Fragile X Syndrome

Research into fragile X syndrome, a common inherited cause of intellectual disability, is starting to generate treatments. BY DEBRA GORDON, M.S.

Holly Roos’ son, Parker, was not quite four years old, but Roos—who has a degree in early education—knew something was wrong. By his second birthday, Parker had never talked, only screamed. He couldn’t hold a fork or pick up a Cheerio between his fingers. By four, Parker only had a vocabulary of about 20 words; he still had significant fine motor delays, couldn’t draw a circle, and rarely used utensils because it was difficult. Parker couldn’t dress himself and wasn’t potty trained.

“But everyone we saw—the pediatrician, the developmental pediatrician—they all said he was fine,” Roos recalls. “They all stressed the fact that boys develop differently than girls.”

A few months later, Roos’ mother, Colleen Usrey, attended a genetics conference and came across an information booth on a condition called fragile X syndrome (FXS). She knew it was the first time Parker had strung together more than two or three words, and the first time he’d ever told his mother that he loved her. Roos burst into tears.
right away that this was something Parker should be screened for. Roos insisted that her pediatrician order the genetic test for the disease, which showed that Parker had it.

By then, Roos had just given birth to another child. Her daughter, Allison, was born with severely crossed eyes, which Roos would soon learn was a symptom of FXS, just like Parker’s language deficits, screaming, and muscle problems. (See box, “Fragile X Syndrome: The Basics.”) She now had two children with the disorder who, she was told incorrectly by one genetic counselor, would eventually require institutionalization.

Today, Parker, 12, and Allison, eight, both still live at home, attend school—allison in a regular classroom full time, and Parker for 60 percent of his day—and receive various therapies for their condition. Parker is participating in a clinical trial of a drug that may one day reverse the intellectual and developmental effects of genetic conditions such as FXS.

**A MAJOR GENETIC DISCOVERY**

An important chapter in the FXS story begins in 1991, when the FMR1 (fragile X mental retardation 1) gene was discovered. The gene sits on the X chromosome. Men and women each have at least one X chromosome, which means either can pass the mutated gene to their children.

Boys and girls can both be affected, but because boys have only one X chromosome, a single mutation in the FMR1 gene is likely to affect them more severely. A small part of the gene code is repeated on a “fragile” area of the X chromosome; the more times this part of the code is repeated, the more likely a problem will occur. Boys with the full genetic mutation have FXS, while half of all girls who receive the mutation have significant limitations in intellectual functioning and in adaptive behavior, which affects many everyday social and practical skills. Sixty percent of the girls who have the mutation without these significant limitations still have learning disabilities.

The full mutation turns the gene off, which means it does not produce a protein called FMRP. This protein controls protein synthesis throughout the brain. Without it, other chemicals required for proper communication between brain cells cannot function properly, leading to the symptoms of FXS.

In addition, notes leading FXS researcher Randi J. Hagerman, M.D., medical director of the MIND Institute at the University of California-Davis, FMRP regulates at least a third of the known proteins in genes associated with autism. That helps explain why autism is so common in people with FXS and why some treatments under investigation for FXS are also being tested in children with autism.

**Fragile X Syndrome: The Basics**

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability in boys. It also affects many girls. However, a person can have FXS even if his or her parents do not have it. The condition occurs in an estimated one in every 3,600 boys and one in 4,000 to 6,000 girls. Its effects in boys tend to be more extreme.

The condition is caused by a mutation in the FMR1 gene related to repetitions of a single code on the gene. People with 55 to 200 repetitions have a “premutation” gene, while those with more than 200 repetitions have the full mutation. (Unlike the full mutation, in which no FMRP protein is produced, the premutation causes too much messenger RNA to be produced. See box, “Fragile X Premutation.”) Every time women pass on the gene, the number of repetitions usually increases.

**PHYSICAL SYMPTOMS OF FXS INCLUDE:**
- Large, protruding ears
- Low muscle tone
- Long face

**MEDICAL PROBLEMS INCLUDE:**
- Seizure disorders
- Frequent ear infections
- Mitral valve prolapse, in which the valve between the left upper and lower chambers of the heart doesn’t close properly
- Strabismus, or crossed eyes
- Presbyopia, in which the eyes don’t focus properly
- Autism; about half of those with FXS will be diagnosed with an autism spectrum disorder and about a third with autism

**COGNITIVE/INTELLECTUAL/BEHAVIORAL SYMPTOMS INCLUDE:**
- Delayed speech, language, and motor skills
- Intellectual disability (formerly called “mental retardation”), characterized by significant limitations both in intelligence and in adaptive behavior, which affects many everyday social and practical skills; in addition, these limitations begin before 18 years of age
- Impulsivity
- Poor eye contact
- Vulnerability to sensory overload
- Aggressive behavior
- Difficulties socializing

Currently, FXS is treated with a combination of medications to address symptoms, including antipsychotics, stimulants, and antidepressants. In addition, a number of therapeutic interventions are used, including speech and language therapy, therapy for behavioral disorders, sensory integration therapy, physical therapy, and occupational therapy.
Fragile X syndrome is more common in boys than in girls, and its effects tend to be more extreme in boys. Autism is common in people with FXS.
CAPTURING BRAIN IMAGES

The missing FMRP protein also leads to physical changes in the brain. Researchers from Stanford School of Medicine and the University of North Carolina in Chapel Hill used MRI to view the brains of children with FXS and those without, between ages one and three, a period of dramatic brain development. The researchers found what they consider an FXS “signature.”

Children with FXS have brains that are a bit larger than normal, particularly those deep brain regions involved in cognitive and emotional regulation and inhibition.

Now that these children have been followed to age six, researchers are finding that their brains have continued to change.

“You see parts of the brain that are the same [as in kids without FXS] and stay that way; parts that are different at the outset and remain different; and parts that appear to be developing normally but then brain development goes awry,” says Allan L. Reiss, M.D., professor of psychiatry and behavioral sciences, pediatrics and radiology at Stanford University in Palo Alto, CA.

One such area—in which development begins normally but goes awry—is the thalamus, which acts like a switchboard operator for sensory information coming into the brain, sending this information to multiple cortical regions, says Dr. Reiss. That might help explain why people with FXS have difficulty processing and integrating certain types of sensory information.

The findings, Dr. Reiss says, may one day provide an objective way for researchers to track the effects of investigational treatments. Right now, researches must rely on cognitive tests and behavioral observation. Dr. Reiss expects that some of the medications under investigation will have a physical effect on the brain that can be captured on MRI.

TURNING SCIENTIFIC DISCOVERY INTO TREATMENTS

As their scientific understanding of FMRP and its actions has increased, researchers have begun to identify possible treatments. They believe that even if the FMR1 gene can’t be forced to produce FMRP, perhaps some of the mistakes that occur because of the missing protein can be fixed.

For instance, FMRP normally halts the activity of proteins that act as docking stations (receptors) for the neurotransmitter glutamate, which is involved in many areas of normal brain functioning. Without FMRP, these receptors operate in overdrive.

Reducing that overdrive, researchers suggested a few years ago, might reverse the abnormalities seen in FXS. That’s just what happened in a mouse model of the disease.

Fast forward to today, when at least three drugs that block these receptors have demonstrated some benefit in children and adults with FXS. In one small study of a compound called AFQ056 in 30 men ages 18 to 35, those with completely nonfunctional forms of the FMR1 gene showed significantly fewer repetitive behaviors, such as rocking and clapping, when on the medication. They also had fewer tantrums and improved social interactions. The most common side effects were fatigue and headaches.

Researchers are also testing drugs that target GABA, another protein that relies on FMRP. GABA receptors are involved in anxiety, depression, insomnia, learning and memory problems, and epilepsy. All of these problems are present in people with FXS, whose brains don’t produce enough GABA receptors.

A compound called STX209 that increases GABA receptor activity is being tested. An early trial in 54 males and females ages 6 to 40 found that after four weeks, participants getting the drug had significantly less irritability, fewer outbursts, and better social interactions than the group getting a placebo. In fact, many participants in the drug group stopped taking antidepressants and antipsychotics while in the study. The main side effects were fatigue and headache. Participants are currently being recruited for a larger trial of STX209, and it is being tested in children with autism, who also have GABA receptor problems.

Researchers are also testing an antibiotic called minocycline (MMP9) that is important for the function of nerve cell synapses, where information flows from one cell to another. People with

FRAGILE X PREMUTATION

Although the full mutation of the fragile X gene has the most severe physical and cognitive effects, individuals with a premutation of the gene have their own issues to contend with. Unlike the full mutation, in which no FMRP protein is produced, the premutation causes too much messenger RNA to be produced, which can be toxic for cells.

The premutation is extremely common, occurring in 1 in 170 women and 1 in 500 men, says Dr. Randi Hagerman, who, with her husband Paul Hagerman, M.D., Ph.D., discovered a new adult neurologic disorder related to the premutation called fragile X-associated tremor/ataxia syndrome (FXTAS). It primarily affects men after age 50, with symptoms that mimic those of Parkinson’s disease and Alzheimer’s disease. In fact, individuals with the condition are often misdiagnosed with those conditions.

In women, the fragile X premutation is the most common cause of primary ovarian insufficiency, in which a woman’s ovaries fail as early as her teenage years, sending her into premature menopause. It is also associated with an increased risk of fibromyalgia, thyroid disorders (particularly hypothyroidism), and seizure disorders.

The premutation is also associated with higher rates of anxiety and depression in both men and women, says Dr. Hagerman, although most have normal intelligence and even tend to be driven, successful individuals. As the number of faulty repetitions in the gene increases, though, people are more likely to have learning problems.
FXS make too much MMP9 due to the missing FMRP protein.

When a study published in 2009 showed that minocycline normalized brain cell connections in one-month-old mice, researchers were deluged with calls from parents asking if the drug was appropriate for their children. Dr. Hagerman began prescribing it to some of her patients with astonishing results. Of 53 patients of both sexes (from toddlers to adults) who received the drug, the participants’ parents estimated that half improved their language and attention span; 44 percent improved their social skills; and a third had far less anxiety. The main side effects were nausea and discolored fingernails. Today, Dr. Hagerman is studying minocycline in a controlled clinical trial.

“I AM SORRY. I LOVE YOU, MOM.”
Holly Roos’ son Parker participated in the STX209 trial when he was 10 years old even though it meant driving four hours each way from their home in Canton, IL, to the trial site in Chicago. One day, while the two were in the kitchen at home, Parker accidently broke a glass. Roos warned him not to move as she went to clean it up. But then, she heard her son say, in a shaky but cheerful voice, “I am sorry. I love you, mom.”

It was the first time Parker had strung together more than two or three words, and the first time he’d ever apologized for anything unprompted. It was also the first time he’d ever told his mother that he loved her. Roos burst into tears.

“I’m like, ‘This is it,’” she recalls. Roos believes that her son had received the study drug, not the placebo, even though participants were not told. Parker, now 12, is currently in the extension phase of the trial, in which all children receive the study drug, and the impact on the family’s life continues to be dramatic. Today, he chatters on so much that Roos and her husband are continually amazed by the opportunities for conversation with Parker, something they felt might never be possible. In addition, his behavior has dramatically improved, Roos says, possibly because he can now communicate when he’s frustrated or overwhelmed.

This summer, Roos took Parker to the local water park, where he went up and down the water slide dozens of times. “That would have completely overwhelmed him before,” she says. Parker also goes to the movies, eats in the school cafeteria with other kids, and has progressed from completing two...
binders of work a day at school to finishing six a day—all dramatic differences from his life pre-treatment.

**DIFFICULT DECISIONS**

Given these improvements, will Roos put her eight-year-old daughter in a clinical trial for the drug? Roos was hesitant at first since Allison is far less affected by FXS than her brother. But after a difficult start to the school year—filled with anxiety, hyperarousal, and social problems—Roos says they have filled out the paperwork. They will be taking Allison in October to see if she qualifies for the study.

“We are hopeful she will qualify and that the medication will help her as much as it has helped her brother,” she says.

But clinical trials for FXS treatments are not just recruiting young children. Explains FXS researcher Elizabeth Berry-Kravis, M.D., Ph.D., a professor of pediatrics, neurology and biochemistry at Rush University Medical Center in Chicago: “It’s important to think of brain plasticity as having two different functions: One is developmental, and the other is ongoing maintenance so that new learning can occur.” Learning doesn’t end after childhood—it’s a lifelong process. In addition, we now know that the brain retains some ability to develop new neurons and is continuously developing and remodeling synapses during adulthood.

What that means in terms of FXS treatments, Dr. Berry-Kravis says, is that treating adults with the condition might still improve their function.

That poses a conundrum for parents like Jayne Weber of Boulder, CO, whose 23-year-old son Ian was diagnosed with FXS when he was 20 months old. Today, Ian lives part-time in his own supervised apartment, works four days a week at a supermarket, and volunteers one day a week with Meals on Wheels. Weber—who, like Roos, works part time with the National Fragile X Foundation—has considered entering him into a clinical trial, but she has mixed feelings. For one, the trials require that blood be drawn from participants, and Ian refuses to let anyone take his blood. Second, the trial requires that participants take no more than three other medications; Ian currently takes six. Weaning him off those medications, several of which are psychiatric drugs, would be difficult. But the true limitation comes from a fear of rocking the delicately balanced life she and her husband have created for Ian.

“If something were to happen at work and he got fired from his job, he would have nothing,” Weber says. “We’re in a place now where he’s happy.” They can wait a few years until some of these drugs reach the market, she says. “Will it be life changing? I don’t know. I’ve heard that parents are very happy with some of these new drugs, but what it will take, how it will happen for me, I just don’t know.”