

## Fragile X Mental Retardation Protein is Reduced in Cerebella of Subjects with Autism

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Autism and fragile X syndrome have multiple behavioral phenotypes in common, however there has been little research into the potential role of fragile X mental retardation protein (FMRP) in autism. We sought to measure protein levels of FMRP in the lateral cerebella of subjects with autism and matched controls. We found significantly reduced levels of FMRP ( $p < 0.0063$ ) in subjects with autism. The loss of FMRP expression in subjects with autism may help explain behavioral deficits, presence of seizure, and reduction in GABA receptors in subjects with autism.

**Declaration of interest:** None

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### Introduction

Fragile X mental retardation protein (FMRP) regulates post-transcriptional events including splicing, nuclear export, and translation of multiple RNAs (1). Anywhere from 25-47% of patients with Fragile X syndrome (FXS), in whom FMRP expression is lost due to transcriptional silencing, display autistic behavior (2,3) and it has been hypothesized that these behavioral deficits may be the result of this decreased FMRP expression (3). A number of structural abnormalities of the cerebellum have been identified in subjects with autism, which may be responsible for motor system dysfunction observed in this disorder (4). We therefore decided to examine protein levels of FMRP in cerebella of adult subjects with autism vs. matched controls. All experimental procedures were approved by the Institutional Review Board of the University of Minnesota, School of Medicine.

### Materials and Methods

Postmortem blocks of lateral cerebellum (N=6 control; N=4 autism) were obtained

from the Autism Research Foundation and various brain banks. The tissue samples were prepared (5,6) and were subjected to SDS-PAGE and western blotting as described previously (5,6). The blots were then incubated with anti-FMRP (Abcam) or anti- $\beta$ -actin antibodies (Sigma Aldrich) followed by an appropriate secondary antibody. We measured FMRP protein using western blotting technique and normalized results against  $\beta$ -actin.

### Results

There was a significant 80% reduction in FMRP protein in cerebella of subjects with autism ( $p < 0.0063$ ) when compared with controls (mean value of  $0.323 \pm 0.132$  for controls vs.  $0.0658 \pm 0.0506$  for subjects with autism) (Figure 1). There was no statistically significant difference in age and postmortem interval (PMI) between the two groups (data not shown).

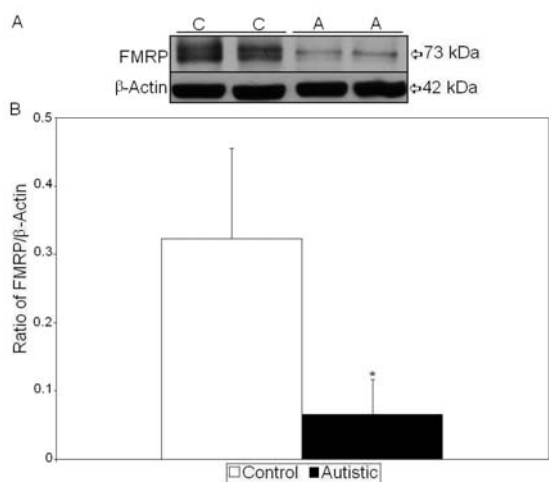
### Discussion

We observed a reduction in FMRP in cerebella of subjects with autism, none of whom were comorbid for FXS. The reduction in FMRP, and consequent dysregulation of downstream genes, may help to explain defects that are common between autism and FXS: social anxiety, mental retardation, seizures, and reduced size of cerebellum (3,7). Reduction in FMRP may also impact the

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GABAergic signaling system as a murine model of FXS also displays reduced expression of a number of GABA<sub>A</sub> receptor subunits (GABR $\alpha$ 1, GABR $\alpha$ 3, GABR $\alpha$ 4, GABR $\beta$ 1, GABR $\beta$ 2, GABR $\gamma$ 1, GABR $\gamma$ 2, and GABR $\delta$ ) (8). Moreover, our laboratory has demonstrated significant reductions in a number of GABA<sub>A</sub> (GABR $\alpha$ 1 and GABR $\beta$ 2) and GABA<sub>B</sub> (GABBR1 and GABBR2) receptor subunits in cerebella from the same set of tissues (5,6). Further studies, examining additional brain areas including superior frontal cortex, and hippocampus need to be undertaken to determine whether reduction of FMRP in brains from subjects with autism is a global phenomenon.



**Figure 1.** A. Representative samples of FMRP and  $\beta$ -actin from cerebella from control (C) and autistic (A) subjects. B. Mean FMRP/ $\beta$ -actin ratios for autistic (filled histogram bars) and control subjects are shown for cerebellum. (Error bars expressed as standard deviation of the mean.) \*,  $p < 0.05$ .

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