The National **Fragile X** Foundation
quarterly
A Journal for Families and Professionals

Inside:

COLUMNS

Readers Respond... 1

From the Executive Director 2
Being Fair

Public Policy Update 3
It's Time to TEAM Up for Our Kids

Braden on Behavior 4
Navigating the Road to Inclusion

Support 6
Guardianship for Your Child

FRAGILE X SYNDROME (FXS)

Sleep in Children With Fragile X Syndrome: A Bio-Psycho-Social Approach 8

Cover Story 12
Married...With (Fragile X) Children

Therapy In Action 14
Doggone It, Mantras Are Great for Learning!!

RESEARCH, REPORTS AND ANNOUNCEMENTS

Focus on Volunteers 10
Four Who (Continue to) Step Up

mGluR5: A Primer 16

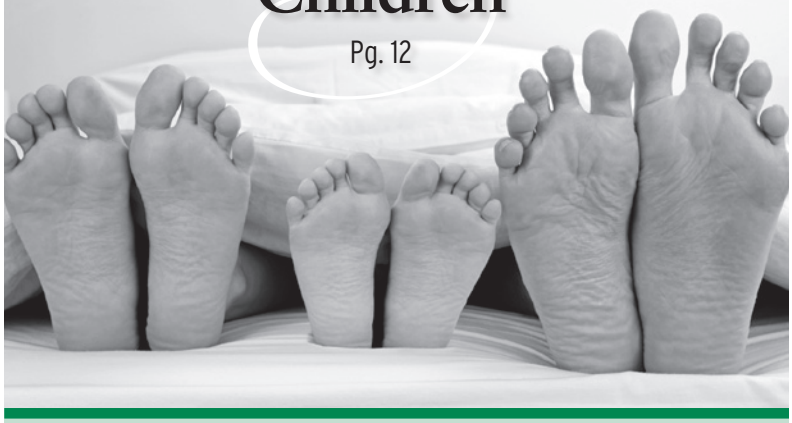
Employment First! 18
NFXF Joins Growing Chorus on Job Rights for People With Disabilities

Focus on 'Fun'draising 22
Spring Fragile X Fundraising Fun

New Board Members 24

Married... With (Fragile X) Children

Pg. 12



Employment First!

Self-Determination Movement Gains Traction

Pg. 18

Join Us in Celebrating!

See page 23

National **Fragile X** Awareness Day
JULY 22, 2011

By Andrew Hidas

mGluR5: A Primer

This is the second in a series of Q&A's focused on better understanding the basic science and importance of terms frequently appearing in Fragile X research. Interview subject Ted Brown is one of those accomplished souls who seem to be not all that rare in the Fragile X research community: a "doctor doctor," or holder of both MD and PhD degrees. As medical director of the Fragile X Clinic at the Institute for Basic Research on Developmental Disabilities (IBR) on Staten Island, New York, and Principal Investigator on the CDC grant supporting the Fragile X Clinical & Research Consortium, Brown is at the forefront of multiple collaborative efforts to research the causes, treatments, and possible cures for Fragile X, in addition to ongoing research on the related condition of autism. A native of Montana (where he was state chess champion as a youth, a fact he does not readily share), he now lives on Staten Island with wife Donna, a speech therapist for children with autism. They met at a Fragile X conference in Australia in 1985 while she was working in Denver with NFXF founder Dr. Randi Hagerman. The couple has two young adult children.

Anyone keeping up with Fragile X research literature in recent years comes across the term "mGluR5" with increasing regularity. Can you give us a sense of what it means and why it's important?

Researchers studying the chemistry of the brain have made some discoveries we're coming to believe are largely responsible for most of the behavioral problems seen in boys and girls with fragile X syndrome. The generally accepted idea based on this research, which began with the work of Dr. Mark Bear's group at MIT and was published in 2002, is that FXS involves a problem with glutamic acid. Glutamic acid is one of 22 amino acids in the human body. Amino acids are the basic building blocks that form protein in every cell. Glutamic acid is an excitatory chemical, meaning it excites the cell it's released on. When an electrical signal goes down the nerve, it stimulates a second nerve to be either excited or inhibited. It causes or prevents the other nerve from expressing a signal. The research on mice suggests that there is an over-reaction to glutamic acid in those with FXS, which causes too much stimulation in the brain. So one of the ideas being studied is to partially block the glutamic acid and thus inhibit the highly excitable behavior we see in FXS. This approach has been quite successful in mice. This targeted approach to therapy has caused a lot of excitement in the medical community.

The basic problem in Fragile X is the lack of FMRP. So if we're to cure the syndrome, it would mean replacing that protein.

How does the glutamic acid get blocked?

There are several ways, but chief among them are various drugs, some of them now in phase II clinical trials. One published study from Novartis involved a small sample of 30 subjects in Europe. Partially blocking the glutamic acid seemed to improve the behavior of children with FXS. All the subjects who had the full mutation improved clinically. Those with just a partially methylated mutation didn't seem to be helped as much. This was curious—we're not sure why it would be. Obviously, more research is needed on this.

Why is there too much glutamate?

The discovery and sequencing of the "Fragile X gene" (scientific term: Fragile X Mental Retardation 1," or "FMR1") in 1991 by Drs. Warren, Nelson, Oostra, Mandel, and Sutherland's labs showed that it plays a central role in typical brain development. That gene is "broken" or "fragile" in those with FXS, so it doesn't produce enough of a key protein known as the Fragile X Mental Retardation Protein (FMRP). This lack creates a chemical reaction that allows glutamic acid to run wild. It's a complicated piece of chemistry.

Are we looking at the many drugs currently being studied as a possible cure for FXS, or are they more for symptom amelioration?

The basic problem in FXS is the lack of FMRP. So if we're to cure the syndrome, it would mean replacing that protein. We're not there yet. The drugs we're studying address the problem of excess glutamate. So it's addressing part of the problem, but it's not a cure.

What would lead toward a cure?

The ideal would be to use genetic engineering to replace the Fragile X gene chemically in those people where it is broken and effectively turned off or "methylated." That would allow it to re-express itself or become "unmethylated," which is its typical state. If we could do that, we might have a chance for a cure.

Are there studies underway along those lines?

Yes, there are plans to increase studies, but we're in the very early stages. We need a lot more experience than we have now.

Given the importance developmental psychologists place on human beings hitting key developmental milestones at certain ages, would an eventual cure focused on re-expression of the gene help older children and adults with fragile X syndrome?

It's hard to say, but studies done with mice didn't show age to be a major factor. It's possible it could be like curing deafness at 12 years old—one can still learn a lot, even having missed out on so much in earlier life.

Let's get back to defining mGluR5. We've covered the "glu" for "glutamate," but what do "M" and "R5" signify?

"M" stands for "metabotropic," which means it involves an internal metabolic pathway. R5 signifies the 5th one, which turns out to be the main one out of 8. So taken as a whole, mGluR5 refers to a protein that is the 5th receptor of the metabolic type for glutamic acid.

Do all mammals have mGluR5?

Yes. Not only mammals, either. We see it in fruit flies and worms, too. The basic chemical system that builds and sustains life evolved very early, so we still see it in primitive life forms. We can watch plants in seabeds just sitting there doing nothing, but their nervous system transmitters and receptors are functional very much like ours, so they are capable of sensing and then pulling a passing organism in to feed themselves. This is based on simple nervous activity, but it requires a lot of things to function correctly.

We can assume human nervous systems are a bit more complicated?

The central nervous system has billions of nerve cells, connecting the activities from all parts of our body. It consists of the brain and spinal cord. When we want to wiggle a toe, an electrical impulse goes from our brain along the spinal cord down through our leg and then to the toe. It's highly organized and complex, but most nervous activity takes place beneath our awareness. Obviously, no one is aware of the glutamic acid activity that causes nerve cells to express over-enthusiastically. This is just how we are made, and most of the time, everything functions in a way that can sustain life. And sometimes, things go wrong.

Dr. Ted Brown is part of a growing contingent of scientists in various academic and research settings around the world who continue to build upon each other's work in determining the causes, treatments, and quest for an eventual cure for Fragile X-associated Disorders.

It seems rather miraculous they go right as often as they do.

Yes, human life is pretty much miraculous, in the fact that we have evolved to this point. We have approximately 25,000 genes, of which some 60 to 70 percent are expressed in the brain. Genes have to be expressed in just the right order in thousands of ways, and if they're not, it causes disruption in normal neural activity. The Fragile X protein appears to be very important for nervous system function, because it modulates the expression of other genes. If 25,000 genes are being expressed, we know that about 5 percent, or 1,250 genes, are under the control of the Fragile X gene. That amounts to a significant impact on neural activity.

Sounds like there's lots of buzz among scientists in the Fragile X field.

Yes, plenty of excitement. There is a lot of basic research underway, too, about what happens when the Fragile X protein is not expressed, what's going on mechanistically in the cell, because there might be other targets we can reach besides just glutamic acid. We're at a point where targeted drugs might make a real difference in people with fragile X syndrome, helping them to live richer lives. ■

The author has edited the Fragile X Quarterly *since 2004.*
Email: Editor@FragileX.org