13

From genes to brain to behavior: the case of fragile X syndrome

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Introduction

In this chapter, we show how neuroimaging can help us understand complex relationships among genetic, brain, and behavioral factors. To this aim, we will use as a model a single-gene disorder that is very well understood: fragile X syndrome. Because of the wealth of information that exists on the molecular, neuroanatomical, and behavioral aspects of this disorder, great strides have been made in understanding the complex interplay among these scientific levels of description, as well as the resulting phenotypes. This, in turn, has begun to guide treatment of the disorder in ways that are far more specific than was previously possible. While the focus throughout the chapter will be on this single-gene disorder and its phenotypic variants, we hope to use this as a "methodological roadmap" and model for understanding other disorders influenced by genetic factors.

Fragile X syndrome

Fragile X syndrome (FXS) is the most common inherited cause of mental retardation. It is caused by a trinucleotide repeat expansion $(CGG)_n$ in the 5′ untranslated region of the fragile X mental retardation 1 gene (*FMR1*) located at Xq27.3. The "full mutation," present in individuals having more than 200 CGG repeats, involves methylation, which stops the synthesis of the *FMR1* protein (FMRP) (Fu et al., 1991; Pieretti et al., 1991; Snow et al., 1993; Verkerk et al., 1991; Yu et al., 1991). Fragile X syndrome is therefore caused by an absence or deficit of FMRP (Tassone et al., 1999). The physical features of FXS include macroorchidism (large testes), a long, narrow face and prominent ears, and mild cardiac, neuroendocrine, and connective tissue problems. However, these physical characteristics can be highly variable in cognitively affected individuals and may not be present at all in young males and females with the full mutation. Males with the full mutation typically exhibit moderate to severe mental retardation, while females as a group show less significant and more variable impairment as a result of the second, normally functioning X chromosome. The cognitive profile of FXS includes deficits in visuospatial processing and working memory, visual-motor coordination, and arithmetic skills (Baumgardner et al., 1995; Freund and Reiss, 1991; Mazzocco et al., 2006). In addition to cognitive impairment, individuals with FXS demonstrate a behavioral phenotype characterized by hyperarousal, social anxiety and withdrawal, social deficits with peers, abnormalities in communication, unusual responses to sensory stimuli, stereotypic behavior, gaze aversion, inattention, impulsivity, and hyperactivity (Bregman et al., 1988; Cohen et al., 1988, 1989, 1991; Hagerman et al., 1991; Hessl et al., 2001; Reiss and Freund, 1992;

Neuroimaging in Developmental Clinical Neuroscience, eds. Judith M. Rumsey and Monique Ernst. Published by Cambridge University Press.

Sudhalter et al., 1990). The severity of the fragile X phenotype depends mainly on the degree of abnormal methylation of the *FMR1* gene and, in females, the degree of skewing of normal X chromosome inactivation (Martinez et al., 2005).

The association of autism with FXS has been somewhat controversial though most investigators find an increased prevalence and severity of autistic behaviors in individuals with FXS compared to IQ-matched persons with idiopathic developmental disability. For example, 25%–40% of individuals with the full mutation meet criteria for autistic disorder (Bailey et al., 1998b; Kaufmann et al., 2004; Philofsky et al., 2004; Rogers et al., 2001); however, a range of autistic symptoms is present in many individuals with FXS who do not meet full diagnostic criteria for autistic disorder.

Since the identification of the gene responsible for FXS in 1991 (Pieretti et al., 1991), an explosion of research has emerged investigating the relationships between molecular variables, behavior, and the brain in FXS. In understanding these relationships, it is important to highlight the complex interplay between various molecular variables. The repeat size and methylation-dependent expression of both messenger RNA (mRNA) and FMRP protein are known to directly influence outcomes, including cognitive function. This is true in both the full mutation (defined by more than 200 CGG repeats) and the "premutation," which is defined by ~50–200 CGG repeats (Allen et al., 2005; Kaufmann et al., 1999; Koukoui and Chaudhuri, 2007). Furthermore, the *FMR1* gene gives rise to at least two distinct molecular pathogenic mechanisms (protein deficiency vs. RNA toxicity) and attendant neurochemical processes, depending on the size of the CGG repeat and the sex of the affected individual. It is therefore more useful to think of a spectrum of involvement beginning with individuals with the full fragile X mutation, where FMRP is generally low or absent, with a gene dose–response curve in females as a consequence of variable X chromosomal activation (fraction of normal X allele active). Next on this continuum are individuals who are mosaic for mutations in the *FMR1* gene (whereby some cells express FMRP and others do not). Depending on the amount of FMRP being expressed, these individuals can exhibit varying severity of the characteristic FXS full-mutation phenotype. Carriers of the premutation (with ~50–200 CGG repeats and absence of aberrant methylation) typically express normal levels of FMRP, but those in the upper portion of the premutation range appear to be at risk for exhibiting lower levels of FMRP and higher than normal *FMR1* mRNA (Tassone et al., 2000a).

In association with the molecular phenomenon of excess *FMR1* mRNA, one could add to this continuum a recently defined late-onset progressive neurologic disorder that has been reported in some older men with the fragile X premutation (Berry-Kravis et al., 2003; Hagerman et al., 2001, 2004; Hall et al., 2005; Jacquemont et al., 2003, 2004). This syndrome has been termed fragile X-associated tremor/ataxia syndrome (FXTAS). Symptoms of FXTAS include intention tremor, gait ataxia, neuropathy, parkinsonian features, cognitive decline, and dementia. The pathogenesis of FXTAS is thought to result from overexpression and toxicity of *FMR1* mRNA (Jacquemont et al., 2007) (see Figure 13.1). As a result of these characteristics, fragile X provides a unique model for developing a "molecules to mind" explanation of a neurogenetic disorder that can then be used to generate hypotheses about the genetic basis of disorders with less clear molecular mechanisms.

FMR1 protein and brain development

Fragile X mental retardation protein is found in both the dendrites and synapses of neurons (Devys et al., 1993; Feng et al., 1997) where it is predominantly associated with actively translating ribosomes during protein synthesis (Khandjian et al., 1996). During normal development, FMRP is produced at synapses in response to synaptic activation, and it has been found to be increased in the brain undergoing active synaptogenesis in response to motor learning or enriched environments (Irwin et al., 2005). In individuals with FXS, reductions or absence of FMRP cause developmental changes at the neuronal

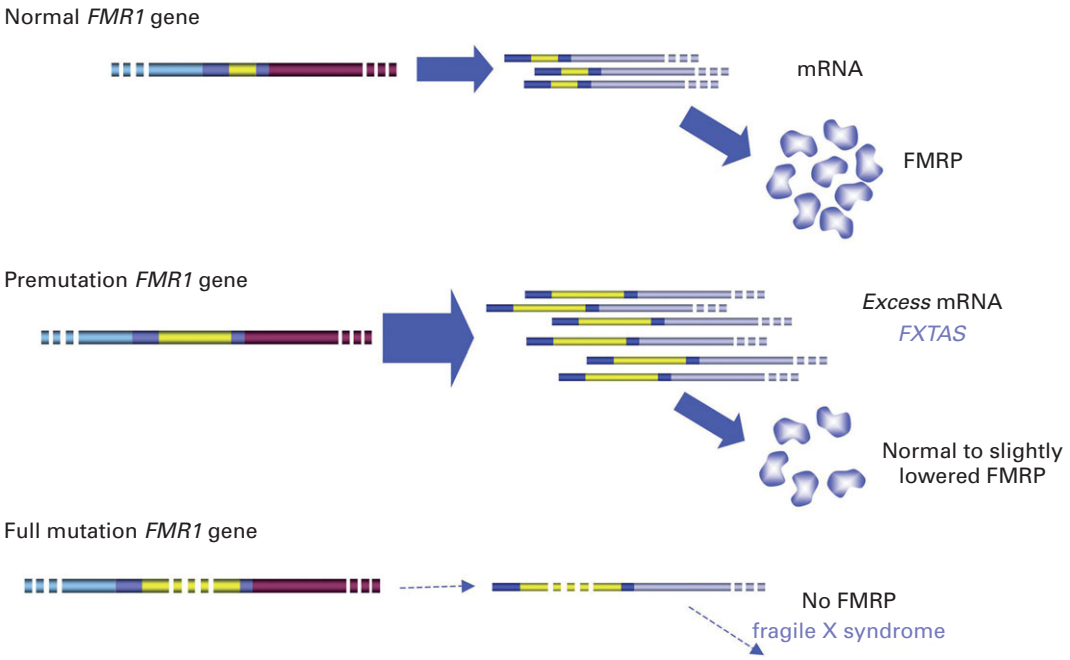

Figure 13.1. The relationship between fragile X mental retardation (*FMR1*) gene activity, fragile X mental retardation protein (FMRP) production, and molecular pathogenic mechanisms in fragile X syndrome. In a normal gene (<55 CGG repeats), mRNA leads to the production of normal amounts of *FMR1* protein (FMRP). In the FX premutation (55–200 CGG repeats), an excess level of messenger RNA (mRNA) is produced, resulting in normal to slightly lowered FMRP and potentially leading to the adult neurological disorder of fragile X-associated tremor/ataxia syndrome (FXTAS). In individuals with the full mutation (>200 CGG repeats), the absence of mRNA and FMRP leads to the developmental disorder fragile X syndrome.

level, predominantly impairments in spine maturation and a failure of normal synaptic pruning. Indeed, evidence of the deleterious effects of suboptimal levels of FMRP on the structure and function of both dendrites and synapses exists from studying human postmortem tissue (Hinton et al., 1991; Irwin et al., 2000; Rudelli et al., 1985) and from observing cortical neurons of an *FMR1*-knockout mouse (Braun and Segal, 2000; Oostra and Hoogeveen, 1997; Pieretti et al., 1991). Consistent with the abnormal neuron phenotypes found in both fragile X patients and FMRP-deficient mice, several FMRP mRNA targets that encode proteins involved in axon guidance or synaptic functions have been identified using microarrays (Brown et al., 2001). These neurodevelopmental processes lead to both structural and functional irregularities that can be visualized using brain imaging methodologies.

In what follows we will review findings that demonstrate the "genes to brain to behavior" approach by combining molecular with either behavioral or brain imaging research in the full fragile X mutation, premutation, and FXTAS phenotypes that exist as part of the spectrum mentioned above.

From genes to behavior

Findings from studies of the full mutation

A large number of published studies have shown that FMRP depletion is significantly related to global

cognitive deficits and behavioral problems, both in males and females with the full mutation (Bailey et al., 1998a; Dyer-Friedman et al., 2002; Kaufmann et al., 1999; Tassone et al., 1999). The results from a longitudinal study of young males with the fragile X full mutation showed that FMRP level is significantly related to the level of cognitive-behavioral development assessed by the Battelle Developmental Inventory (Bailey et al., 2001). Furthermore, in research comparing fully methylated versus partially methylated (mosaic) males, those who were fully methylated were found to be more likely to show a decrease in IQ over time (Merenstein et al., 1996). Even more specifically, Wright-Talamante et al. (1996) reported that there was no significant IQ decline in young males with less than 50% methylation of the full mutation, suggesting that a small to moderate amount of FMRP production partially protects against significant IQ decline. Loesch et al. (2004) also demonstrated a strong relationship between FMRP depletion and overall cognitive deficit, as well as specific deficits in processing speed, short-term memory, and the ability to control attention, especially in the context of regulating goal-directed behavior, in subjects with the fragile X full mutation. With respect to behavior, a common and significant problem observed in many males with FXS is the tendency to demonstrate autonomic hyperarousal in the face of environmental stressors, particularly in social contexts. Hyperarousal in FXS is manifest as overt symptoms of anxiety, turning away of the face and body from others, stereotypic motor and language characteristics, and attempts to escape from the stressful conditions. As might be surmised from this description, such behaviors can be a detriment to the establishment of developmentally appropriate peer relationships. Motoric restlessness and impulsive behavior are also quite common in males with FXS, particularly during the preschool and early school-age years.

In females with the full mutation, strong evidence has been demonstrated for the relationships between specific cognitive scores and the activation ratio – the ratio of affected/unaffected activated X chromosomes, which is highly correlated with FMRP (Abrams et al., 1994; Reiss et al., 1995b). For example, in a study of molecular and phenotypic correlations in females with fragile X, it was found that the X inactivation ratio was strongly and positively correlated with a composite measure of executive function (Sobesky et al., 1996), suggesting that these essential cognitive skills are especially sensitive to levels of FMRP. Like males with FXS, females with the full mutation are also at risk for behavioral difficulties, though manifestations of hyperarousal and hyperactivity may be less severe.

Findings from studies of the premutation

As described in the section above, the association of cognitive and behavioral dysfunction with the molecular finding of reduced FMRP has been clearly established. In contrast, there is far less certainty about molecular or brain mechanisms that may put individuals with the fragile X premutation at higher risk for cognitive and behavioral dysfunction. Further complicating this area of investigation is an increasing awareness that the premutation should not be considered a homogeneous molecular diagnostic category. In particular, the concept of a "continuum" of effects may apply to individuals with the premutation as well as to the entire spectrum of effects associated with *FMR1* mutations. Finally, environmental influences may be particularly relevant for individuals with the premutation. The great majority of mothers of children with the full mutation carry the premutation. Thus, caregiver stress and burden related to having one or more children with serious developmental disability come into play when considering the assessment of psychological outcomes in this group.

Not surprisingly, findings pertaining to cognitive impairment and molecular variables in individuals with the premutation have been inconsistent. Many studies have shown no differences in neuropsychological or behavioral profiles between premutation carriers and non-carriers (Franke et al., 1998; Johnston et al., 2001; Kaufmann et al., 1999; Myers et al., 2001; Reiss et al., 1993). Other studies of both men and women suggest that some individuals

with the premutation may demonstrate subtle, yet detectable, neurocognitive problems (Cornish et al., 2005; Loesch et al., 2003a, 2003b; Moore et al., 2004a). However, the aforementioned studies failed to demonstrate a correlation between severity of cognitive impairment and CGG repeat length.

Perhaps the most persuasive evidence of cognitive involvement in females with the fragile X premutation comes from a recent study by Allen et al. (2005). This study utilized a large sample size (66 males and 217 females) and used *FMR1* repeat size as a continuous variable, rather than using a dichotomous designation of premutation versus full mutation. Results indicated a small, yet significant negative effect from increasing CGG repeat on verbal IQ, explaining approximately 4% of the variance in this measure.

Fragile X-associated tremor/ataxia syndrome findings

A number of studies have now been conducted on the progressive neurologic syndrome associated with the fragile X premutation known as FXTAS, in which associations between molecular factors and behavior have been demonstrated as well. Many of the features of FXTAS, both neuropathologic and radiologic, have been shown to be correlated with CGG repeat length in males. For example, in male premutation carriers with FXTAS, increasing numbers of intranuclear inclusions in neuronal and astrocytic cells have been observed with increasing CGG repeat length (Greco et al., 2006). The fact that elevated *FMR1* mRNA has been found in peripheral blood leukocytes of carriers (Tassone et al., 2000b, 2000c) coupled with findings of the presence of *FMR1* mRNA within the nuclear inclusions in FXTAS brains (Tassone et al., 2004), supports an RNA toxic gain-of-function model for FXTAS pathogenesis (for a review, see: Hagerman and Hagerman 2004). This RNA toxic gain-of-function mechanism, in which the degree of clinical involvement increases with increasing CGG repeat length, also predicts that those patients with larger repeat sizes will show an earlier onset of clinical involvement. This hypothesis has been supported by work from Tassone et al. (2007), who observed highly significant correlations between the ages of onset of both tremor and ataxia symptoms and the size of the CGG repeat.

What we have summarized above represents information that has been gained from comparing molecular variables with measures of behavior and symptomatology. Linking these variables has been invaluable in furthering our understanding of the phenotypic consequences of these genetic anomalies. Brain imaging technology has further allowed researchers to make these linkages even more specific by relating molecular variables to variations in brain morphology. In the next section we will summarize these findings, again delineating what has been discovered across the full spectrum of fragile X involvement.

From genes to brain

Findings from studies of the full mutation

There has been a great deal of work employing structural imaging techniques in individuals with the full mutation. A number of structural abnormalities have been observed in this group, including hypoplasia of the cerebellar vermis, increased size of the fourth and lateral ventricles (Eliez et al., 2001; Franke et al., 1998; Johnston et al., 2001; Kaufmann et al., 1999; Mostofsky et al., 1998; Reiss et al., 1988, 1991, 1993, 1995a), larger caudate nuclei, and significantly increased thalamic volume in girls (Eliez et al., 2001; Reiss et al., 1995a). In addition, white matter connectivity has been assessed in FXS using diffusion tensor imaging (DTI). Compared with controls, subjects with FXS demonstrate evidence of aberrant white matter structure (reduced fractional anisotropy), mostly in fronto-striatal and parietal sensorimotor tracts (Barnea-Goraly et al., 2003). This finding suggests that low levels of FMRP may contribute to morphological changes in white matter tracts, possibly due to an influence on neuronal growth and targeting as a result of reduced or absent FMRP.

A recent volumetric neuroimaging study examined children (age 2–7) with the fragile X full mutation, mosaicism, and control groups of children with developmental delay or Down syndrome (Kates et al., 2002). This study reported relative reductions in temporal lobe gray matter, along with relative enlargement of parietal white matter volume, the latter of which was seen only in individuals with FXS and not in control groups with either developmental language delay or Down syndrome. Interestingly, the parietal white matter enlargement was seen only in participants with the full mutation and not in a group with mosaicism. This is a strong indicator that the reduction or absence of FMRP in the full mutation group was responsible for this enlargement, possibly corresponding to maturational and synaptic pruning failures.

Findings from studies of the premutation

Similar to studies examining potential cognitive effects, there are some data suggesting that the fragile X premutation (independent of FXTAS – see next section) may be associated with variations in brain morphology. For example, a brain magnetic resonance imaging (MRI) study (Moore et al., 2004b) examining gray matter density in 20 male premutation carriers and 20 age- and IQ-matched controls found significantly reduced gray matter density in several regions, including the cerebellum, amygdalo-hippocampus complex, and thalamus in the premutation group. Within this group, increased age, increased CGG repeat size, and decreases in the percentage of blood lymphocytes expressing FMRP were associated with decreased gray matter density in the amygdalo-hippocampus complex. Though a significant association between *FMR1* mRNA and brain morphology was not observed in this study, the fact that CGG repeat size and FMRP were correlated with brain structure ~~in this study~~ supports a putative gene-brain-behavior mechanism of clinical involvement in male premutation carriers. More research spanning these domains is needed to establish whether the mechanism of involvement is analogous to FXS and involves reduced FMRP (for example in premutation carriers with high repeat number), is analogous to FXTAS and involves toxic elevation of *FMR1* mRNA, or whether there are multiple genetic and environmental influences on brain function and behavior in this group.

Fragile X-associated tremor/ataxia syndrome findings

Another controlled study of adult male premutation carriers, in this case with and without FXTAS, involved a molecular analysis of *FMR1* expression, quantitative neuroimaging, and cognitive testing (Cohen et al., 2006). The study reported significant whole-brain, cerebrum, and cerebellar volume loss, as well as increases in whole-brain white matter hyperintensity volume associated with FXTAS. These changes correlated with CGG repeat number and became more severe with age. Associations were also observed between CGG repeat length and cognitive ability in the premutation carriers, including the sample without FXTAS, suggesting that molecular abnormalities may contribute to cognitive decline prior to manifestation of obvious structural abnormalities.

With these studies we have come a long way in understanding, not only the phenotypic consequences of this single-gene disorder, but how these factors relate to abnormalities in specific brain regions. What follows is a review of studies that bring this relationship "full circle" to understanding how gene alterations lead to specific brain abnormalities, which in turn result in behaviors and symptoms related to the phenotypes expressed.

From genes to brain to behavior

Findings from studies of the full mutation

There are a number of examples in the literature, across the fragile X phenotypes that we have been discussing, that have demonstrated direct links between genetic factors, localized brain function,

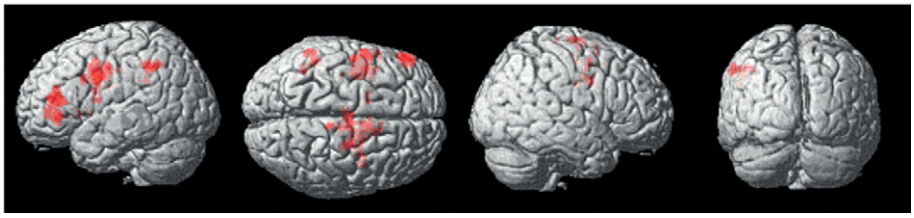

Figure 13.2. An example of the relationship between genes, brain and behavior. Brain areas (prefrontal and parietal) which show, for participants with fragile X syndrome, a significant correlation between FMRP and brain activation for 3-operand arithmetic equations. Adapted from Rivera et al., 2002, *Human Brain Mapping*, **16** (4), 206–218.

and the ensuing cognitive impairments associated with dysfunction occurring in those brain regions. Several functional MRI (fMRI) studies have now demonstrated a "dose–response" effect of FMRP on brain activation. One such study examined the neural substrate of visuospatial working memory in females with FXS using standard 1-back and 2-back tasks (Kwon et al., 2002). Behaviorally, subjects with the full mutation performed significantly worse on the more difficult, 2-back task than did age-matched controls. In terms of brain activation, comparison subjects showed a significant increase in the inferior frontal gyrus, middle frontal gyrus, superior parietal lobule, and supramarginal gyrus on the 2-back compared to the 1-back task, while subjects with FXS showed no change in activation between the two. Furthermore, molecular measures correlated with brain activation on this task since significant correlations were found during the 2-back task, between FMRP expression and activation in the right inferior and bilateral middle frontal gyri and the bilateral supramarginal gyri.

In an fMRI study of mental arithmetic in females with the full mutation, Rivera et al. (2002) found that, in response to increasing arithmetic complexity (i.e., going from 2-operand to 3-operand addition and subtraction problems), participants with FXS did not recruit the prefrontal-parietal-cerebellar network known to be involved in arithmetic processing in unaffected participants. With respect to molecular measures, this investigation showed that as levels of FMRP increased in individuals with FXS, so did task-related activation in areas that are involved in arithmetic processing in typically developing subjects, providing evidence of a direct relationship between decreased FMRP expression and impairments in mental arithmetic performance in persons with FXS (see Figure 13.2).

Menon et al. (2004) used fMRI with a response inhibition task (go/no-go) in 10- to 22-year-old females with the full mutation and age- and gender-matched typically developing controls. Although behavioral performance on the go/no-go task was equivalent in the two groups, females with FXS showed abnormal activation patterns in several cortical and subcortical regions, with significantly reduced activation in the supplementary motor area, anterior cingulate and midcingulate cortex, basal ganglia, and hippocampus. The investigators also found neural responses in the right ventrolateral prefrontal cortex (PFC) and bilateral striatum that correlated with the level of *FMR1* gene expression. In addition to task-related activation impairments, reduced levels of "deactivation" were observed in the ventromedial PFC, and, furthermore, these reductions were correlated with the level of FMRP. As a whole, these results provide direct evidence that decreased FMRP expression underlies impairments in cognitive performance in persons with the full mutation.

Findings from studies of the premutation

Potential gene-brain-behavior relationships are also beginning to emerge in studies of those with the fragile X premutation. Recently, Hessl and colleagues

reported findings from an fMRI study of amygdala function in 12 adult men with the premutation (who did not exhibit clinical evidence of FXTAS) who were compared to a group of 13 premutation-negative men who were matched on age and IQ (Hessl et al., 2007). When viewing fearful facial expressions compared to viewing scrambled faces (fear-control contrast), the premutation group showed less overall activation as well as significantly different patterns of activation compared to controls. The control group showed strong activation in the superior temporal sulcus (STS) bilaterally, left and right lateral orbitofrontal gyrus, bilateral insula, and amygdala. These areas, usually associated with social cognition or emotion processing, were not activated in the premutation group. Follow-up region-of-interest (ROI) analyses confirmed that premutation carriers failed to activate the amygdala, whereas the control group showed robust bilateral amygdala activation. In the premutation group, neither CGG repeat length nor *FMR1* mRNA was significantly associated with amygdala activation; however, we did find that these measures were negatively associated with left insular activation during this task. Though the male premutation participants in this study (average age of 43 years) did not demonstrate overt symptoms of FXTAS, the findings of aberrant brain activation in this group might reflect presymptomatic brain changes associated with elevated mRNA instead of, or in addition to, specific pathogenic effects on the brain associated with the premutation.

Fragile X-associated tremor/ataxia syndrome findings

We have also recently completed fMRI studies in males with FXTAS using tasks involving the cerebellum, as well as prefrontal and parietal cortices (Rivera et al., under review). The results of this study show a dissociation between cerebellar activity for a motor timing task and a cognitive, mental arithmetic task. Relative to controls, premutation carriers exhibit *hyperactivation* of the cerebellum (particularly more inferior/posterior and contralateral regions) while performing a motor timing task, and *hypoactivation* of the cerebellum during simple mental arithmetic. This dissociation suggests cerebellar dysfunction that is more than just a diminished capacity for functional activation and more specifically points to potential neuropathogenic mechanisms for this dysfunction.

Therapeutic advances in fragile X syndrome

Advances in our understanding of the development of FXS have led to a number of targeted therapeutic treatments in FXS. One example of these advances is the metabotropic glutamate receptor 5 (mGluR) theory of FXS, which posits that exaggerated signaling in mGluR pathways may underlie many of the cognitive, behavioral, and neurological symptoms of FXS (Bear et al., 2004). In the absence of FMRP, excessive mGluR-mediated dendritic translation is predicted to lead to excessive internalization of α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) receptors, excessive synaptic weakening, and the structurally immature-appearing elongated dendritic processes, which have been documented in both the *FMR1*-knockout mouse and in post-mortem brain tissue of humans with FXS. These insights into the defects in synaptic integrity and plasticity in FXS have led to the proposal of several pharmacotherapeutic targets in FXS to attempt to normalize synaptic connectivity, including AMPA receptor activation. One such compound is an AMPA receptor-positive modulator (ampakine). Clinical trials of ampakine, which can enhance synaptic strength and may partially correct the synaptic transmission defect in FXS, are now ongoing (Berry-Kravis et al., 2006). The hope is that this treatment can lead to improvement in cognitive and behavioral functioning in individuals with FXS.

Likewise, fMRI studies have also begun to guide therapeutic treatments for FXS. For example, imaging studies have indicated that the basal forebrain and hippocampus show significantly reduced activation during a memory encoding task (Greicius et al., 2004). These brain areas are ones in which

the neurochemical acetylcholine is found in high concentrations and in which the highest *FMR-1* transcription is found (Abitbol et al., 1993). Such findings have led to clinical trials of the medication donepezil (Kessler et al., under review), which has been shown to enhance acetylcholine function in the brain, to determine whether the compound will have a beneficial effect on behavior or cognition in individuals with FXS.

Conclusions

In this chapter, we have used the model of FXS, a single-gene disorder that has a range of phenotypic variants, to demonstrate a gene-to-brain-to-behavior approach in understanding neuropathological development. Because knowledge of the specific molecular basis and the neurobiology of fragile X has grown tremendously, it also represents an important genetic model for other neurodevelopmental disorders. Symptomatic commonalities among FXS and other pervasive developmental disorders such as autism and Rett syndrome may reflect an overlap in underlying neural circuits and pathways and hence shared pathophysiological mechanisms. Therefore, the possibility exists that new therapeutics developed to treat FXS also may have efficacy in treating individuals with these other disorders. Autism, for example, occurs in approximately 30% of children with FXS with an additional 20% meeting the criterion for pervasive developmental disorder-not otherwise specified (PDD-NOS) (Hatton et al., 2006; Kaufmann et al., 2004; Rogers et al., 2001). The remaining 50% of children with FXS who do not meet criteria for autism spectrum disorders often exhibit autistic symptoms including poor eye contact, unusual hand mannerisms such as hand flapping, and tactile defensiveness. Because 2%–6% of individuals with autism will have the fragile X mutation (Persico and Bourgeron, 2006; Reddy, 2005; Wassink et al., 2001), FXS is the most common known single-gene disorder associated with autism at this time. Targeted treatments for the neuropathology and neurobiological abnormalities of FXS may thus turn out to be helpful in treating autism spectrum disorders. Therein lies the promise of a truly successful roadmap for the "molecules to mind" brand of translational research, in which converging research in molecular, behavioral and neuroscience disciplines, across multiple model systems, will lead us in the direction of new therapeutics for complex human diseases.

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