts might have infertility, or cousins who might already be pregnant could have an affected child. Therefore, this may evoke complex reactions from extended family members.

It is common for carriers of a genetic condition to feel responsible for passing it on to their children. Feelings of guilt are also a common reaction in parents of children who have any type of birth defect, even when not inherited. In reality, we have no control over what genes we pass on to our children, and whether those genes have positive or negative effects on them. It might be helpful to consider that we all carry genes that have the potential to cause genetic disorders, many of which do not surface in our children but do get passed along through generations. Genes are always changing and mutating, and that is what makes us all unique.

FRAGILE X-ASSOCIATED PRIMARY OVARIAN INSUFFICIENCY (FXPOI)

FXPOI occurs in approximately 22 percent of females with a fragile X premutation. It can cause irregular or absent menstrual periods, reduced fertility or infertility, and premature or early menopause—these are all effects of abnormal ovarian functioning.

FXPOI has also been called POF (premature ovarian failure), but this term does not describe the condition as accurately. Women with FXPOI may have inadequate, but not absent, ovarian function such as in POF. FXPOI includes a spectrum of ovarian dysfunction, of which POF is at the more severe end.

FXPOI is also not the same as menopause, because in some cases women with FXPOI can get pregnant, as their ovaries can intermittently release eggs. Also, some women with FXPOI do experience occasional menstrual periods, whereas in menopause the cycles do not return.

It is important for women or teens with a premutation to keep track of their menstrual cycles and to discuss the potential for FXPOI with their health care providers. Because of the decrease in estrogen production (which is common in those with any type of ovarian insufficiency) blood hormone levels may be helpful in assessing those at risk for FXPOI. Women with FXPOI should be followed by an OB/GYN or reproductive endocrinologist familiar with ovarian insufficiency.

When women discover they are infertile, they can experience a profound grief reaction. Often, their long-held dreams of becoming pregnant and having biological children are now lost. In addition, the fact that if a pregnancy were to be conceived, there would be a risk for fragile X syndrome can complicate the options and the decisions faced by a carrier and her partner. (See section on reproductive options, page 18.)

FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME (FXTAS)

FXTAS is an adult-onset neurological condition that occurs in some carriers of the FMR1 premutation. Though it occurs more commonly in male carriers, some females also develop features of FXTAS. Current estimates suggest that approximately 30 percent of male carriers and 8 percent of female carriers develop some features of FXTAS.

FXTAS is often initially misdiagnosed as Parkinson's disease, Alzheimer's, or a stroke. Though any male carrier is at risk for FXTAS, it is diagnosed more often when there are grandchildren in the family with fragile X syndrome (as FXS is already known to these families and their providers). In some families with children who have FXS, it is unknown which maternal grandparent is a carrier until the diagnosis of FXTAS is suspected.

The features of FXTAS include balance problems (ataxia), shaking when reaching for something but not while resting ("intention" tremors), memory loss, mood instability or irritability, numbness of the extremities (neuropathy), lack of normal inhibitions, and cognitive decline. Those with FXTAS also show specific findings on magnetic resonance imaging (MRI) exams. (The technical term is "increased T2 signal in the middle cerebellar peduncles," also called an "MCP sign.") This can be seen by radiologists familiar with the MRI patterns in FXTAS.

Some of the psychological, cognitive or neurological features of FXTAS are often attributed to the aging process and not initially recognized as symptoms of the condition. This is especially true for symptoms such as impulsivity, short-term memory loss, depression, mood instability or irritability. It is important to pay attention to any unexplained personality or neurological changes in older adults at risk for FXTAS.

Females may also have these features of FXTAS, and may also have a predisposition to develop autoimmune disorders such as abnormal thyroid function.

There is a wide range of the progression of symptoms in those with FXTAS. Some individuals remain stable over many years with only minimal symptoms, while others can decline steadily and/or rapidly.

The diagnosis of FXTAS can be confusing and frightening. Neurologists are still in the early stages of understanding its impacts and range of treatments. Some families struggle with the stress of another family member affected by Fragile X, and its potential impact on family dynamics. Sometimes the routine of caring for a child with FXS is complicated by the emergence of additional demands to take care of the newly diagnosed adult with FXTAS.

TESTING FOR FRAGILE X

Prior to 1991, a laboratory test could identify people with fragile X syndrome only by looking under a microscope to see if there was a thinning or "fragile"

site on the X chromosome. This was not a highly accurate test, especially for affected females and both male and female carriers, because those with premutations did not have the typical "fragile X" chromosome as seen under the microscope. Although chromosome analysis detects many other causes of intellectual disability (such as Down syndrome), it is not an accurate test for Fragile X.

Since 1991, a DNA test that is over 99 percent accurate has been available for Fragile X. The test directly examines the FMR1 gene. FMR1 testing is performed on a blood sample (and can be done on other tissues as well, such as amniotic fluid). There are two technologies that laboratories use to analyze the FMR1 gene. One, called Southern blot, measures the approximate size of the CGG repeat and will determine the methylation status of the FMR1 gene. (See page 5.) The other technology, PCR (polymerase chain reaction), is more precise for measuring CGG repeat counts that are less than 200, in particular for determining the exact CGG repeat number in premutations and smaller alleles. PCR should be used in conjunction with Southern blot to test for Fragile X. Occasionally PCR is used alone for carrier screening in individuals in the general population without a family history of FXD. However, the most comprehensive testing for fragile X syndrome includes both PCR and Southern blot.

The testing takes place over a span of two to four weeks and costs $300-$500, depending on a variety of factors such as insurance coverage, laboratory, phlebotomy (blood drawing) and shipping fees, etc.

SECTION 3

Treatments for Fragile X-Associated Disorders

FRAGILE X SYNDROME

The most effective and available methods to help individuals with fragile X syndrome are largely provided through special education (discussed below) and various forms of therapy, including speech/language therapy and occupational therapy. Psychotherapy may be helpful, particularly for females, to help cope with anxiety, depression or other mental health and behavioral issues.

Many children with fragile X syndrome have difficulty with sensory over-stimulation, such as an inability to screen out noises and visual stimuli, and discomfort with certain fabrics or food textures. They often are highly sensitive to touch. Sensory integration therapy, which is a branch of occupational therapy, is often utilized for children with these types of sensory issues.

In order to provide the best educational, therapeutic, or vocational program for any individual, it is important to assess his or her overall development. Strengths and weaknesses, specific behavioral issues, and medical needs must be evaluated on an individual basis. This evaluation is recommended for both children and adults.

Certain medications may be helpful, especially in managing the hyperactivity, poor attention span or anxiety of children and adults with fragile X syndrome. Medications can also help treat mental health issues in older individuals.

In the United States, 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 in general education classrooms) for all children who qualify, up to age 21.

IDEA requires a multidisciplinary evaluation for any child who may be eligible for special education services. This means that a variety of professionals,

along with the parents of the child, assess the child's needs and determine appropriate interventions. Interventions vary, based upon the child's age and individual profile.

School-aged children eligible for special education have their own Individualized Education Program (IEP). The areas that should be addressed in the IEP include development of skills related to cognitive abilities, speech and language, behavior, fine and gross motor skills and integration, and academic tasks such as reading and writing. Educational settings range from home-based programs for infants to a variety of school-based classrooms.

All states have programs to evaluate and provide educational services to children with special needs, beginning in infancy, although the types of available programs differ from state to state. A good place to begin in identifying the educational resources in your area is to contact the principal at your local elementary school. It is never too early to let your local school officials know that your child will be enrolling and will likely need special services.

FRAGILE X-ASSOCIATED PRIMARY OVARIAN INSUFFICIENCY

Women with FXPOI should discuss medical interventions with their doctor. They may need to consider treatment such as hormone therapies if they are experiencing discomfort from the symptoms of ovarian insufficiency (hot flashes, etc.). Couples who wish to pursue infertility treatments or learn about their reproductive options should meet with a reproductive endocrinologist and genetic counselor familiar with FXD to discuss these issues. (See next page on reproductive issues for carriers.) Support groups such as IPOFA or RESOLVE can also be of help to infertile couples. Log on to www.pofsupport.org/.

FRAGILE X-ASSOCIATED TREMOR/ ATAXIA SYNDROME

Current treatments for FXTAS include physical and occupational therapy, and various medications to control tremors, ataxia, depression and dementia. As with the other FXD conditions, ongoing consultations with a knowledgeable physician are invaluable in helping to manage FXTAS symptoms to the person's greatest possible benefit.

CLINICS FOR FRAGILE X-ASSOCIATED DISORDERS

Many individuals benefit from an evaluation at one of the nationally recognized clinics within the Fragile X Clinical and Research Consortium. These clinics, all at major medical centers, are rapidly growing in number. They are staffed by physicians, genetic counselors, therapists, and other providers with expertise in Fragile X-associated Disorders. Contact the NFXF for more information and/or a referral to a Fragile X clinic in your area.

REPRODUCTIVE OPTIONS FOR CARRIERS

Upon learning they are an FMR1 carrier, many women (and men) have questions about their reproductive options for the future. Any couple at risk for FXD and considering or planning a pregnancy should meet with a genetic counselor to explore these issues.

If you are a female carrier, reproductive options include the following:

- Upon conception, you can choose no intervention.
- Upon conception, you can pursue prenatal diagnosis (amniocentesis at 15-20 weeks or CVS at 10-14 weeks of pregnancy). Both of these prenatal tests will determine the FMR1 status of the pregnancy. More information about these tests can be found on the NFXF website.

- You can elect to use a non-carrier egg donor.
- You can pursue preimplantation genetic diagnosis (PGD). This is an assisted reproductive technology that is available at a limited number of centers nationally. The technique involves withdrawing eggs from the carrier, and then after fertilizing and testing the eggs, implanting only unaffected fertilized eggs. This technology has limited availability and success due to the ovarian difficulties in some carriers, complexity of the technology, the expense, and other factors.
- You can choose to adopt children.
- You can choose to not have any (or additional) children.

For male carriers, the following pertains:

- All of your daughters but none of your sons will be carriers.
- Prenatal diagnosis to determine the CGG repeat size in a female fetus is available to pregnant partners of male carriers.
- Male carriers do not have any increased risk for infertility or decreased fertility.
- Sperm sorting to increase the chance of having a male (and thus not passing on the premutation) is available.

Anyone who is concerned about FXD, is undergoing carrier testing, or who has a positive FMR1 test should meet with a genetic counselor. Your physician or health care provider can refer you to a genetic counselor in your area or you can locate one at www.NSGC.org.

SUPPORT FROM THE NFXF

Receiving a diagnosis of FXD presents a distinct challenge for individuals and their families. The challenge relates to both known and unknown effects of the specific conditions. Having a child or other family member with FXD or any disability means extra work—sometimes a lot of it. Anyone diagnosed with a Fragile X condition will find his or her (and entire family's) life changed. However, as countless families who have lived with FXD can readily attest, a changed life does not mean it will be a bad life—just a different life.

SECTION 3

Treatments for Fragile X-Associated Disorders

Fortunately, there is now plentiful information about FXD available, thanks to the Internet, Fragile X clinics (see www.fragilex.org/html/clinics.htm), parent networks, written material, and organizations such as The National Fragile X Foundation. There is much information available about symptoms, what services to seek, what you can do in your home, school and community, and what to anticipate in the future. As recently as 20 years ago, parents with newly diagnosed children had very little information with which to guide them, and at that time, neither FXTAS nor FXPOI had even been discovered. Since then, a huge amount of scientific information, clinical insight, and practical knowledge has been discovered and made available to the Fragile X community.

Fragile X-associated Disorders affect people all over the world, which has given rise to support groups on every continent. Many people who have weathered the rough times make themselves available to support those new to Fragile X. This support can often be found through the NFXF regardless of where you live or how far along you are in dealing with the implications of Fragile X in your family.

Researchers around the world are studying and seeking ways to reduce the impact of FMR1 gene changes and the three associated conditions. They make substantial and inspiring progress every year.

The National Fragile X Foundation is here to help you by providing the latest information and guidance. All questions are welcome. If you are worried that your question is too trivial or uninformed, rest assured that it has no doubt been wondered about and asked before by many others, and there are more willing and competent resources than ever to assist you in obtaining an answer.

The NFXF website (www.FragileX.org) is regularly updated, and you can call or email for individual responses to any of your questions or concerns. Perhaps the most important point to remember is this: *You're not alone*.

Phone: 1-800-688-8765
Email: Treatment@FragileX.org
Website: www.FragileX.org

The National **Fragile X** Foundation

SERVING THE FRAGILE X COMMUNITY SINCE 1984

You're Not Alone

OUR MISSION

The National Fragile X Foundation unites the Fragile X community to:

Enrich lives through educational and emotional support;
Promote public and professional awareness;
Advance research toward improved treatments and a cure for Fragile X.

The National **Fragile X** Foundation

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The National Fragile X Foundation is a charitable 501(c)(3) organization, Tax ID No. 84-0960471