

Adult Fragile X-Associated Syndromes

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Expansions of the CGG-repeats stretch at the 5'-UTR of the Fragile X Mental Retardation 1 (*FMR1*) gene have pleiotropic effects that lead to a variety of Fragile X-associated syndromes: the neurodevelopmental Fragile X syndrome (FXS) in children, the late-onset neurodegenerative disorder Fragile X-associated tremor-ataxia syndrome (FXTAS) that mainly affects adult men, the Fragile X-associated primary ovarian insufficiency (FXPOI) in adult women, and a variety of psychiatric and affective disorders that are under the term of Fragile X-associated neuropsychiatric disorders (FXAND). In the adult syndromes, the pathological mechanisms are primarily caused by a gain-of-function due to the toxic actions of CGG RNA and FMRpolyG peptide.

Keywords: FXTAS ; FXPOI ; FXAND ; premutation ; *FMR1*

1. Introduction

The Fragile X Mental Retardation 1 (*FMR1*) gene is located on the X chromosome and encodes the polysome-associated RNA-binding protein FMRP, which plays key roles in neuronal development and synaptic plasticity through the regulation of mRNAs at the level of traffic, stability, splicing and both somatic and presynaptic translation ^[1]. The 5'-UTR of the *FMR1* gene contains a stretch of CGG repeats that causes a series of pathological conditions when exceeding 54 repeats, although there is increasing evidence of an association between the "gray zone", ranging from 45 up to 54 triplet copies (which forms an unstable *FMR1* allele that can be expanded in successive generations ^[2]) with atypical parkinsonism ^[3]. The silencing of the *FMR1* gene occurs over 200 CGG repeats (the so-called full mutation, FM), resulting in severe diminished FMRP expression during development and in consequence the onset of the Fragile X syndrome (FXS, OMIM #300624). FXS is the most common cause of monogenic intellectual disability, with a high incidence of autistic features, hyperactivity behaviour and seizures, and usually accompanied by macroorchidism and distinct facial features ^[4].

The so-called premutation (PM), whose carriers can exhibit diverse symptomatology comprising both neural and non-neural pathological traits with different degrees of severity and compromised well-being, is defined in the range of 55 and 200 repeats. The worldwide prevalence of the PM is approximately 1:300 in females and 1:850 in males ^[5]. The risk to develop FXTAS (OMIM #300623) is higher in men than in women: from 17% to 75% of the PM male carriers as age increases, and only from 8 to 16% in PM carrier women ^{[6][7]} who exhibit a diverse phenotype much milder than those observed in men, possibly due to the female inactivation of chromosome X ^[8]. FXTAS is a late onset neurodegenerative disorder characterized by intention tremor usually accompanied by slow movement and parkinsonism, which develop into cerebellar gait ataxia and dystonia as the disease progresses, and by cognitive deficits (e.g., short-term memory loss, executive functions impairment, language capacity affectation), mood disorders and neuropsychiatric alterations, peripheral neuropathy, sleep disturbance and other signs ^{[9][10]}. The main radiological signs consist of an increased signal in brain white matter, especially in the middle cerebellar peduncles (MCP) in men ^[11]. MCP are the main afferent pathway to the cerebellum and are primarily composed by white fibers projected from the contralateral pontine nuclei as part of the cortico-ponto-cerebellar pathway that control motor tasks, planning and initiation of movements ^[12]. In addition, FXTAS patients show smaller volume in overall brain and particularly cerebellum related to PM carriers without diagnosis ^[13]. The presence of eosinophilic intranuclear ubiquitin-positive inclusions in brain, spinal cord and peripheral tissues is a hallmark of this disorder ^{[14][15][16]}.

More prevalent in women is the development of the Fragile X-associated primary ovarian insufficiency (FXPOI, OMIM #311360): 24% of the PM women whereas the prevalence of POI in the general population is 1% ^[17]. This form is the most common inheritable ovarian dysfunction, which symptoms include irregular menstruation cycles, reduced fertility and early menopause onset ^[18]. More precisely, FXPOI involves ovarian hormonal dysfunction alongside with follicle depletion before the age of 40 years, having a direct impact on menstrual cycle regularity (that can lead to amenorrhea) and the ability to conceive, together with a variety of indirect consequences derived from chronic hypoestrogenism, such as early onset of osteoporosis and bone fracture, impaired vascular endothelial function, earlier onset of coronary heart disease

and increased cardiovascular mortality, and higher risk of psychiatric symptomatology (e.g., anxiety, depression, etc.) than women with normal ovarian functionality ^{[19][20][21][22][23][24]}.

2. Is There a Fragile X Spectrum Disorder?

Some authors have suggested that all clinical manifestations associated with the PM of the *FMR1* gene constitute a spectrum of varying degrees of penetrance and severity of these clinical signs, in which the final diagnosis of FXTAS or FXPOI may represent extreme forms of cognitive and endocrine impairment that may be present in other PM carriers in a milder manner. Therefore, the motor, cognitive and reproductive impairments generally ascribed to FXTAS and FXPOI diagnoses do not follow a strict boundary between sexes. Meanwhile PM women who are asymptomatic for classical FXTAS may develop subtle motor and cognitive impairments that are suspicious to be cerebellar-dependent ^[25], PM men can develop intranuclear inclusions in brain as well as in testicular tissues, prominently in the Leydig cells that are responsible for secreting testosterone to maintain spermatogenesis ^{[15][16][26]}. A potential association of such inclusions with cases of infertility ^[26] resembles the situation of granulosa cells and POI in PM women. Moreover, there is also a major risk of macroorchidism in PM men, a clinical feature usually linked to FXS that has been correlated with lower verbal and intelligence quotient (IQ) in the examined individuals ^[27].

Thus, manifestation of specific traits can be largely dependent on unknown genetic interactions, and/or the degree of mosaicism between the gain- and loss-of-function components of the CGG expansion that may differ throughout neural and non-neural tissues. For instance, patients who presented both *FMR1* mRNA increase and FMRP decrease manifested a symptomatology resembling combined FXS and FXTAS ^[28], although the mosaicism of methylated and unmethylated FM alleles can also explain the coexistence of FXS and FXTAS-related diagnosis in the same individuals ^{[28][29]}. It has been documented that pediatric PM carriers may develop attention deficit hyperactivity disorder (ADHD), anxiety, autistic features, seizures and other psychiatric symptoms that are reminiscent of FXS but to a much lesser extent and prevalence compared to FXS patients ^[30]. Therefore, PM boys have higher risk to be diagnosed of autism spectrum disorder (ASD) or ADHD than age-matched PM girls, although in both groups the risk was higher than in controls, leading to the hypothesis that reduced protein levels of *FMR1* are responsible for the mild signs of the developmental and cognitive impairments observed in PM carriers that are characteristic of FXS patients ^{[31][32]}.

However, the majority of PM children do not have psychiatric conditions but they are at higher risk than the general population to develop them in the mid-adulthood, independently of a FXTAS diagnosis. The term Fragile X-Associated Neuropsychiatric Disorders (FXAND) has been coined to group the diverse neuropsychiatric problems observed in PM carriers that precede the onset of characteristic FXTAS but recognizes a series of mental disturbances in those PM carriers that do not fall into the diagnosis of FXTAS and can be more common than expected in these individuals ^[33]: anxiety, high sensitivity to external stimuli, depression, ADHD, obsessive-compulsive disorder, chronic pain and fatigue, sleep disturbance, and drug abuse (probably as part of a self-medicating behaviour) ^{[33][34]}. This term also considers non-neurological symptoms, as in the case of autoimmune conditions that mainly appear in PM females (hypothyroidism, fibromyalgia, irritable bowel disease, etc.) ^[19].

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