



Decreased fragile X mental retardation protein (FMRP) is associated with lower IQ and earlier illness onset in patients with schizophrenia



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ABSTRACT

The purpose of this study was to investigate Fragile X Syndrome (FXS)-related mechanisms in schizophrenia, including CGG triplet expansion, *FMR1* mRNA, and fragile X mental retardation protein (FMRP) levels in lymphocytes. We investigated 36 patients with schizophrenia and 30 healthy controls using Southern blot analysis, mRNA assay, and enzyme-linked immunosorbent assay (ELISA). General intellectual functions were assessed with the Wechsler Adult Intelligence Scale-III, and the clinical symptoms were evaluated with the Positive and Negative Syndrome Scale. Results revealed that, relative to healthy controls, CGG triplet size and *FMR1* mRNA were unaltered in patients with schizophrenia. However, the FMRP level was significantly reduced in patients compared with controls. We found an association between lower FMRP levels, reduced IQ, and earlier illness onset in schizophrenia. Chlorpromazine-equivalent antipsychotic dose did not correlate with FMRP levels. These results raise the possibility of impaired translation of *FMR1* mRNA, altered epigenetic regulation, or increased degradation of FMRP in schizophrenia, which may play a role in dysfunctional neurodevelopmental processes and impaired neuroplasticity.

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1. Introduction

Fragile X mental retardation protein (FMRP) is an RNA binding protein, which is abundant in the soma and dendritic spines of neurons. FMRP is a translational suppressor for several genes encoding proteins critical for synaptic transmission and plasticity, such as subunits of glutamate receptors and postsynaptic proteins (O'Donnell and Warren, 2002; Bear et al., 2008; Rousseau et al., 2011). The absence of FMRP characterizes fragile X syndrome (FXS), which is a prevalent form of inherited mental disabilities (Reiss and Hall, 2007). In FXS, the absence of FMRP is due to the silencing of the *FMR1* gene, which is caused by the expansion of a CGG trinucleotide repeat (Xq27.3, >200 repeats in the full syndrome; 55–200 repeats in premutation carriers) and increased methylation of the promoter region (O'Donnell and Warren, 2002; Bear et al., 2008; Rousseau et al., 2011).

There is increasing evidence that *FMR1*/FMRP is also involved in the pathogenesis of other disorders, such as premature ovarian insufficiency, fragile X-associated tremor/ataxia syndrome, and

autism (Hagerman et al., 2010). Moreover, the spectrum of fragile X-related disorders might include some forms of schizophrenia, anxiety, and mood disorders (Bourgeois et al., 2009; Fatemi and Folsom, 2011). This hypothesis was recently supported by the observation of Fatemi et al. (2010), who described reduced FMRP expression in the lateral cerebellum of patients with schizophrenia, bipolar disorder, and major depressive disorder. FMRP is implicated in glutamatergic and GABA-ergic processes, which are key pathophysiological mechanisms of schizophrenia (Fatemi and Folsom, 2011).

The purpose of the present study was to investigate whether FMRP is decreased in the peripheral blood of patients with schizophrenia and to assess its relationship with *FMR1* mRNA level. In addition, we explored the relationship between FMRP expression and clinical characteristics of the patients. We hypothesized that FMRP is associated with IQ, given that the absence of this protein is accompanied by a severe cognitive disability in patients with FXS.

2. Methods

2.1. Participants

Participants comprised 36 outpatients with schizophrenia and 30 healthy volunteers. The control participants were university/hospital employees and their non-biological relatives and acquaintances. All participants were assessed with

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the Structured Clinical Interview for DSM-IV axis I disorders (SCID-CV; First et al., 1996) and the Wechsler Adult Intelligence Scale-III (Wechsler, 1997). Full medical records were available, and all patients had a previous diagnosis of schizophrenia. We used the SCID-CV to confirm this diagnosis. The control participants had no Axis I psychiatric disorders and had a negative family history for psychotic disorders. Exclusion criteria included neurological disorders, head injury, and history of psychoactive substance dependence. For the assessment of clinical symptoms, the Positive and Negative Syndrome Scale (PANSS) was used (Kay et al., 1987). In the PANSS, positive and negative symptoms are evaluated by 7–7 items (minimum score=7, maximum score=49 for positive and negative symptoms separately), and general psychopathology symptoms are evaluated by 16 items (minimum score=16, maximum score=112). All patients received anti-psychotic medications at the time of testing (olanzapine: $n=14$, risperidone: $n=11$, quetiapine: $n=4$, risperidone plus quetiapine: $n=7$). Antipsychotic doses were converted into chlorpromazine equivalents (Woods, 2003). The patients did not receive any other psychotropic medications at the time of testing. Table 1 summarizes the clinical and demographic characteristics of the participants. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics board. All participants gave written informed consent.

2.2. Molecular biological measurements

All molecular measurements were based on published standard protocols. Peripheral blood was drawn from the cubital vein of the participants. CGG repeat size was determined using Southern blot analysis (Steyaert et al., 2003). We measured *FMR1* mRNA using Affymetrix Quantigene (Vala Sciences Inc., CA) by adopting the protocol of Tassone et al. (2000). For the quantitative measurement of FMRP levels, we used a new enzyme-linked immunosorbent assay (ELISA) method (Iwahashi et al., 2009). This method uses a combination of avian and murine antibodies, and it is highly sensitive and specific for FMRP in peripheral blood lymphocytes. The correlation of this ELISA approach with Western blot analysis of lymphocyte extracts is $r=0.99$ (Iwahashi et al., 2009). Further advantages of this method are that it is suitable for the quantification of FMRP levels in biologically relevant ranges, specific for the intact FMRP protein, applicable in non-transformed cells, and scalable for large sample numbers. Concentrations of FMRP were determined using SoftMax Pro 4-parameter fit logistics curve (pM; Iwahashi et al., 2009).

3. Results

Table 2 summarizes the results. Given that the variables were not normally distributed, as revealed by Kolmogorov–Smirnov tests, we used non-parametric Mann–Whitney U -tests. Patients with schizophrenia displayed normal CGG triplet size and *FMR1* mRNA level. In contrast, the level of FMRP was significantly reduced in patients relative to controls (Table 2). Earlier age at illness onset and lower IQ were associated with decreased FMRP levels in patients with schizophrenia (illness onset: Spearman's $R=0.59$, $p < 0.001$; IQ: Spearman's $R=0.66$, $p < 0.001$). Regarding the IQ, a similar trend was observed in healthy controls, but it did not reach the level of statistical significance (Spearman's $R=0.24$, $p=0.17$) (Fig. 1). There was no significant difference between male and female participants ($p > 0.5$).

Table 1
Demographic and clinical characteristics.

	Schizophrenia ($n=36$)	Control ($n=30$)
Male/female	22/14	20/10
Age (years)	35.5 (6.9)	36.4 (8.3)
IQ*	97.5 (9.6)	103.3 (8.9)
Age of illness onset (years)	24.0 (4.6)	–
PANSS positive	19.7 (5.4)	–
PANSS negative	17.8 (6.3)	–
PANSS general	46.7 (9.1)	–
Antipsychotics (chlorpromazine-equivalent, mg/day)	460.5 (120.9)	–

Data are mean (standard deviation). PANSS—Positive and Negative Syndrome Scale.

* $t(64) = -2.50$, $p < 0.05$.

Table 2
CGG triplet size, *FMR1* mRNA, and FMRP levels.

	Schizophrenia ($n=36$)			Control ($n=30$)		
	Mean	S.D.	Range	Mean	S.D.	Range
CGG triplet size	28.4	3.7	17–32	28.7	3.1	19–33
<i>FMR1</i> mRNA level	1.6	0.4	1–1.9	1.7	0.3	1–1.8
FMRP level*	78.4	75.3	18–340	124.8	91.0	40–420

FMR1—Fragile X Mental Retardation 1; FMRP—Fragile X Mental Retardation Protein.

* $Z = -3.25$, $p < 0.005$ (Mann–Whitney U test).

We conducted a multiple regression analysis to control for age and gender in patients with schizophrenia (data were log-transformed); this model also included age at illness onset and IQ. The analysis indicated that illness onset and IQ were significant predictors of the FMRP level (illness onset: $b^*=0.43$, $t(31)=2.67$, $p < 0.05$; IQ: $b^*=0.46$, $t(31)=3.30$, $p < 0.05$).

Finally, PANSS scores and the daily chlorpromazine-equivalent dose of antipsychotics did not correlate with FMRP levels (Spearman's $R: -0.2 < R < 0.2$, $p > 0.1$).

4. Discussion

The results of the present study demonstrated that the mechanism behind low peripheral FMRP in patients with schizophrenia is different from that observed in FXS. Patients with FXS display CGG triplet expansion, and decreased *FMR1* mRNA and FMRP, whereas patients with schizophrenia are characterized by reduced FMRP together with normal CGG triplet size and *FMR1* mRNA. This suggests that the dysfunction may be related to abnormal translation of *FMR1* mRNA, although the CGG triplet is a key factor in determining translational efficacy, and it was not altered in patients. An alternative explanation is that the degradation of FMRP is accelerated in schizophrenia. Future studies should also take into consideration the potential role of epigenetic regulations of *FMR1* (Stöger et al., 2011).

The most important finding of the study was that decreased FMRP was associated with earlier illness onset and lower IQ. This suggests that reduced FMRP may be related to neurodevelopmental changes, neuroplasticity, and cognitive functions. In an extensive meta-analysis of thousands of cases and controls, it was confirmed that greater premorbid IQ decrement is associated with earlier illness onset (Khandaker et al., 2011). In the case of cross-sectional studies, however, neuropsychological functions are linked to current IQ instead of to IQ trajectory during the disease course (Kremen et al., 2008).

Similarly to our previous study (Kéri and Benedek, 2011, 2012), we found no significant correlation between IQ and FMRP in healthy controls, although the tendency was similar to that revealed in patients with schizophrenia. This similar tendency may suggest that FMRP may be implicated in neurodevelopment and neuroplasticity underlying the emergence of general cognitive abilities, and it is not disease specific for schizophrenia. Previously, we observed similar correlations between visual functions and FMRP expression in healthy controls (Kéri and Benedek, 2011, 2012), with a special reference to contrast sensitivity functions disrupted in FXS and schizophrenia (Slaghuis, 1998; Kogan et al., 2004). In this case, similarly to IQ, FMRP may be important, even under non-pathological circumstances, in the physiological range of expression.

Loat et al. (2006) studied the relationship between *FMR1* allele length and cognitive functions in low ability, control, and high-IQ children. In males, there was a significant negative correlation

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