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Fragile X Gene Premutation: To Recognize Early and Treat Neuropsychiatric Problems

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Commentary

Mutations in the Fragile X Mental Retardation 1 (*FMR1*) gene cause a spectrum of genetic disorders such as neurodevelopmental in childhood and neurodegenerative in adulthood. Two types of mutations are recognized that has a different pathophysiological mechanism leading to their corresponding phenotypes under the umbrella of fragile X-related disorders (FXD). First, the full mutation of the *FMR1* gene (FM, ≥ 200 CGGs) causes hypermethylation that leads to silencing of *FMR1* and an absence of Fragile X Mental Retardation Protein (FMRP); and clinically fragile X syndrome (FXS) ensures. FMRP expresses in many tissues and plays an important role in the development of synapses and regulation of synaptic plasticity [1-3]. Thus, FXS emerges in an early childhood and is characterized by intellectual disability (ID) in 85% of boys and autism spectrum disorder (ASD) in up to 50% of boys and 20% of girls [4,5]. Early language and motor milestones and social-communication skills are more affected in patients with ASD and FXS than in those with FXS only [6,7]. Second, the premutation or "carriers" (PM, 55-200 CGGs) of the *FMR1* gene leads to elevated levels of the *FMR1* mRNA. Rapidly accumulating data on molecular pathology of *FMR1* PM over the last decade has brought much insight into the field [8,9]. For example, higher length of CGGs repeats was found to correlate with the higher mRNA levels, and the high level of mRNA causes RNA toxicity related to the sequestration of proteins that are important for neuronal function [10]. These PM neurons are more susceptible to die in cell culture and are more vulnerable to environmental toxins such as alcohol and pesticides [9,11]. Importantly, cellular mechanisms such as calcium dysregulation, mitochondrial dysfunction, oxidative stress, chronic DNA damage repair changes and the formation of the toxic protein FMRpolyG are all related to the toxicity of the PM that can lead to the neurodegenerative disorder such as fragile-X-associated tremor/ataxia syndrome (FXTAS) [10,12-15]. Furthermore, the translation of mRNA with greater than 120 CGG repeats is inefficient and there is deficit of FMRP as well. The carriers are found in roughly 1:200 females and 1:400 males (1.5 million females in the US; over 20 million worldwide), the prevalence 10 times higher than in FXS [16]. Thus, an emerging potential neuropsychiatric impact of the PM is enormous worldwide, beyond FXTAS and fragile-X-associated primary ovarian insufficiency as the most serious adult-onset clinical manifestations of the PM [8,17]. Indeed, we now know of high prevalence both medical/neurological (i.e., migraine headaches, chronic pain, fibromyalgia, chronic fatigue and autoimmune problems) and adult psychiatric disorders that may be related to PM of the *FMR1* gene that recently Hagerman and colleagues in 2018 elegantly labelled Fragile X-associated Neuropsychiatric Disorder (FXAND). To date, an overall lack of knowledge about these problems exists among clinicians. Not surprisingly, this is true among the medical professionals in countries in transitions [18].

Our opinion is that all primary care providers, including paediatricians, ought to be vigilant as for the FXAND that may cause psychiatric disorders in paediatric population suggesting that they also need to be screened for the *FMR1* gene mutations [11]. For example, babies with the PM demonstrated a greater sensitivity to sensory stimuli compared to controls, children showed a high rate of attention-deficit/hyperactivity disorder and ASD, and other developmental problems; and anxiety is the most common problem in the PM carriers, which typically begins in childhood. Importantly, the psychiatric problems occur usually before the neurological disorders related to the PM of the *FMR1* gene. Our clinical experience is that puberty is the period when these psychiatric problems in children reach clinical significance. The aforementioned molecular studies showed a link among the psychiatric problems occurred in the PM carriers and its intracellular molecular abnormalities.

As the knowledge in the field of fragile X continues to grow in the 21st century that ought to expand to the PM of the *FMR1* gene, and in paediatric population as its early recognition of their psychiatric problems can improve quality of life of these individuals and their families.

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