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Fragile X mental retardation protein levels are decreased in major psychiatric disorders

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Dear Editors

In individuals with fragile X syndrome (FXS), there is a silencing of the fragile X mental retardation (FMR1) gene, usually due to an expansion of a CGG repeat in the 5' untranslated region (Oostra and Willemsen, 2009). The subsequent loss of the FMR1 gene product, fragile X mental retardation protein (FMRP), an RNA-binding protein that travels between the nucleus and cytoplasm, results in disruption of post-transcriptional regulation of many target RNAs (De Rubeis and Bagni, 2010), leading ultimately to multiple pathologies associated with FXS.

FXS is characterized by mental retardation and autistic behavior. Indeed many cases of FXS also have overlapping diagnoses of autism, with one source estimating approximately 47% overlap (Demark et al., 2003). Recently, our laboratory has discovered significant reductions of FMRP in post-mortem autistic cerebella and superior frontal cortex (Fatemi et al., 2010a,b,c). When compared to matched controls, we observed a 75% reduction in FMRP expression ($p < 0.038$) in cerebella of adults with autism and a 50% reduction in FMRP expression ($p < 0.042$) in superior frontal cortex of adults with autism (Fatemi et al., 2010a,c). Associations between FMR1 dysregulation and other major psychiatric disorders have not been extensively studied, however an association between cytoplasmic FMR1 (CYFIP1) and schizophrenia has been examined (Tam et al., 2010).

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The goal of the present study was to examine the levels of FMRP in the lateral cerebella of patients with diagnoses of schizophrenia, bipolar disorder, and major depression as compared to controls. Our hypothesis was that FMRP expression would be decreased in these subjects as compared to normal control subjects.

All experimental procedures were approved by the Institutional Review Board of the University of Minnesota School of Medicine. Postmortem blocks of lateral cerebellum were obtained from the Stanley Medical Research Institute. Samples were stored at -80°C until use and derived from four groups ($n=15$ from subjects with bipolar disorder; $n=13$ from subjects with major depression; $n=12$ from subjects with schizophrenia; $n=14$ from control subjects). Tissues were homogenized, assayed for total protein concentration, and protein was isolated via SDS-PAGE and western blotting as previously described (Fatemi et al., 2008). The blots were incubated with anti-FMRP (Millipore) or anti- β -actin (Sigma Aldrich) and subsequently exposed to the appropriate secondary antibody. Sample densities were analyzed blind to diagnostic nature of the tissue using a BioRad densitometer and the BioRad Multi Analyst software. The molecular weight of approximately 73 kDa FMRP immunoreactive bands were quantified with background subtraction. Results obtained are based on at least two independent experiments.

FMRP data were normalized against β -actin and shown as ratios of FMRP to β -actin. We observed no differences in β -actin among the major psychiatric groups versus control, indicating that any change in FMRP is not due to differences in numbers of neurons or glia. We observed a 78% reduction of FMRP/ β -actin in cerebella from subjects with schizophrenia ($p=0.002$), a 60% reduction in cerebella from subjects with bipolar disorder ($p<0.008$), and a 68% reduction in cerebella from subjects with major depression ($p<0.005$) when compared with controls (figure 1). Relationships between FMRP/ β -actin and demographic and brain covariates were examined. None of the covariates were significant predictors of FMRP expression (for detailed demographic information for this collection of tissues, see table 1 in Fatemi et al., 2001).

This is the first demonstration of the reduction of FMRP in brains of subjects with schizophrenia, bipolar disorder, and major depression. There has been a case study of a woman with schizophreniform disorder who displayed a polymorphism of FMR1 (Jnsson et al., 1995). To date, however, linkage analysis has not shown an association between FMR1 and schizophrenia (Jnsson et al., 1995; Ashworth et al., 1996). Our current results build upon our previous postmortem findings of significant reductions of FMRP in autistic individuals without diagnoses of FXS (Fatemi et al., 2010a). Because FMR1/FMRP have been demonstrated to have a variety of targets (Brown et al., 2001), it is possible that this gene/protein has an impact on cognition. Further studies are needed to elucidate the role of FMRP in major psychiatric disorders. Additional future experiments should include identification the specific cell types in the cerebellum that are FMRP positive, and measurement of mRNA levels for FMRP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A. Representative samples of FMRP and β -actin from control (C), bipolar (B), depressed (D), and schizophrenic (S) subjects. B. Mean FMRP/ β -actin ratios for control, bipolar, depressed, and schizophrenic subjects are shown for cerebellum. (Error bars expressed as standard error of the mean.) **, $p < 0.05$.