Gynecology and Reproductive Endocrinology

A comprehensive FMR1 gene mutations genotype-FMRP study: Expanding an insight into fragile X-associated disorders

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Abstract

Expansion mutations of the Fragile X Mental Retardation 1 (FMR1) gene (normal 10−45 CCGs) cause clinical phenotypes of FX-associated disorders. Fragile X syndrome (FXS) is caused by full-mutation (FM, >200 CGGs) and epigenetic silencing of the FMR1 gene, which leads to reduction/lack of the gene's protein (FMRP). FXS is the most common monogenetic cause of inherited intellectual disability (ID) and autism spectrum disorder (ASD). In premutation (PM, 55-200 CGGs), 20% women may develop an early menopause (FXPOI).

Methodology: DNA- AmplideX® FMR1 PCR assays were performed on 42 subjects with FMR1 gene mutations. 31/42 subjects also had an advanced FMRP analysis using the Luminex 200 capture immunoassay. A set of neurobehavioral/clinical assessments were also applied.

Findings: The cohort consisted of 37/42 (84% males) individuals with FXS and 5/42 with PM 56-113 CGGs, mostly unmethylated (60% females). Within sub-cohort with FMRP (N=31), 39% males had FXS+ASD (IQ 36.4±17.0) vs 61% FXS-only (IQ 49.8±17.5), P< 0.03. FMRP values were 2.8-fold higher in non-ASD compared to ASD. FMRP levels were in line with clinical phenotypes and IQ scores (Fig 1). Individuals within the normal range of IQ (N=6) had 2.8- and 5-fold higher FMRP levels compared to ones with mild (N=14; P>0.01) and moderate ID (N=11; P<0.01), respectively. Social anxiety (SA) diagnosis was very common. The PM subgroup mean FSIQ score was 80.3±16.3 (females, 1 FXPOI). The FMRP level [pg/ng] was slightly higher in females (17.1±13.2 vs. 13.1±10.0 in males). Those females had a higher frequency of psychiatric disorders under an umbrella of Fragile X-associated Neuropsychiatric Disorder (FXAND).

Conclusion & Significance: The results underscore the link between FMR1 expansion, gene methylation and FMRP deficit in FXS. FMRP levels were in agreement with clinical phenotypes, including ASD diagnosis and IQ/ID scores. Complexity of PM clinical presentations relative to measured molecular markers suggests a need for well-powered, multi-analyte studies to characterize PM genotype-phenotype relationships Disorder (FXAND).

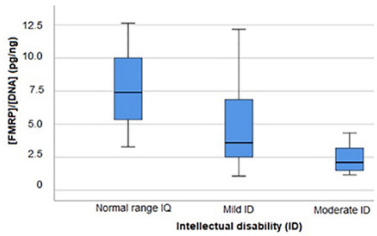

Figure 1. Individuals within normal range of IQ (70) had 2.8- and 5-fold higher FMRP levels compared to ones with mild (55-69) and moderate-severe (≤54) ID, respectively.

Biography

Dejan B. Budimirovic, MD earned his undergraduate degree from a pre-medical nursing program and his medical degree from Belgrade University, where he graduated magna cum laude. He then completed residencies at Belgrade, Harvard, and New York University School of Medicine, respectively. He is an attending child neuropsychiatrist, main sub-Investigator in several dozen clinical trials to date, and the medical co-director of the Fragile X Clinic at Kennedy Krieger Institute, Johns Hopkins Medical Institutions. Under his leadership, the Clinic has been critical in establishing now thriving the Institute's Clinical Trials Unit. He is also an assistant professor of psychiatry & behavioral sciences at Johns Hopkins University School of Medicine. Dejan is board certified by the American Board of Psychiatry and Neurology in adult, child, and adolescent psychiatry. He is an active member of the FXCRC and its Clinical and Clinical Trials Committees.

2nd World congress on Fetal and Maternal Medicine
Webinar | July 12, 2021

Citation: **Dejan Budimirovic,** *A comprehensive FMR1 gene mutations genotype-FMRP study: Expanding an insight into fragile X-associated disorders*, **FM 2021, 2nd World congress on Fetal and Maternal Medicine, July 12, 2021**