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Helping Patients and Families Understand Fragile X Syndrome

### FRAGILE X SYNDROME AND RELATED CONDITIONS

Diagnosis of the genetic disorder, Fragile X syndrome can be devastating for our young patients and their families, knowing that both patients and their families can be affected by this condition. As a clinician how do we guide patients and their families through this process of understanding their diagnosis? You are listening to ReachMD, The Channel for Medical Professionals. Welcome to The Clinician's Roundtable.

I am your host Dr. Mark Nolan Hill, Professor of Surgery and Practicing General Surgeon and our guest is Dr. Randi Hagerman, Professor and Chair of Fragile X Research and Medical Director of the MIND Institute (Medical Investigation of Neurodevelopmental Disorders) at the University of California, Davis School of Medicine.

#### DR. MARK NOLAN HILL:

Welcome Dr. Hagerman.

#### DR. RANDI HAGERMAN:

Thank you it's a pleasure to be here.

#### DR. MARK NOLAN HILL:

We are discussing options for treatment and the emotional aspects of having Fragile X syndrome. Dr. Hagerman what do you tell the parents and grandparents of a child on which you just made this diagnosis?

#### DR. RANDI HAGERMAN:

Well we talk about the features of Fragile X syndrome and what they can expect over time. I think it is helpful to have this diagnosis because there is so much available now for treatment and with the new targeted treatments; there is the potential that we could really reverse some of the cognitive deficits over time with these new treatments.

**DR. MARK NOLAN HILL:**

Now when you say targeted treatments, what do you mean by that?

**DR. RANDI HAGERMAN:**

I mean treatments that are targeted specifically to the neurobiological abnormalities that occur with Fragile X syndrome and specifically that means the research has shown that the mGluR5 pathway in Fragile X is significantly upregulated. This is the metabotropic glutamate 5 pathway and the Fragile X protein usually inhibits this pathway. So when the Fragile X protein is not there, this pathway is upregulated and it leads to weak, synaptic connections all over the brain and we are using now mGluR5 antagonists. We are studying these medications in control trials and we are very hopeful that this can reverse the dendritic connection abnormalities in the brain and make a big difference in terms of improvement in behavior and cognition in this disorder.

**DR. MARK NOLAN HILL:**

When you talk to the parents and the grandparents and you actually evaluate them, do you find that they have symptoms as well?

**DR. RANDI HAGERMAN:**

Oh! absolutely for every child with Fragile X syndrome that we identify, there are a number of individuals in the family tree who may be carriers or also may have the full mutation of Fragile X, so for instance say we identify a little boy or a little girl with the full mutation, we know that the mother is always the carrier of a child that has a full mutation. Full mutation meaning more than 200 CGG repeats and the full Fragile X syndrome. So the mother is typically a carrier herself. Sometimes she has a larger CGG expansion, but then she receives a gene from either her mother or her father. If she received it from her father, then all of her sisters are obligate carriers. Because a carrier father will pass on his X chromosome with the mutation in it to all of his daughters. His sons get the Y chromosome, so they are off the hook in terms of Fragile X syndrome, it never passes from father to son because it's carried on the X.

**DR. MARK NOLAN HILL:**

So really once you make the diagnosis in a child, you certainly are not just dealing with that child. You are dealing with the entire family?

**DR. RANDI HAGERMAN:**

The entire family and the whole spectrum of different types of disorders that can be associated with a permutation or the full mutation. So this includes about 20% of women with the pre-mutation can have primary ovarian failure or menopause before age 40, about 30% of women can have depression or anxiety who have the pre-mutation, mood instability is very common. We have also just published a paper on a high rate of migraine headaches, fibromyalgia, and even hypothyroidism in older female carriers. These problems are seen in close to 50% of older female carriers and sometimes they can occur in male carriers too. So a variety of neurological problems can occur and then of course the most serious neurological problem in an older carrier, that is someone in their 50s, 60s, or 70s is the Fragile X associated tremor ataxia syndrome or FXTAS and that includes an intention tremor, balance problems, ataxia, frequent falling, they can develop cognitive decline, particularly the males and it eventually can go into a dementia.

**DR. MARK NOLAN HILL:**

I take it that we do not know any reason why these mutations happen?

**DR. RANDI HAGERMAN:**

Well that's a very interesting question. I think that the expansion of the CGG repeat on the front end of Fragile X gene probably occurred evolutionarily because it improves cognition in individuals when the CGG repeat expands to a certain extent, but once you get into the pre-mutation range, there is a problem with just the physical aspects of how that expanded repeat can replicate itself and there is slippage and that's how you get the full mutation.

If you have just joined us, you are listening to the Clinician's Roundtable on ReachMD. I am your host, Dr. Mark Nolan Hill and our guest is Dr. Randi Hagerman, Professor and Chair of Fragile X Research and Medical Director of the MIND Institute (Medical Investigation of Neurodevelopmental Disorders) at the University of California, Davis School of Medicine. We are discussing options for treatment in patients who have Fragile X syndrome and related conditions.

**DR. MARK NOLAN HILL:**

Dr. Hagerman when the parents and grandparents ask you what's in store for this child, their child that has Fragile X syndrome, what do you tell them?

**DR. RANDI HAGERMAN:**

If it's a female, a girl with a full mutation maybe less affected. She may not have mental retardation. She may just present with emotional difficulties, anxiety, moodiness, sometimes mild attentional problems, and learning difficulties in school like math problems, and these problems are relatively easy to treat, there are medications like serotonin agents that can help with anxiety. The stimulants can help with the attentional problems, Special Ed support and tutoring can help with the learning disabilities. If it's a boy with the full mutation, he is more likely to have mental retardation or intellectual disability. About 85% of the boys have a significant cognitive deficit. Right now the medications that we use for behavior don't boost IQ. You can use serotonin agents, stimulant meds, usually an atypical antipsychotic like Abilify can be remarkably helpful in stabilizing mood, decreasing aggression, helping with anxiety, and ADHD symptoms, but its really the targeted treatments that we think will be helpful in terms of boosting IQ over time and we are very excited about carrying out these studies and really seeing if we can make a significant difference in the autism and intellectual disability for these kids.

**DR. MARK NOLAN HILL:**

Well what is the most common misdiagnosis of this syndrome?

**DR. RANDI HAGERMAN:**

Many individuals who have autism may not have been tested for Fragile X syndrome, so it's important for all physicians to know that any

child with autism should have a Fragile X DNA test and if their CGG repeat number is either in the pre-mutation range or the full mutation range. Those 2 types of mutations can cause autism.

**DR. MARK NOLAN HILL:**

So the treatment for an autistic child that does not have Fragile X and a treatment of an autistic child that does have Fragile X is different?

**DR. RANDI HAGERMAN:**

Well there are some medications that are used in common for both disorders like stimulants and serotonin agents, but the mGluR5 antagonists would be specific for Fragile X syndrome, although we will be doing research to see if it could help other forms of autism.

**DR. MARK NOLAN HILL:**

At the present time are all autistic children tested for Fragile X?

**DR. RANDI HAGERMAN:**

They should be, but this is really up to the physician who is seeing the child and it's definitely recommended in all of the medical literature that children with autism should have Fragile X DNA testing.

**DR. MARK NOLAN HILL:**

So what do we tell the parents and grandparents when they ask, well can my child have children?

**DR. RANDI HAGERMAN:**

Well actually individuals with Fragile X can reproduce. They have a mutation on one of their X chromosomes if it's a female. So 50% of her children would be affected by Fragile X syndrome and 50% would get the normal X and wouldn't be affected. For males that have Fragile X syndrome, they would pass on the mutation to all of their daughters, but it would go back to a pre-mutation form and their sons would not have this mutation. So it never passes from father to son because the father would give his Y chromosome to the son.

**DR. MARK NOLAN HILL:**

Dr. Hagerman you certainly are one of the world leaders in this whole area. Curious how did you get involved in this type of research.

**DR. RANDI HAGERMAN:**

Well I got involved with Fragile X in 1980 and that is because I read at a paper by Gillian Turner from Australia, which described the syndrome and there hadn't been anything written in the American literature then, so I asked the cytogenetic laboratory if they could start testing for this disorder which they could and within 2 years, I had more than 25 patients diagnosed with Fragile X syndrome. I have never had a blood test be positive as frequently as Fragile X. So I became very involved. I wrote papers and many more patients were referred to me and you know it has been an interesting road of research and discovery not only of treatments for Fragile X syndrome, but also finding about the premature ovarian failure and also identifying FXTAS in the grandparents.

**DR. MARK NOLAN HILL:**

Where do you get most of your subsidization for your research activities?

**DR. RANDI HAGERMAN:**

Funding has been through NIH, either through NICHD, through NIA, NINDS are the main funders of our research.

**DR. MARK NOLAN HILL:**

Finally Dr. Hagerman I want you to look in to your crystal ball and you have been doing this since 1980, this wonderful research. Tell me where will we be, lets say 10 to 15 years from now with respect to Fragile X syndrome and other related conditions?

**DR. RANDI HAGERMAN:**

Well I believe that we will be doing much more extensive targeted treatment. The National Fragile X Foundation which also funds our research has developed a clinic consortium of centers all over the US, over 14 centers in the US and we are adding to this internationally. Establishing centers in China, Thailand, India even Kenya to be able to make the diagnosis of Fragile X syndrome and to be able to carry out targeted treatment studies. So I think in 10 years this will be very advanced, our ability to make significant improvements in behavior and cognition in individuals with Fragile X syndrome, and I think by that time we will have better treatments for FXTAS also.

**DR. MARK NOLAN HILL:**

I want to thank our guest, Dr. Randi Hagerman. We have been discussing the genetic disorder, Fragile X syndrome and related condition.

I am Dr. Mark Nolan Hill and you have been listening to the Clinician's Roundtable on ReachMD, The Channel for Medical Professionals. Be sure to visit our web site at [www.reachmd.com](http://www.reachmd.com) featuring on-demand pod casts of our entire library and thank you for listening.