Review

Come FLY with us: toward understanding fragile X syndrome

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The past few years have seen an increased number of articles using Drosophila as a model system to study fragile X syndrome. Phenotypic analyses have demonstrated an array of neuronal and behavioral defects similar to the phenotypes reported in mouse models as well as human patients. The availability of both cellular and molecular tools along with the power of genetics makes the tiny fruit fly a premiere model in elucidating the molecular basis of fragile X syndrome. Here, we summarize the advances made in recent years in the characterization of fragile X Drosophila models and the identification of new molecular partners in neural development.

Keywords: dFmr1, Drosophila, FMRP, fragile X syndrome

Received 30 November 2004, revised 18 February 2005, accepted for publication 19 February 2005

Fragile X syndrome is the most common form of inherited mental retardation, with the estimated prevalence of one in 4000 males and one in 8000 females (Warren & Sherman 2001). In addition to cognitive deficits, the phenotype of fragile X syndrome includes mild facial dysmorphism (prominent jaw, high forehead and large ears), macroglossism in post-pubescent males and subtle connective tissue abnormalities (Warren & Sherman 2001). Many patients also manifest attention-deficit hyperactivity disorder and autistic-like behaviors. As one of the first identified human disorders caused by trinucleotide repeat expansion, fragile X syndrome is typically caused by a massive CGG trinucleotide repeat expansion within the 5’ untranslated region (UTR) of the fragile X mental retardation 1 gene (FMR1), which results in transcriptional silencing of FMR1 (Fu et al. 1991; Kremer et al. 1991; Oberle et al. 1991; Pieretti et al. 1991; Verkerk et al. 1991). Identification of other mutations (e.g. deletions in patients with the typical phenotype) has confirmed that FMR1 is the only gene involved in the pathogenesis of fragile X syndrome, and the loss of FMR1 product – fragile X mental retardation protein (FMRP) – causes fragile X syndrome (De Boulle et al. 1993; Lugenbeel et al. 1995; Wohrle et al. 1992).

FMRP, along with its autosomal paralogs, the fragile-X-related proteins FXR1P and FXR2P, compose a well-conserved, small family of RNA-binding proteins (fragile X-related gene family) that share over 60% amino acid identity and contain two types of RNA-binding motifs: two ribonucleoprotein K homology (KH) domains and a cluster of arginine and glycine residues (RGG box) (Siomi et al. 1995; Zhang et al. 1995). How the loss of a single protein, FMRP, leads to mental retardation and a plethora of behavioral problems has been intensively investigated since the cloning of FMR1 gene in 1991. FMRP was found to form a messenger ribonucleoprotein (mRNP) complex that associates with translating polyribosomes (Feng et al. 1997). It has been proposed that FMRP is involved in synaptic plasticity through the regulation of mRNA transportation and translation (Fig. 1).

Given the power of Drosophila genetics in dissecting biological pathways, within the last several years, the fruit fly has been increasingly used to gain insights into the physiological roles of FMRP. Here, we are reviewing the role of Drosophila fragile X mental retardation gene (dFmr1) in development, synaptogenesis and behavior as well as discuss new functional partners revealed by genetic studies.

dFmr1 protein is highly similar to mammalian Fmrp and is ubiquitously expressed during development

Unlike their mammalian counterparts, the fly genome harbors a single Fmr1 gene homolog, also referred to as dfmr1 or dtxr (dFmr1 here, as per Flybase annotation). Sequence comparisons show a high level of similarity between the functional domains of fly and mammalian Fmrp, with overall 56% similarity and 35% identity (Gao 2002; Zhang et al. 2001). Thus, dFmr1 is comprised of two KH domains, ribosomal- and self-association domains, an RGG box as well as a nuclear localization signal (NLS) and nuclear export signal (NES), although it remains to be determined whether the
latter domain functions as an export sequence (an essential leucine has been substituted to glutamine) (Wan et al. 2000).

It has been shown that both mammalian Fmrp and dFmr1 protein are phosphorylated in vivo on conserved serine residues, and this might regulate their activities (Ceman et al. 2003; Siomi et al. 2002). Not only is dFmr1 highly homologous to mammalian Fmrp but also it exhibits similar homopolymer RNA-binding properties. In vitro translated dFmr1 protein can bind strongly to poly(G), weakly to poly(U) but not to poly(A)/poly(C) (Wan et al. 2000). Mutations in each of the

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Figure 1: Model of Drosophila fragile X mental retardation protein (dFmrp) function in the neuron. dFmrp (yellow hexagon) enters into the nucleus (a) via its NLS and forms a messenger ribonucleoprotein (mRNP) complex (b) by interacting with specific RNA transcripts (red hairpin structure) and proteins (green eight-point star). dFmrp could also form a mRNP complex in cytoplasm without entering into the nucleus. The dFmrp-mRNP complexes are then transported out of the nucleus (c) via its NES. In cytoplasm, the dFmrp-mRNP complex can associate with ribosomes (orange oval) and interact with the RNA-induced silencing complex (RNA-induced silencing complex (RISC); blue ribbon) (d & e). The dFmrp-mRNP complex could be transported (f) into dendrites after the dFmrp-mRNP has been assembled into a large transport complex which is shown with details in the dashed square. Once transported into the postsynaptic region, both complexes can be regulated to modulate (g) local protein synthesis (strings of green circles) from specific mRNAs in response to synaptic stimulation signals such as activation of the metabotropic glutamate receptor (mGluR). Certain dFmrp-mRNP complexes may also be transported into axon (h) and function presynaptically. Components in the dFmrp-mRNP transport complex; the LGL protein encoded by lethal(2) giant larvae (dlgl) interacts with both dFmrp-mRNP (probably via other unidentified proteins) and the PAR cell polarity complex (PAR3 and PAR6). The whole complex can be transported along microtubules via motor protein kinesin. α-PKCa leads to the phosphorylation of LGL, and this could modulate its interaction with nonmuscle myosin II. It could provide an interesting mechanism that enables the switch of dFmrp-mRNP cargos from dendritic microtuble to postsynaptic actin. Cdc42 and Rac1 are two proteins participating in the trafficking in polarized cells. Rac1 could interact with dFmrp, and this interaction may be antagonized by cytoplasmic FMRP interacting protein (CYFIP), which has been shown to be an interactor for both Rac1 and Drosophila fragile X mental retardation gene (dFmr1).
KH domains abolish homopolymer binding, consistent with a functional role for these motifs as suggested from human genetics studies (De Boulle et al. 1993). This level of conservation taken together with the genetic tools available in Drosophila makes the fly an unparalleled model system for fragile X syndrome.

Sequence analyses of available expressed sequence tags (ESTs) suggest that dFmr1 possesses alternative splicing and polyadenylation sites, which is consistent with Northern blots showing the presence of more than one transcript (Dockendorff et al. 2002; Zhang et al. 2001). Immunohistochemical data show that dFmr1 is ubiquitously expressed during the early stages of embryogenesis, with strong expression in the mesoderm, the brain lobes and ventral ganglia developing at later stages (Dockendorff et al. 2002; VVan et al. 2000; Zhang et al. 2001). Other tissues where dFmr1 has been detected are the developing imaginal discs, testes, ovaries and the ring gland (Zarnescu et al. 2005; Zhang et al. 2001). Just like its mammalian counterpart(s), dFmr1 is enriched in all neurons and with low or absent levels in glia. In addition, the protein is detected largely in the cytoplasm and not in the nuclei of all cells examined to date (Morales et al. 2002; Van et al. 2000; Zhang et al. 2001).

The loss of dFmr1 leads to the defects in behavior, synaptogenesis and spermatogenesis

To characterize the physiological functions of dFmr1, several loss-of-function mutations ranging in strength from weak hypomorphs to nulls have been isolated in the dFmr1 locus (Dockendorff et al. 2002; Inoue et al. 2002; Lee et al. 2003; Morales et al. 2002; Zhang et al. 2001). dFmr1 is not essential for viability, although some variability has been reported in the numbers of adult homozygotes (Dockendorff et al. 2002; Morales et al. 2002). Such differences in the numbers of viable homozygotes could be due to genetic background effects. Homozygous mutant adults appear morphologically normal but display abnormalities in behavior, synaptogenesis and spermatogenesis, some of which may be viewed as resembling the phenotypes observed in fragile X patients.

The loss of dFmr1 leads to several behavioral defects

Examination of locomotor activity in adult flies lacking dFmr1 revealed a statistically significant arrhythmic behavior (Dockendorff et al. 2002; Morales et al. 2002). dFmr1 mutants exhibit erratic activity patterns with brief periods of high activity. As the overall activity of dFmr1 nulls is unchanged, this suggests that the arrhythmicity observed is not due to defects in motor function and locomotion ability, but rather in the circadian clock. Interestingly, just like mutants lacking normal circadian function, dFmr1 nulls can be driven to display normal rhythms and even anticipate lights turning on and off when trained in light/dark cycles (Dockendorff et al. 2002; Inoue et al. 2002). This suggests that the molecular clock in itself is intact, and the defects observed may be due to downstream effectors of the clock. To address the first possibility, the expression of known molecular components of the circadian clock, such as timeless and period, were examined in dFmr1 mutants; however, no significant changes have been found (Dockendorff et al. 2002; Inoue et al. 2002; Morales et al. 2002). To address the possibility of downstream effects, using a reporter construct (CRE-luciferase) to monitor the downstream activity of the molecular clock, it was found that the amplitude of oscillations was reduced, suggesting that at least the CREB (cAMP response element binding) protein, a known molecular output of the clock, is controlled by dFmr1 function (Dockendorff et al. 2002). Indeed, fragile X patients have shorter sleep duration, greater variation in sleep duration and sleep timing problems, which might be related to the disturbance of circadian rhythms (Hagerman & Hagerman 2002).

Other tested behaviors included phototactic, geotactic and chemotactic abilities, which appear unaffected (Dockendorff et al. 2002; Morales et al. 2002; Zhang et al. 2001). Male courtship activity was found reduced in dFmr1 mutants at the level of maintaining courtship and was not due to a specific sensory deficit. In addition, dFmr1 mutant larvae were shown to exhibit altered crawling behavior, with shorter linear paths and more frequent turns in environments controlled for geotactic, phototactic and chemotactic cues (Xu et al. 2004). Taken together, these data suggest that dFmr1 loss-of-function mutants can execute simple behavioral tasks but exhibit deficits in the more complex behaviors analyzed to date.

dFmr1 regulates synaptic morphology and function

Using Drosophila larval neuromuscular junction (NMJ, a metabotropic type of synapse), it was shown that the loss of dFmr1 resulted in an increased number of synaptic boutons and overelaboration of synaptic terminals, similar to the dendritic overgrowth phenotype reported in the Fmr1 knockout mouse as well as fragile X patients (Hinton et al. 1991; Nimchinsky et al. 2001; Zhang et al. 2001). As expected, dFmr1 gain of function results in underelaborated synaptic terminals with enlarged synaptic boutons (Zhang et al. 2001). Using tissue-specific drivers to overexpress the protein either presynaptically or postsynaptically, it was found that dFmr1 functions on both sides of the synapse, but is predominantly presynaptic (Zhang et al. 2001). Electrophysiological studies found that evoked synaptic neurotransmission is significantly increased at NMJ in dFmr1 mutants, suggesting that the average synaptic efficacy is upregulated in these mutants (Zhang et al. 2001). In addition, miniature excitatory junctional currents had a mildly increased frequency in nulls compared with controls and also showed a significant increase in frequency when dFmr1 was overexpressed on the presynaptic but not postsynaptic side (Zhang et al. 2001). This result was surprising in that both loss-of-function and gain-of-function conditions resulted in increased efficacy of synaptic transmission, suggesting that the physiology of the
synapse is highly sensitive to the level of dFmr1 protein. A similar effect was observed with electroretinograms recorded at the histaminergic photoreceptor synapse, although in this case the transmission efficacy was decreased by modulating the level of dFmr1 protein (Morales et al. 2002). These results are similar to the observation that in mouse the level of Fmrp is critical and overexpression of Fmrp could overcorrect the behavioral phenotypes affected in Fmr1 knockout mice (Peier et al. 2000).

**dFmr1 is a negative regulator of neurite extension and branching**

Just like its mammalian counterpart, dFmr1 protein plays a role in dendrite morphogenesis. A detailed developmental analysis of multiple dendritic (MD) neurons in dFmr1 mutants showed that dFmr1 protein is a negative regulator of neurite extension (Lee et al. 2003). In contrast, overexpression of dFmr1 allows the extension of the major dendritic branches but blocks the formation of higher order structures thus reducing the overall dendritic complexity (Lee et al. 2003).

Other studies focused on the dorsal cluster neurons (DC), which have been implicated in the control of eclosion and the lateral (LNv) neurons, which control circadian rhythms (Dockendorff et al. 2002; Morales et al. 2002). In the absence of dFmr1, DC neurons exhibit a failure of axon extension, while LNv neurons show overextended axons. This suggests that although dFmr1 controls at least some aspects of their cellular architecture, it may have distinct functions in various neurons, perhaps by regulating different mRNA targets. Interestingly, overexpression of dFmr1 in both wildtype and mutant backgrounds results in failure of axonal extension, suggesting once again that dosage is critical for normal functions (Morales et al. 2002).

Recently, the mushroom body (MB), a highly plastic brain region, essential for many forms of learning and memory, was also studied (Michel et al. 2004; Pan et al. 2004). Phenotypic analyses showed that, in the absence of dFmr1, MB neurons display a more complex architecture, including overgrowth, overbranching and abnormal synapse formation (Michel et al. 2004; Pan et al. 2004). Interestingly, whole brains mutant for dFmr1 exhibit a more severe MB phenotype (Michel et al. 2004) compared with brains where only subsets of MB neurons lack dFmr1 (Pan et al. 2004). These phenotypes are consistent with a cell non-autonomous function for dFmr1. Taken together, these data showed that dFmr1 is a potent negative regulator of neuronal architecture and synaptic differentiation in the nervous system.

**The loss of dFmr1 leads to abnormal spermatogenesis and oogenesis**

Although dFmr1 mutants are viable and lack obvious morphological abnormalities, they cannot be maintained as a stock, using standard fly husbandry (Zhang et al. 2004). A detailed analysis of dFmr1 expression during spermatogenesis showed that the protein is upregulated in the late and larger spermatocytes (first four stages of spermatogenesis) compared with the more mature, elongated spermatids (last two stages of spermatogenesis) (Zhang et al. 2004). Consistent with this expression pattern, an age-dependent enlargement (100% penetrant in newly eclosed, but insignificant in 3-day-old males) in the middle region of the testes was observed. This enlargement is not due to an overproliferation of spermatids but rather due to the accumulation of misarranged spermatid bundles. Moreover, at the next developmental stage, coiled spermatid bundles appear to be degenerating in dFmr1 mutant testes, and thus very few individual spermatozoa are present in the mutant seminal vesicles (Zhang et al. 2004). The studies using electron microscopy showed that the basis of this degenerative phenotype is the loss of the central pair of microtubules without effects on the overall integrity of the axoneme (Zhang et al. 2004).

In a recent study, it was found that loss of dFmr1 function also leads to defects in oogenesis (Costa et al. 2005). Drosophila oocytes develop at the posterior end of egg chambers consisting of 16 germ cells surrounded by a monolayer of follicle cells (Spradling et al. 1997). dFmr1 protein is upregulated in the developing oocyte, and phenotypic analyses of null ovaries show that dFmr1 plays a role in the formation of the 16-cell germ cell cyst (Costa et al. 2005). Thus egg chambers lacking dFmr1 function have either too many or too few cells, suggesting a possible role for dFmr1 in cell division. In addition, dFmr1 loss of function results in egg chambers containing either no or an extra oocyte, suggesting that dFmr1 functions in oocyte differentiation (Costa et al. 2005).

**mRNA targets and genetic interactors of dFmr1**

Given that FMRP is involved in the translational control of specific mRNAs in mammals, it is important to identify the Drosophila mRNA targets of dFmr1 protein. Several mRNA targets of dFmr1 protein also have been identified, including futsch, rac1, pickpocket1 (ppk1) and orb (Costa et al. 2005; Lee et al. 2003; Xu et al. 2004; Zhang et al. 2001). Most recently, we also conducted a microarray analysis of the mRNA targets associated with dFmr1 protein and found some but not all of the reported dFmr1 protein-associated mRNAs (Zarnescu et al. 2005). This is not surprising, as experimental conditions and the choice of biological material differ among the various reports, and thus, each identified target requires individual validation. Interestingly, two of the mRNA targets we identified to be associated with the lethal(2) giant larvae (dlgl)/dFmr1 complex have been previously implicated in circadian rhythms (Zarnescu et al. 2005), a biological process controlled by dFmr1 (Dockendorff et al. 2002; Morales et al. 2002).

Gain of function for dFmr1 at the NMJ results in a smaller number of large synaptic boutons, which faithfully resembles...
the loss of function phenotype for futsch, the Drosophila ortholog of microtubule-associated protein MAP1B (Zhang et al. 2001). Moreover, loss-of-function futsch is sufficient to rescue the synaptic hyperplasia phenotype due to loss of function for dFmr1. Taken together, these genetic data suggest that dFmr1 and futsch are functionally antagonistic. Furthermore, immunoprecipitation experiments show that futsch mRNA associates with dFmr1 protein and more importantly the latter controls the levels of futsch protein, presumably at the level of translation (Zhang et al. 2001). This regulation is also conserved in mouse where the translation of MAP1B was found to be negatively regulated by FMRP (Lu et al. in press).

Interestingly, the loss of futsch is not sufficient to rescue other dFmr1-associated phenotypes, such as circadian rhythm defects and male infertility, suggesting that dFmr1 protein might act on specific targets in different tissues and distinct developmental contexts (Dockendorff et al. 2002; Zhang et al. 2001). These data underscore the importance of comprehensive phenotypic studies and the identification of dFmr1 protein-associated mRNA targets as well as its functional partners.

In addition, immunoprecipitation experiments showed that Rac1 mRNA specifically associates with dFmr1/mRNP complexes (Lee et al. 2003). The removal of Rac1 function in MD neurons during development resulted in underelaborated higher order dendritic branches, a phenotype opposite to the loss of dFmr1. Gain-of-function Rac1 in a subset of MD neurons increases dendritic branching, while dFmr1 overexpression results in reduced arborization (Lee et al. 2003). Furthermore, concomitant overexpression of Rac1 and dFmr1 in the MD neurons partially restores the reduced branching phenotype produced by dFmr1 overexpression alone. Taken together, these data suggest that dFmr1 mediates dendritic elaboration and branching, in part via regulating Rac1 mRNA. Rac1 could also function with dFmr1 at the protein level, and this interaction is modulated by cytoplasmic FMRP interacting protein (CYFIP), a previously known Rac1 interactor (Kobayashi et al. 1998; Schenck et al. 2003). CYFIP associates with either constitutively active Rac1V12 or dFmr1 in mutually exclusive complexes. Genetic interactions in Drosophila eye and central nervous system provided further evidence for CYFIP acting as an antagonist of Rac1 as well as dFmr1 (Schenck et al. 2003). This study provided evidence to support the possibility that CYFIP, which interacts with Rac1 in an activity-dependent manner, acts as a link between two processes underlying synaptic remodeling: cytoskeleton reorganization regulated by Rac1 and control of local protein translation via dFmr1 protein (Fig. 1).

In order to identify novel genetic interactors of dFmr1, we took a forward genetic approach using the fly eye as a model system (Zarnescu et al. 2005). We used an overexpression paradigm, whereby ectopic expression of dFmr1 under the control of an eye-specific promoter results in a visible rough eye phenotype, which we used as a basis for a saturating

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**dFmr1 protein-mediated translation control and microRNA pathway**

Studies performed in mammalian systems found that FMRP was associated with polyribosomes in an RNA-dependent manner (Corbin et al. 1997; Eberhart et al. 1996; Feng et al. 1997; Khandjian et al. 1996; Stefani et al. 2004). FMRP could act as a translational repressor of reporter constructs both in vitro and in transfected cells. In Drosophila, the dFmr1 protein was also found to function as a translational suppressor as well (Lee et al. 2003; Zhang et al. 2001).

The accumulation of work from several groups is now suggesting that the RNA interference (RNAi) pathway is the major molecular mechanism by which FMRP regulates translation. The initial critical observation came from biochemical studies in Drosophila cell culture. There, it was demonstrated that the dFmr1 protein associates with Argonaute 2 (AGO2) and the RNA-induced silencing complex (RISC), which mediates RNAi (Caudy et al. 2002; Ishizuka et al. 2002). RNAi, now a widely used experimental tool, is a conserved gene-silencing response to double-stranded RNA (dsRNA) (Novina & Sharp 2004). Silencing is initiated when dsRNA triggers are processed into small interfering RNAs (siRNAs). This is catalyzed by a group of related RNase III enzymes known as the Dicer family. The siRNAs are incorporated into the effector complex, RISC, which uses siRNA as a guide to select complementary mRNA substrates (Novina & Sharp 2004). Most components of RISC also can be utilized by endogenous microRNAs (miRNAs) (Bartel 2004) which are a new class of non-coding RNAs that are believed to control translation of specific target mRNAs by base pairing with complementary sequences in the 3’ UTR of these messages (Bartel 2004). The functions of miRNAs and siRNAs are facilitated by binding of microRNAs (miRNAs) to Argonaute family (Bartel 2004).
While recent data in *Drosophila* suggest that AGO1 is mainly involved in the endogenous miRNA pathway and that AGO2 is required for siRNA-mediated gene silencing, the loss of dFmr1 or FMRP does not seem to affect the siRNA pathway (Caudy et al. 2002; Ishizuka et al. 2002; Okamura et al. 2004). Therefore, it is still unclear what role, if any, FMRP plays in siRNA-mediated gene silencing. The association of the dFmr1 protein with RISC raises the possibility that FMRP may regulate the translation of its target genes through miRNAs. Indeed, FMRP was found to be associated with miRNAs in both *Drosophila* and mammals (Caudy et al. 2002; Ishizuka et al. 2002; Jin et al. 2004). To further test the functional importance of these interactions, our group examined the genetic interaction between dFmr1 and AGO1. We found that AGO1 is required for dFmr1-mediated regulation of synaptic plasticity. Moreover, partial loss of AGO1 could suppress the neuronal apoptosis caused by the overexpression of dFmr1 (Jin et al. 2004). Together, these data suggest that AGO1 is critical for the biological functions of FMRP in neural development and synaptogenesis (Jin et al. 2004). It recently has been found that dFmr1 also interacts genetically with AGO2, and the ppp1 mRNA level appears to be regulated by dFmr1 and AGO2 (Xu et al. 2004).

These observations strongly support the idea that dFmr1 protein might regulate the translation of its mRNA via mRNA interaction. A likely scenario is that once dFmr1 protein binds to its specific mRNA ligands, it recruits RISC along with miRNAs and facilitates the recognition between miRNAs and their mRNA ligands. Thus, dFmr1 protein might modulate the efficiency of translation of its mRNA targets using miRNAs. This mechanism would allow this activity to be rapid and reversible, as would be needed in protein synthesis-dependent synaptic plasticity.

**Drug discovery for fragile X syndrome in Drosophila**

In addition to the typical use of *Drosophila* (i.e. screening for novel genes and their mutations), the fruit fly is becoming the model of choice when a combination of gene alteration, pharmacological and functional assays of a phenotype is needed. Such a combined approach is particularly valuable in studies of complex systems such as the CNS (Manev et al. 2003). It was discovered a few years ago that one of the phenotypes of *Fmr1* knockout mice is the enhanced metabotropic glutamate receptor (mGluR) activity (Huber et al. 2002). This led to the proposition of the ‘mGluR hypothesis’ as the underlying mechanism for cognitive deficits present in fragile X patients (Bear et al. 2004). Recently, it has been shown that the enhanced mGluR activity is a conserved feature of fly dFmr1 mutant as well (McBride et al. 2005). More importantly, it was demonstrated that administration of various mGluR antagonists rescues the behavioral phenotypes previously reported in the fly (McBride et al. 2005). These findings are opening the exciting possibility that a similar approach might work to ameliorate some of the cognitive and behavioral deficits in human patients.

**Concluding remarks**

Recent developments of *Drosophila* models for fragile X syndrome have provided new avenues to understand the molecular pathogenesis of this disease. Despite that the fly genome only harbors a single *Fmr1* gene homolog and some of the functions ascribed to dFmr1 in fly might be carried out by the paralogs in mammals, the power of fly genetics should enable the field to identify and dissect biological pathways regulated by FMRP. The next exciting step will be taking the discoveries made in the fly and apply them towards a better understanding of fragile X syndrome.

**References**


Acknowledgments

Supported, in part, by grants from the Rett Syndrome Research Foundation (PJ), the FRAXA Research Foundation (DCZ) and National Institute of Health grants to DCZ and STW.