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Psychiatric Features in High-Functioning Adult Brothers With Fragile X Spectrum Disorders

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To the Editor: The awareness of psychiatric disability in the fragile X premutation (55–200 CGG repeats on Xq27.3) is low because these problems are not as obvious as in the full-mutation fragile X syndrome.^{1–5} Symptoms of hyperactivity, social deficits, and autism spectrum disorders as well as anxiety disorders and mood disorders are present in premutation carriers of both genders.^{1,2,6,7} Some individuals with the premutation have a mild-to-moderate deficit of fragile X–related mental retardation protein (FMRP).⁸ The level of FMRP decreases with increased CGG repeat number more evident in the upper end of the premutation range, leading to physical and behavioral features similar to fragile X syndrome.^{9,10} We present 2 cases of brothers with average and above intellectual abilities but emotional/neurocognitive deficits associated with the presence of expanded alleles from a larger fragile X family pedigree (see [Figure 1](#)) with significant psychopathology.

The brothers' 62-year-old mother was identified as a premutation carrier with an unknown CGG repeat size. She is affected by hypertension and underwent menopause at age 49 years. One of the brothers' sisters, who has 2 children with fragile X syndrome, was diagnosed with bipolar II disorder with intermittent hypomanic episodes and panic disorder without agoraphobia (predominantly, but not only, in social situations; diagnosis made using the *Structured Clinical Interview for DSM-IV Axis I Disorders* [SCID-I]¹¹). The maternal grandfather died in his early 50s after a sudden stroke. The maternal grandmother is 86 years old and healthy. The brothers' father suffered from alcoholism and died recently at age 67 years. A paternal uncle committed suicide in his 30s, while both paternal grandparents were "odd" and either depressed or irritable and had been hospitalized in psychiatric institutions. The paternal grandfather had received electroconvulsive treatment and had a history of alcoholism.

Case 1. Mr A is a 40-year-old man with full mutation and methylation mosaicism, including a

methylated allele (190 CGG repeats) and unmethylated alleles in both the premutation and the full-mutation range (98 and 225–547 CGG repeats, respectively; full mutation detected in approximately 30% of the cells). His *FMR1* messenger RNA (mRNA) level was 5.8-fold above normal, and he showed decreased FMRP expression level of approximately 20% of normal (see [Figure 2](#)).

His developmental history included a premature birth, delayed motor development, and delayed onset of language. He showed poor eye contact, signs of attention deficit and hyperactivity, and language and reading problems in childhood. His medical history included leg cramps, recurrent sinusitis, and varicose veins. He complained about poor balance and visual-motor coordination deficits since childhood. The medical examination demonstrated a prominent jaw, flat feet, increased deep tendon reflexes of 3+, macroorchidism, a mild hearing loss, and motor coordination problems including inability to tandem walk. His cognitive testing¹² at age 40 years demonstrated a full scale intelligence quotient (FSIQ) of 107 (68th percentile, in the average range), and his general memory score¹³ was 98 (45th percentile). On psychiatric interview, Mr A reported several manic episodes with psychotic features during his teenage years, meeting SCID-I criteria for bipolar disorder type I, most recent episode manic with psychotic features in full remission at the time of the evaluation. He had had 3 psychiatric hospitalizations during his teenage years. As an inpatient, he was started on lithium treatment, which he did not tolerate and discontinued, followed by haloperidol and benzotropine. After 3 years, he discontinued medications and psychiatric treatment and remained relatively symptom-free. Currently, he meets SCID-I criteria for alcoholism.

Although Mr A presented with an IQ considered to be average, which is remarkable for an adult man with *FMR1* mosaicism, he showed features of premutation and full-mutation involvement related to high mRNA levels and low FMRP levels. Overall, we hypothesize that Mr A demonstrates a “double hit” phenomenon—he is affected by both lowered FMRP and elevated mRNA levels.

Case 2. Mr B is a 41-year-old male premutation carrier with 118 CGG repeats and the brother of Mr A. Elevated *FMR1* mRNA levels (3.92-fold elevation) and a moderate decrease in FMRP expression were observed in blood (approximately 65% of normal levels; see [Figure 2](#)). Mr B had normal development. His medical history included migraines, a blocked nasal passage secondary to a deviated septum, asthma, and eczema. On examination, he presented with a long, narrow face, long ears (> 7 cm), and a prominent jaw. His neurologic examination showed slightly increased reflexes and a loss of vibratory sensation in the lower extremities. On psychiatric interview, he reported an untreated major depressive episode lasting 6 months at age 20 years; therefore, he met SCID-I criteria for major depressive disorder, single episode in full remission, at the time of the evaluation. His cognitive testing¹¹ at age 41 years demonstrated a superior FSIQ of 122 (93rd percentile), and his general memory score¹³ was 103 (58th percentile).

We present 2 brothers with expanded *FMR1* alleles, elevated *FMR1* mRNA levels, and a distinct psychopathological profile, including mood disorders and substance abuse. The high prevalence of premutation alleles in the general population (approximately 1:250–810 in males and 1:130–250 in females) warrants increased awareness of the possible connection to medical and psychopathological features.^{14,15}

Individuals who have both lowered FMRP and elevated *FMR1* mRNA (ie, a “double hit”), carriers with a CGG repeat number in the upper premutation range and some mosaic full mutations, may be more common than previously thought, and they often present with psychiatric features.¹⁶ The phenomenon of double involvement of toxic elevation of *FMR1* mRNA and reduced FMRP is worthy of further study, and it may represent a new phenotype in between the premutation and the full mutation with a more severe psychopathology that combines features of both types of mutations.

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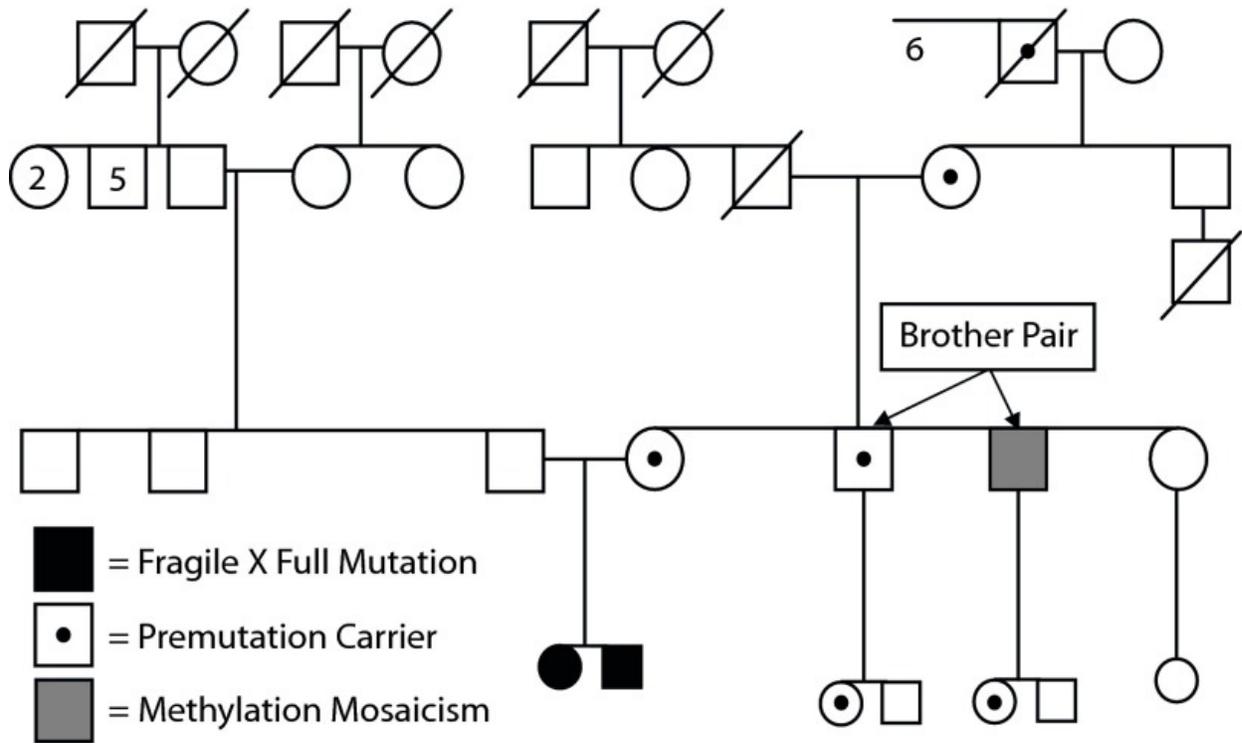
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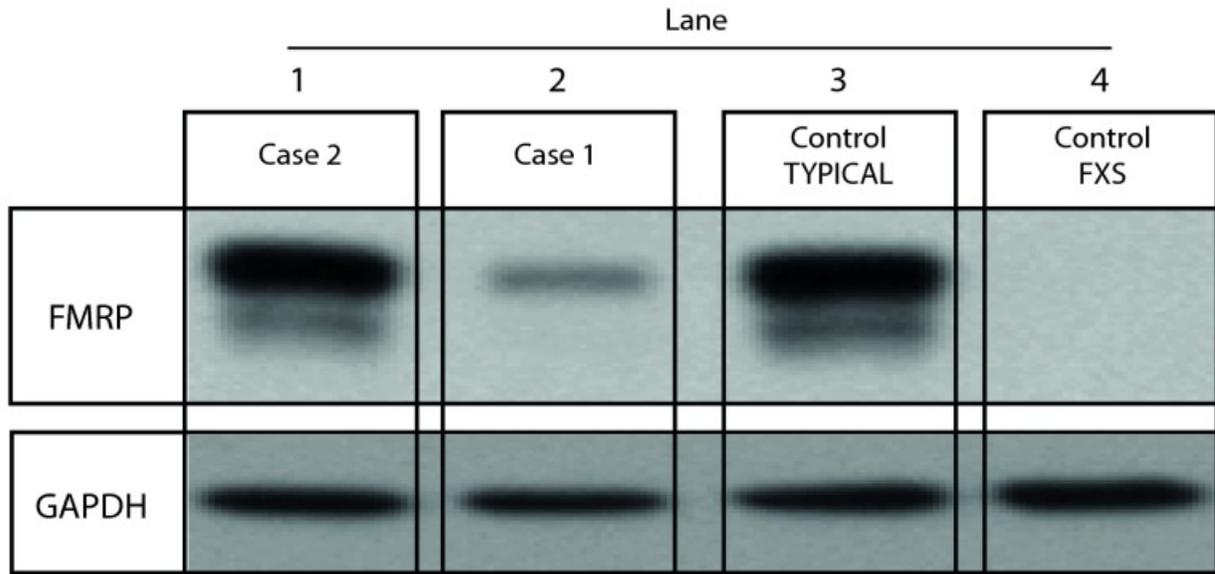
Figures and Tables

Figure 1



Family Pedigree of 2 Brothers With Fragile X Spectrum Disorders

Figure 2



Western Blot for FMRP Levels^a

^aWestern Blot analysis of protein extracts isolated from whole blood from case 1 (lane 2), case 2 (lane 1), a control with normal *FMR1* allele (TYPICAL, lane 3), and a full control (FXS, lane 4). A protein extract of 2 mg/lane was loaded for each sample. Anti-FMRP antibodies were used with a 1:1,000 dilution and GAPDH with 1:10,000 dilution.

Abbreviations: FMRP = fragile X–related mental retardation protein, FXS = fragile X syndrome, GAPDH = glyceraldehyde 3-phosphate dehydrogenase.

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