

Fragile X Syndrome and Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is now known to be a common condition affecting approximately 1% of the population (Levy et al., 2009; Lord, 2011). Family and twin studies suggest high heritability (0.8) although the pattern of inheritance is not consistent with Mendelian genetics. The evidence, rather, points to complex genetics with many common alleles interacting to cause the phenotype. Recent studies suggest that *de novo* copy number variants, which are stretches of DNA several hundred to several million base pairs in size consisting of microinsertions, microdeletions and transpositions in the human genome, may also account for 10% or more of the cases. One strategy for understanding the underlying neurobiology of ASD is to characterize highly penetrant single-gene mutations that share clinical features with ASD. One such hereditary disorder is Fragile X syndrome (FraX).

FraX is the most common inherited cause of intellectual disability, affecting approximately one in 4,000 males (Lightbody & Reiss, 2009). The genetic basis of the disorder was first noted when a constriction or fragile site was observed at the end of the X chromosome in affected individuals, prompting the name of the disorder. The fragile site is caused by a mutation in the 5' non-coding region of a gene (fragile X mental retardation; *FMR1*) that causes a CGG trinucleotide repeat to expand to more than 200 copies. In normal individuals, this site contains approximately 30 copies; and in those with the pre-mutation, the site has 50 to 200 copies. The expanded CGG repeat causes hypermethylation of the promoter region of the *FMR1* gene, thus limiting the expression of its product, FMR1 protein (FMRP).

One-half or more of the males affected with FraX satisfy the diagnostic criteria for ASD, depending upon the diagnostic instrument used (Hall et al., 2010). The shared behaviors include

gaze aversion, stereotypies, communicational problems and repetitive vocalizations. Epilepsy frequently occurs in both disorders. Unlike ASD, males with FraX also have characteristic physical features including a long narrow face, prominent ears, hypotonia and enlarged testes. Whereas the IQ can range from above normal to well below in ASD, males with FraX invariably exhibit intellectual disability.

The neuropathologic feature most consistently described in FraX is abnormal dendritic spines, which are long and thin with a small synaptic contact area. A recombinant mouse was developed in which *fmr1* gene was inactivated so that as in FraX, no FMRP is expressed. These mice exhibit the dendritic pathology observed in FraX with a high density of long, immature spines.

Not surprisingly, FMRP is expressed predominantly in brain and in the testes. FMRP was found to be an mRNA binding protein that was associated with polyribosomes, thereby implicating it in the regulation of protein synthesis. Subsequent studies demonstrated that FMRP functions as a translational repressor of certain mRNAs. Furthermore, FMRP is concentrated in the dendritic spines where it regulates protein synthesis at synapses (McKinney et al., 2005). Thus, the synaptic pathology of FraX is consistent with the loss of FMRP function.

The synaptic role of FMRP became clearer when its interactions with metabotropic glutamate receptor 5 (mGluR5) in long-term depression were elucidated (Kao et al., 2010). Activation of mGluR5 drives translation of dendritic mRNAs including FMRP, which serves to inhibit subsequent translation. In the absence of FMRP, dendritic protein synthesis is poorly regulated, resulting in spine dysgenesis. A compelling demonstration of this role of FMRP came from experiments in which *fmr1* $-/-$ mice were rendered heterozygous for the mGluR5 null mutation (*Grm5* $+/-$). The reduced mGluR5 activity reversed seven out of eight phenotypic

characteristics of FraX observed in the *fmr1* $-/-$ mice. MPEP [2-methyl-6-(phenylethynyl)-pyridine] is a potent allosteric negative modulator for mGluR5 that crosses the blood–brain barrier. MPEP has been shown to reverse many of the behavioral, electrophysiologic and morphologic phenotypes associated with FraX in the *fmr1* $-/-$ mice (Krueger & Bear, 2011).

This translational research on the most common heritable cause of intellectual disability, FraX, has led to the identification of a potential therapeutic intervention. It remains to be seen whether the treatment simply ameliorates symptoms such as anxiety or whether continuous treatment reverses the underlying synaptic deficits. Furthermore, a major unanswered question is whether the potential therapeutic effects of activating mGluR5 observed in *fmr1* $-/-$ mice extend to some or most individuals with ASD.

References

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