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FRAGILE X SYNDROME: AN AGING PERSPECTIVE

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Abstract

Cognitive and behavioral correlates of molecular variations related to the FMR1 gene have been studied rather extensively, but research about the long-term outcome in individuals with fragile X spectrum disorders remains sparse. In this review, we present an overview of aging research and recent findings in regard to cellular and clinical manifestations of aging in fragile X syndrome, and the FMR1 premutation.

Keywords

fragile X syndrome; aging; neurodegeneration; FMRP

INTRODUCTION

Fragile X syndrome (FXS) is the most common inherited form of autism and intellectual disability (ID), and is caused by a CGG repeat expansion mutation in 5' non-coding region of the fragile X mental retardation 1 (*FMR1*) gene (>200 repeats, full mutation).

Epidemiological studies estimate FXS to be found in 1 in 3600 individuals in the general population, with recent estimates of the full mutation allele frequency in males as approximately 1 in 2500 [Hagerman, 2008; Fernandez-Carvajal et al., 2009]. The pre-mutation (55–200 repeats), however, is more widespread occurring in 1 in 130–250 females and 1 in 250–810 males [Dombrowski et al., 2002; Hagerman, 2008; Fernandez-Carvajal et al., 2009].

The expansion in full mutation individuals results in hypermethylation of the CpG island, an epigenetic mechanism that renders the *FMR1* gene transcriptionally silent [Sutcliffe et al.,

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Call-Outs

The study of the neurobiology of FXS is likely to teach us as much about molecular aspects of aging as it has regarding neurodevelopment, and it should provide useful models for targeting treatments for intellectual disabilities and for aging syndromes. Pre-mutation carriers express 2–8 times the normal amount of *FMR1* mRNA, which ultimately leads to RNA toxicity. This, combined with mitochondrial dysfunction causes the emergence of FXTAS symptoms typically after age 50. FMRP is a critical protein for aging in all individuals and those with FXS may suffer significant problems with aging because of the lack of FMRP.

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1992]. This diminishes or eliminates cellular levels of the *FMR1* gene product, the fragile X mental retardation protein (FMRP). FMRP is most commonly expressed in neurons, and plays a vital role in synaptogenesis and synaptic plasticity. Ramifications of this hypermethylation translate into notable behavioral and physical abnormalities of FXS such as hyperactivity, anxiety, attention problems, hand flapping, hand biting, gaze avoidance, loose connective tissue, prominent ears, and flat feet [Hagerman, 2002]. Adult patients with FXS may also present with a high-arched palate, long face, and macro-orchidism [Hagerman, 2002]. Additionally, diagnosed individuals experience cognitive deficits with severity directly correlating to FMRP levels [Tassone et al., 1999; Loesch et al., 2004]. Neuropsychological symptoms of FXS may vary with age [Harris et al., 2008], and case studies also report characteristic signs of brain atrophy and deterioration in these individuals as well [Dunn et al., 1963; Rudelli et al., 1985; Desai et al., 1990; Hinton et al., 1991; Irwin et al., 2000; Sabaratnam, 2000]. A study about mortality in FXS by Partington et al. [1992] did not show differences compared to the general population, and identified cardiovascular, cerebrovascular, and cancer as commonest causes of death in FXS.

Conversely, pre-mutation carriers have been known to express relatively normal levels of FMRP and show few to no intellectual, behavioral, or physical abnormalities early in life. It should be noted, though, that within this demographic, males are at higher risk for some conditions, such as autism spectrum disorder [Cummings et al., 2002], when compared to their female counterparts or to males without a developmental disability [Farzin et al., 2006; Clifford et al., 2007; Chonchaiya et al., 2011]. Both genders do express elevated levels of *FMR1* mRNA, leading to RNA toxicity [Garcia-Arocena and Hagerman, 2010]. This combined with evidence of mitochondrial disease which also can be present in FXS [el Bekay et al., 2007; Ross-Inta et al., 2010], is more often associated with adult-onset diseases that include primary ovarian insufficiency (FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS). The latter is a progressive disease presenting with clinical features such as intention tremor, cognitive decline, and autoimmune disease [Coffey et al., 2008; Grigsby et al., 2008; Seritan et al., 2008; Bourgeois et al., 2009], as well as evidence of brain atrophy and nuclear inclusions [Greco et al., 2002, 2006]. Interestingly, a significant percentage of people with FXS are mosaic; that is, either some cells carry the pre-mutation while others have the full mutation, or all cells have the full mutation but some are methylated while others are unmethylated. Mosaic individuals present with clinical features of both FXS and pre-mutation carriers.

This article includes recent findings in regard to the cellular and clinical manifestations of individuals affected by FXS and the pre-mutation. It also summarizes what is known about the long-term cognitive and neuropsychological outcomes of geriatric patients in these two clinical groups, as well as a discussion of FXTAS and its disease mechanisms.

AGE-RELATED PHENOTYPES

FMRP is most commonly expressed in neurons, particularly in high levels at the dendritic spines, cytoplasm, and ribosomes bound to the endoplasmic reticulum [Eberhart et al., 1996; Willemsen et al., 1996; Weiler et al., 1997; Bassell and Warren, 2008]. However, this protein is diminished in individuals with FXS [Sutcliffe et al., 1992]. Notably, many of the

neuropsychological phenotypes described above correlate with area specific abnormalities in the FXS brain [Reiss et al., 1988, 1994, 1995]. Case reports regarding aged FXS brains have also found global atrophy, Purkinje cell loss [Sabaratnam, 2000], heterotopias, deterioration of the corticospinal tract thought to have been amyotrophic lateral sclerosis (ALS) [Desai et al., 1990], and dendritic spine abnormalities including long, thin, and immature spines [Rudelli et al., 1985; Hinton et al., 1991; Irwin et al., 2000] similar to what has been seen in the knock out (KO) FXS mouse [Comery et al., 1997; Irwin et al., 2002]. Moreover, while FXS is the most common known cause of autism, Harris et al. [2008] reported that preliminary measures showed this diagnosis increases in older individuals with FXS when compared to younger ones [Harris et al., 2008].

Conversely, pre-mutation carriers follow a different disease mechanism related to the *FMR1* gene. These individuals express 2–8 times the normal amount of *FMR1* mRNA [Tassone et al., 2000; Kenneson et al., 2001; Tassone et al., 2001; Primerano et al., 2002; Allen et al., 2004; Tassone et al., 2007], which ultimately leads to RNA toxicity. This, combined with mitochondrial dysfunction [Ross-Inta et al., 2010; Napoli et al., 2011], causes the emergence of FXTAS symptoms typically after age 50. FXTAS occurs in individuals with the pre-mutation except in rare exceptions, which are discussed shortly. Clinically, FXTAS presents with a wide variety of symptoms such as an intention tremor, cognitive decline, dementia, and peripheral neuropathy [Hagerman and Hagerman, 2004b]. There is also evidence of global brain atrophy including areas related to executive function, enlargement of the ventricles, loss of axons and myelin and other indications of white matter disease in the periventricular region and in the middle cerebellar peduncles (MCP sign) [Adams et al., 2007]. Nuclear inclusions that are specific to FXTAS occur throughout the brain, but they are most prominent in the amygdala and hippocampus [Greco et al., 2002, 2006]. Other areas of the body can also be affected with inclusions in both humans and animal models with the premutation and they include the pituitary, testicles, heart, islets of Langerhans, adrenal glands and peripheral nervous system [Louis et al., 2006; Greco et al., 2007; Brouwer et al., 2008; Gokden et al., 2009; Hunsaker et al., 2011]. Important to note is that the severity of these FXTAS symptoms all appear to correlate with CGG repeat size [Greco et al., 2002, 2006; Adams et al., 2007; Leehey et al., 2007; Tassone et al., 2007; Cornish et al., 2008; Grigsby et al., 2008; Soontarapornchai et al., 2008], with more repeats leading to increased levels of expression [Tassone et al., 2000]. In terms of nuclear inclusions, animal models suggest that their size and prevalence accrue with age [Willemsen et al., 2003].

Of much concern are possible overlapping mechanisms between FXS and FXTAS. There is evidence of mitochondrial dysfunction in individuals with FXS [el Bekay et al., 2007] and in pre-mutation carriers both with and without FXTAS [Ross-Inta et al., 2010; Napoli et al., 2011]. Also, since a significant percentage (up to 40%) of those with FXS are mosaic, with some cells carrying the pre-mutation and some cells with the full mutation, the pathogenic mechanism of RNA toxicity seen in pre-mutation carriers may “reach across” to FXS because of cells carrying an unmethylated allele in those with mosaicism. There is one case report of a male with a high level of mosaicism who had significant deterioration in both motor and cognitive function beginning in his 60s [Hall et al., 2010] and another case of an unmethylated full mutation male with FXTAS [Loesch et al., 2011]. The Hall et al. case had both tremor and ataxia and cognitive decline and he received a diagnosis of Parkinson’s

disease. The Loesch et al. case also had alcoholism in addition to tremor and ataxia and he also demonstrated the MCP sign on MRI so he met the diagnosis of definite FXTAS even though he had a full mutation as described above. There have been similar case reports of rapid decline such as one highlighting a mosaic female who developed tremor and ataxia as well [Desai et al., 1990]. Her cognitive decline eventually developed into dementia with preliminary findings suggestive of amyotrophic lateral sclerosis (ALS). She was also noted to have developed intranuclear inclusions.

CELLULAR PATHWAYS

FMRP is typically known as a repressor of specific mRNA translation and protein synthesis within the synapses [Penagarikano et al., 2007], and is involved in a number of significant cellular processes. For example, a notable set of pathways affected by FMRP are group 1 metabotropic glutamate receptors (mGluR1 and mGluR5) [Bear et al., 2004], which are predominantly expressed on the surface of dendritic spines. Distinctively, mGluR1 is largely located in the cerebellum and hippocampus, while mGluR5 is more widely distributed throughout the brain except in the cerebellum [Bear, 2005]. Decreased FMRP leads to up-regulated downstream effectors of these mGluRs, and is associated with abnormal dendritic spine morphology suggestive of insufficient pruning of unnecessary synaptic connections during development and a lack of maturation [Bassell and Warren, 2008; Pfeiffer and Huber, 2009]. This, combined with their neuroanatomical location, suggests that mGluRs, and thus FMRP, play a major role in synaptogenesis and synaptic plasticity. Because these processes are vital for adult neurogenesis, dysregulation of mGluRs decreases long-term potentiation (LTP) in areas of the brain such as the neocortex [Wilson and Cox, 2007] and amygdala [Fendt and Schmid, 2002], negatively affecting both learning and memory. Increased levels of downstream effectors have also been shown to lead to long-term depression (LTD) of neural connections [Bassell and Warren, 2008; Pfeiffer and Huber, 2009]. Since they are widely dispersed throughout the brain and related to many of the physical and neuropsychological phenotypes observed in FXS, mGluRs have become a promising focal point for FXS targeted treatments. In fact, in animal models, administration of mGluR antagonists has corrected many clinical features that are observed in FXS [McBride et al., 2005; Yan et al., 2005; Tucker et al., 2006; de Vrij et al., 2008].

Metabotropic glutamate receptors (mGluRs) have also been associated with the amyloid precursor protein (APP), which is mainly expressed in neurons and dendrites and promotes synaptic formations in the developing brain [Akaaboune et al., 2000]. It is also important for cortical hyperexcitability and synaptic plasticity [Westmark and Malter, 2007; Westmark et al., 2010]. Excess proteolytic by-products of APP known as beta-amyloid ($A\beta$) peptides, however, are related with impaired synaptic function [Kamenetz et al., 2003] and characteristic plaques in Alzheimer's disease (AD). FMRP is known to repress APP translation by directly binding to APP mRNA [Westmark and Malter, 2007]. Therefore, a lack of FMRP leads to increased levels of APP. Moreover, studies show that elevated mGluR downstream effectors, by way of *FMR1* KO models or administration an mGluR activator, resulted in increased cellular APP levels (Westmark and Malter, 2007). A recent study by Sokol et al. [2011] elucidated that mGluR activity releases FMRP from APP mRNA, thus freeing it for translation [Sokol et al., 2011]. Ultimately, excess APP leads to enhanced

neuronal pruning and cell death [Nikolaev et al., 2009], as well as an overall deficiency in adult neurogenesis. Furthermore, increased APP provides more substrate for proteolytic cleavage it into A β peptides. Thus, a deficiency in FMRP may predispose an individual to AD in later life.

FMRP is involved in a variety of other signal-transduction cascades that are linked to LTD [Kim and Alger, 2010; Zhang and Alger, 2010]. It also regulates pathways that are involved in aging and cognition, especially mTOR (mammalian target of rapamycin, a protein kinase that integrates the input from upstream pathways for cell metabolism, protein synthesis, and transcription) [Hoeffler and Klann, 2010; Sharma et al., 2010; Tassone, 2010; Wang et al., 2010].

The study of the neurobiology of FXS is likely to teach us about molecular aspects of aging as it has regarding neurodevelopment. It should also provide useful models for targeting treatments for intellectual disabilities and for aging syndromes [Wang et al.,2010].

COGNITION AND AGING IN FXS

Cognitive and behavioral correlates of molecular variations in FXS (e.g., FMRP levels) have been studied rather extensively, but research about the long-term outcome in the geriatric population of FXS remains sparse [Utari et al., 2010].

Einfeld et al. [1999] carried out a 7-year follow-up study of 46 individuals with FXS from adolescence into young adulthood (mean age 22.4; SD 5.47 years). They found improvements in disruptive behavior (similar to patients with autism) but an increase in antisocial behavior. Declines in IQ scores have been documented in many males and females with FXS throughout childhood and into adolescence [Lachiewicz et al., 1987; Hagerman et al., 1989; Hodapp et al., 1991; Fisch et al., 1992, 1994; Wright Talamante et al., 1996; Fisch et al., 2002], but no study of more than 10 subjects has been conducted regarding IQ changes with aging into late adulthood in individuals with FXS. Clinically, it is thought that the IQ remains stable throughout adulthood but there are no data available to support this. In fact, Borghgraef et al. [2002] suggested that this is not the case.

Borghgraef et al. [2002] described a small 10-year follow-up study of 10 males with FXS with ages ranging from 33 years to 65 years. A significant overall IQ decline was documented on the McCarthy scales in three subjects, a significant decline in verbal abilities in five subjects, and a significant decline in performance abilities in two subjects. A decline was also seen in adaptive skills in three of seven subjects and an increase in one subject. They summarized that the declines were most remarkable in the verbal area with the use of language decreasing over time. Wiegers et al. [1993] also found IQ decline in 39 males with FXS ages 4–26 years. However, on a Dutch adaptive behaviors scale, the self-help skills improved with age, although the social skills did not; the latter were the lowest area of functioning [Wiegers et al., 1992]. These inconsistencies and limited body of literature demonstrate the need for further study of aging in adults with FXS.

IQ DECLINE

The first longitudinal follow-up study about IQ decline in FXS was published in 1987 [Lachiewicz et al., 1987]. Research in both male and female individuals with FXS [Dykens et al., 1989; Hagerman et al., 1989; Dykens et al., 1993; Brun et al., 1995; Wright Talamante et al., 1996; Hall et al., 2008, 2010] demonstrated IQ decline in a subgroup of males during childhood, but found that females were usually protected from significant IQ decline. Those with the highest IQs often experienced the greatest decline, suggesting that high functioning males may be most at risk for this decline [Hagerman et al., 1989; Wright Talamante et al., 1996]. In retrospect, this may be related to early toxicity from elevated mRNA in those who were mosaic (see studies of FXTAS). In support of this hypothesis is the finding of a very limited number of small FXTAS like inclusions in the study of three brains of individuals with FXS who had some level of mosaicism [Hunsaker et al., 2011]. No published study has focused on the effect of aging on IQ decline in later adulthood and the geriatric population with FXS.

AGING IN INDIVIDUALS WITH INTELLECTUAL DISABILITY AND AUTISTIC FEATURES

Patients with FXS have a number of autistic features and approximately 30% have autism [Rogers et al., 2001]. Individuals with FXS and autism spectrum disorders [Cummings et al., 2002] are characterized primarily by impairments in social skills and a deficit in communication skills [Kau et al., 2004; Kaufmann et al., 2004; Budimirovic, 2006]. Hernandez et al. demonstrated that, based on DSM-IV [American Psychiatric Association, 1994], autism is a stable diagnosis over time once it is present in boys with FXS aged 3–8 years [Hernandez et al., 2009]. Results from the ongoing London and South East Region Fragile X Syndrome Longitudinal Study (LASER_FRAXL) with a 10-year follow-up of boys initially aged 5–15 years show an increase in Childhood Autism diagnosis [WHO, 1992] from 30% to 60%, and for ASD conditions from 60% to 85% [Turk, 2011].

Individuals with autism or autism spectrum disorders [Cummings et al., 2002] without fragile X also have brain abnormalities similar to fragile X, including a large brain, Purkinje cell dropout, and sometimes a small cerebellum [Bauman and Kemper, 1985; Courchesne et al., 1988, 1994a, b; Bailey et al., 1998]. There have been few studies of aging in individuals with autistic features or autism, and no studies in the geriatric age group. In a study by Piven et al. [1996], the Autism Diagnostic Interview Revised (ADI-R) [Lord et al., 1994] was given to the parents of 38 high-functioning adolescents and adults with autism, ages 13–28 years. The ratings of current behavior were significantly less abnormal on all three domains than the retrospectively assessed lifetime scores from age 4. Similar results were replicated by Bolte et al. [2000] in 93 individuals with autism aged 15–37 years, and by Gilchrist et al. [2001].

Other studies of aging in individuals with autistic features or autism have also focused on adolescence to early or (at most) mid adulthood. Gillberg and Steffenburg [Gillberg and Steffenburg, 1987] found that behavioral problems increased in adolescence, similar to FXS [Hagerman, 2002], but that considerable improvement occurs in early adulthood; although

significant adaptive and social problems persist lifelong [Rumsey et al., 1985; Venter et al., 1992; Kobayashi and Murata, 1998; Seltzer et al., 2003]. An additional study followed a cohort of patients over 11 years and found improvements in self-care skills, communication skills, and educational achievements [Beadle-Brown et al., 2000]. The overall picture into mid-adulthood in individuals with autism spectrum disorders is one of gradual improvement, although there is significant stress in the family home where approximately 50% of the adults live [Seltzer et al., 2001]. The same type of stress in the parents, particularly the mothers, also occurs in families with FXS [Franke et al., 1996; Sobesky, 1996; Franke et al., 1998;]. Rates of anxiety and depression in mothers of individuals with FXS vary from 25% to 60% [Franke et al., 1998; Sobesky, 1996; Roberts et al., 2008; Rodriguez-Revengea et al., 2009]. The effects of aging on the brains of individuals with autism or FXS (or both conditions) are unknown.

FXTAS

Since FXTAS was discovered in 2001, most of the aging research in fragile X-associated disorders has focused on pre-mutation carriers, looking at the physical, behavioral, and cognitive phenotype [Amiri et al., 2008]. In an initial study, we reported on five elderly men with the fragile X pre-mutation [Hagerman et al., 2001]. These individuals presented with executive function deficits and generalized brain atrophy. All of these men had elevated mRNA levels and relatively normal levels of FMRP. These findings persuaded us to propose that it was perhaps the elevated mRNA levels that caused significant neurological and cognitive problems. In a subsequent study, we reported on 26 male subjects over 50 years of age with the pre-mutation [Jacquemont et al., 2003]. These men presented with short-term memory loss, executive function deficits, Parkinsonism, and general cognitive decline. Our research team has since reported similar findings in a larger sample [Grigsby et al., 2007; Leehey et al., 2007; Tassone et al., 2007; Brega et al., 2008; Seritan et al., 2008; Leehey et al., 2011]. While there is one report of FXTAS in an unmethylated male with the full mutation [Loesch et al., 2011], FXTAS has not been reported in those that are fully methylated. The theorized mechanisms for predisposition to dementia in the full mutation and premutation are thought to be different. For pre-mutation carriers, a “toxic gain-of-function” mechanism has been proposed, indicating a causative effect of excess mRNA on neurodegeneration [Hagerman et al., 2001; Hagerman and Hagerman, 2004a; Amiri et al., 2008]. On the other hand, Westmark and Malter [2007] described findings indicating that a lack of FMRP may be causative of neurodegeneration related to an Alzheimer like phenomenon in the full mutation, although Luo et al. [2010] demonstrated that FMRP is important for neurogenesis and that the lack of FMRP may have deleterious effects on aging in those with FXS because of a lack of neurogenesis [Luo et al., 2010].

CONCLUSION

Although there is extensive research about the neurobiological basis, phenotype, and behavioral features of FXS, the developmental trajectories and aging process for affected individuals remains widely unspecified and understudied. This lack of information limits the availability of planning support for caregivers and community agencies.

Males with FXS who have an inactive gene that is fully mutated and methylated are at risk for brain atrophy with aging because the absence of FMRP. Males with FXS who have an active or partially active gene may be at risk for FXTAS with aging because of the presence of mosaicism with features of an active gene and sometimes elevated mRNA. Females with the full mutation FXS typically have a higher IQ than full mutation males, but they still have a deficiency of FMRP, which may cause problems with aging similar to FXS males. However, they appear to be relatively protected from FXTAS since it seems to occur in a small minority of female carriers [Coffey et al., 2008; Rodriguez-Revenga et al., 2009] and it has never been reported in females with the full mutation.

FMRP is a critical protein for aging in all individuals and those with FXS may suffer significant problems with aging because of the lack of FMRP. However, aging in FXS is just beginning to attract attention, and further research is necessary to fully understand what subgroups of patients with FXS may have problems with aging and what the benefits of treatment may be. The use of new targeted treatments for FXS, including mGluR5 antagonists, GABA A and B agonists, minocycline and others may indeed have a beneficial effect on aging, but first the benefits in behavior and cognition need to be documented and these studies are currently in process [Berry-Kravis et al., 2009; Wang et al., 2010; Berry-Kravis et al., 2011; Jacquemont et al., 2011]. Hopefully, increasing knowledge about FXS and its developmental trajectory throughout adulthood will facilitate the development of targeted treatments, multidisciplinary, evidence-based interventions, and long-term support for affected adults and their caregivers.

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