

Fragile X Syndrome: A Genetic Model for Autism with Targeted Treatments

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Autism is a disorder that is defined behaviorally and the biological causes of autism are multiple. Research has advanced dramatically in the last few years particularly in understanding the genetic causes of autism. The molecular tools which can now be utilized in the medical workup of children diagnosed with autism have expanded remarkably just in the last 2 years. Whereas in the last decade we could identify approximately 10% of the causes of autism (Reddy, 2005; Wassink, Piven, & Patil, 2001), a recent study has demonstrated that this percentage has increased to 40% when the genetic workup is thorough including sophisticated metabolic and molecular studies (Schaefer & Lutz, 2006). A recent advance in diagnostic testing includes the CGH array (Comparative Genomic Hybridization) that can identify subtle duplications or deletions of genetic material. These changes can impact the functioning of genes that are critical for the development of nerve connections (synapses) in early development or allow these synaptic connections to be flexible (synaptic plasticity) and respond to environmental stimuli. Mutations in genes that guide where connections in the brain are made and genes involved with inhibitory connections (GABAergic) or stimulatory connections (glutamatergic) are also contributory to autism (Belmonte & Bourgeron, 2006). Although the blueprint for these networks in the central nervous system (CNS) is genetic, the environment influences how these systems develop. For instance, environmental stimuli including educational programs, such as ABA therapy for autism is a positive influence that can enhance appropriate synaptic connections. There are also negative influences on these systems, such as emotional trauma, depression or toxins that can impair synaptic connections. Chronic seizures can also negatively impact brain development and for individuals with fragile X syndrome, autism is more likely to occur in those with seizures (Garcia-Nonell et al., submitted).

One of the many known causes of autism is fragile X syndrome (FXS). Approximately 2 to 6% of children with autism have FXS and a simple blood test will diagnose this disorder. FXS is a genetic disorder caused by a trinucleotide repeat (CGG repetitive sequence) in the control or promoter region of the fragile X mental retardation 1 gene (*FMR1*). This gene is on the bottom end of the X chromosome and it normally produces a protein, FMRP, which is important for normal brain development. FMRP is an RNA binding and carrier protein that carries the messages produced from many other genes to the synapse. FMRP subsequently regulates their translation into proteins that are important for synapse formation and plasticity (Hagerman, 2006). The reason why fragile X mutations can cause autism is because FMRP (the protein missing in FXS) has so many important functions related to synaptic development and because FMRP influences the expression of many other genes which themselves may also be related to the development of autism.

The name fragile X was derived from the appearance of the X chromosome in a specialized tissue culture media, because it looked like the end of the chromosome was broken (fragile X chromosome). However, over the last decade *FMR1* DNA testing which detects the number of CGG repeats, has replaced the chromosome or cytogenetic test for fragile X. Normal individuals will have from 5 to 44 CGG repeats in the *FMR1*

gene. Carriers will have 55 to 200 CGG repeats called the premutation and individuals with fragile X syndrome will have >200 CGG repeats or a full mutation. Typically the FMR1 gene will turn off or methylate with the full mutation so that little or no message of the gene is made and there is a subsequent lack of FMRP. The deficiency of FMRP produces changes in the production of many proteins that are important for synapse development and synaptic plasticity including MAP1B and PSD95 (Bagni & Greenough, 2005). This is one of the main reasons that autism and autism spectrum disorders occurs in FXS. In addition, the GABA_A receptors are down regulated in FXS (D'Hulst et al., 2006; Kooy, 2003) and the glutamate system, specifically the metabotropic glutamate 5 (mGluR5) receptor is upregulated, leading to long term depression (LTD) or weakening of synaptic connections (Bear, Huber, & Warren, 2004; Huber, Gallagher, Warren, & Bear, 2002; Huber, Roder, & Bear, 2001). This imbalance of GABA and glutamate systems probably contributes to the autism that is associated with FXS.

Autism occurs in approximately 30% of children with FXS and PDDNOS occurs in an additional 20% (Harris et al., 2006; Hatton et al., 2006; Kaufmann et al., 2004; Rogers, Wehner, & Hagerman, 2001). Those children who do not have autism spectrum disorders, (approximately 50%) often still have poor eye contact and/or unusual hand mannerisms, such as hand flapping. Tactile defensiveness is very common making hair and nail cutting difficult. Because 2 to 6% of individuals with autism will have the fragile X mutation (Persico & Bourgeron, 2006; Reddy, 2005; Wassink et al., 2001), FXS is the most common identifiable single gene associated with autism. Fragile X represents an important genetic model for autism because we know so much about the molecular basis and the neurobiology. This information has led to targeted treatments to reverse the neuropathology and neurobiological abnormalities in fragile X syndrome. Specifically these treatments include the mGluR5 antagonist fenobam and the GABA_A agonist ganaxolone. Treatment trials will begin this year in individuals with FXS and these targeted treatments may also be helpful for a subgroup of individuals with autism but without the fragile X mutation if the cause of their autism causes similar abnormalities in the GABA and glutamate systems as in FXS.

We now also have evidence that even the premutation can cause autism in a limited number of cases, although a broad spectrum of social deficits can occur particularly in male carriers (Aziz et al., 2003; Cornish et al., 2005; Farzin et al., 2006; Goodlin-Jones, Tassone, Gane, & Hagerman, 2004). The premutation can also cause both tremor and ataxia (balance problems) in aging carriers leading to a neurodegenerative disorder called the fragile X-associated tremor/ataxia syndrome (FXTAS) (Hagerman et al., 2001; Jacquemont, Hagerman, Hagerman, & Leehey, 2007). The fragile X premutation is also the leading cause of premature ovarian failure (POF) in women. Approximately 4 to 14% of women with POF will demonstrate the premutation. Overall, approximately 1 in 130 females and 1 in 800 males in the general population will carry the premutation and approximately 1 in 3600 will carry the full mutation (Beckett, Yu, & Long, 2005; Crawford et al., 2002; Dombrowski et al., 2002). The mechanism for clinical involvement for the premutation is different than the full mutation. The premutation typically has normal levels of FMRP, but the level of FMR1 mRNA is dramatically increased (2 to 8 times normal) compared to controls (Tassone et al., 2000). A variety of

proteins become dysregulated and eventually these proteins are sequestered into inclusions in carriers who suffer from FXTAS (Greco et al., 2006). The dysregulation of proteins in the neuron occurs can lead to neuronal cell death and vulnerability of the neuron to oxidative stress; with age but we hypothesize that this may also occur early on in development leading to the autism that is seen in a subgroup of carriers in childhood. Once a child is diagnosed with FXS or the fragile X premutation, then genetic counseling is important because a variety of problems can occur in other family members, such as a grandparent or uncle that may have tremor, ataxia or dementia or an aunt with POF or a sibling with emotional difficulties.

There are many reasons to make the diagnosis of FXS including genetic counseling and improved treatment. Therefore all individuals with autism or autism spectrum disorders need to have fragile X DNA testing to identify the premutation or the full mutation. Any physician can order this test and it is typically covered by insurance or Medicaid.

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