



The SAGE Encyclopedia of Lifespan Human Development

Fragile X Syndrome

Contributors: Susan M. Rivera

Edited by: Marc H. Bornstein

Book Title: The SAGE Encyclopedia of Lifespan Human Development

Chapter Title: "Fragile X Syndrome"

Pub. Date: 2018

Access Date: April 10, 2018

Publishing Company: SAGE Publications, Inc.

City: Thousand Oaks,

Print ISBN: 9781506307657

Online ISBN: 9781506307633

DOI: <http://dx.doi.org/10.4135/9781506307633.n335>

Print pages: 899-901

©2018 SAGE Publications, Inc.. All Rights Reserved.

This PDF has been generated from SAGE Knowledge. Please note that the pagination of the online version will vary from the pagination of the print book.

Fragile X syndrome (FXS) is a neurodevelopmental disorder associated with a single-gene mutation on the X chromosome and represents a leading hereditary cause of intellectual disability. This entry reviews what is known, across the life span, in individuals with both FXS and the fragile X premutation.

Genetic Characteristics

The fragile X mental retardation 1 (*FMR1*) gene is located on the long arm of the X chromosome. Because FXS is an X-linked disorder, the phenotype (observable characteristics) in males is more severe than that of females, who have an extra copy of the X chromosome to compensate, but both sexes show lower cognitive functioning when compared to mental age-matched typically developing individuals. In individuals with the fragile X full mutation (FXS), there is an excess number (defined as greater than 200) of cytosine and guanine (CGG) repeats at the 5' promoter region of the gene. This number or more of CGG repeats results in a methylation, or shutting down, of production of the *FMR1* gene protein, called FMRP. FMRP is responsible for many important brain functions including dendritic spine formation and the establishment and maintenance of synaptic connections. Thus, a dramatic decrease or absence of FMRP can have significant consequences for brain and cognitive development. Intellectual disability is the primary phenotype of children and adults with FXS, although a profile of cognitive strengths and weaknesses has been documented. Areas of relative strength include vocabulary, long-term memory, and face and emotion discrimination. Weaknesses have been identified in visual memory, visual-spatial and visual-motor coordination, processing of sequential information, numerical processing, and inhibitory control. Comorbid conditions include autism spectrum disorders, attention-deficit/hyperactivity disorder, and anxiety disorders.

Spectrum of Involvement

Although for years research focused almost exclusively on the fragile X full mutation, which results in the medical condition known as FXS, recent investigations have resulted in an understanding of fragile X as a spectrum of involvement, to include individuals who have a number of CGG repeats (between 45 and 200) that is greater than is typical in the general population, but that does not result in intellectual disability. It is estimated that 1 in 260–813 males and 113–259 females worldwide are carriers of the fragile X premutation allele. These individuals, who are referred to as having the *FMR1* premutation, or as *premutation carriers*, are at increased risk of passing on the mutated form of the gene to their offspring in either the form of a premutation or a full mutation. Premutation carriers do not exhibit the intellectual disability that is seen in FXS but show evidence of social withdrawal and increased rates of mood and anxiety disorders. In addition, female premutation carriers are at risk of developing fragile X-associated premature ovarian insufficiency that can affect fertility, and male (and to a lesser extent, female) premutation carriers are at risk of developing fragile X tremor ataxia syndrome—a neurodegenerative disorder that occurs in approximately 30–40% of male carriers aged over 50 years. The principal features of fragile X tremor ataxia syndrome include intention tremor, cerebellar ataxia, Parkinsonism, autonomic dysfunction, and cognitive impairment. Although the pathogenic mechanism for FXS is decreased FMRP, in premutation carriers, it is thought to be atypically increased levels of *FMR1* messenger RNA (mRNA). When taking the entire spectrum into account, we can think of this as a dose–response mechanism, where across CGG repeat size, decreases in FMRP (which occur only at the high end of the premutation range and in the full mutation) and atypically increased *FMR1* mRNA

(occurring only in the premutation range) can be used to predict both brain responses and behavior.

Infancy

Much of the early work on very young children with FXS was done to assess their level of cognitive functioning with respect to developmentally matched typically developing peers. Indeed, it was traditionally the case, given subtle physical signs of FXS, that infants were often not identified until they were toddlers or preschoolers, when the lack of meeting developmental milestones was more obvious. This time frame for diagnosis is changing, and more and more individuals with FXS are being tested and identified as infants. In turn, more recent experimental work on infants with FXS, especially in the domains of visual processing and number discrimination, has identified brain pathways that are impaired, and relatively spared, in FXS. We now know that infants with FXS appear to have intact functions of the *ventral stream* of the brain (the visual pathway running through the temporal lobe of the brain, responsible for color and form identification) and that dysfunctions of the dorsal stream (the visual pathway running through the parietal lobe of the brain, responsible for motion perception and visually guided reaching) appear to be limited to those visual events that implicate attentive tracking mechanisms (i.e., the ability to keep track of objects moving through space and time). Likewise parietal lobe functions related to spatial visual attention (e.g., being able to recognize objects in the periphery) appear to be spared in FXS, whereas those related to temporal visual attention (e.g., being able to see things flickering at a fast rate) are affected.

With respect to number discrimination, it has been shown that certain elemental building blocks of number such as detecting ordinal relations between objects (i.e., recognizing which came first, second, or third) and small number discrimination (e.g., recognizing that two is more than three) are impaired, whereas others such as large number magnitude estimation (e.g., recognizing that 8 is more than 16) are intact. This pattern fits with the above-referenced data on visual processing in that, despite robust findings of impaired numerical abilities in FXS in later development, it is more specifically the numerical processing abilities that are reliant on object-tracking mechanisms that appear to be developmentally impaired.

There is relatively far less work done on very young children with the fragile X premutation. This fact is largely because those infants must be identified either through cascade testing (when a known family member has carrier status or the full mutation, and other family members are tested) or through newborn screening trials. In one published study of infants with the fragile X premutation, testing in the typically developing range of cognitive functioning found similar low-level visual processing deficits (corresponding to attentive tracking functions of the dorsal stream) as with infants with FXS. This finding is perhaps at first surprising, given that these infants with the FX premutation show no intellectual disability; however, it speaks to the concept of FX as a spectrum of involvement, where a smaller *dose* of *FMR1* gene dysfunction results in a low-level visual deficit that may potentially impact function by causing the developing system to *compensate* in unknown ways.

Childhood and Adolescence

Children and adolescents with FXS have receptive and expressive language delays and a marked pattern of impairment in math and spatial reasoning. Also prominent in the profile of these individuals is a pattern of social avoidance, anxiety, autism symptomology (the severity

of which improves with age), attention disorders, and hyperactivity.

Brain imaging research, particularly that done in girls with FXS who show a range of protein expression of the *FMR1* gene, has shown that for cognitive domains (e.g., arithmetic and working memory) more atypical brain activation is related to decreased FMRP expression, clearly indicating the dose–response mechanism of the *FMR1* gene. This *dose–response* is also evident in a brain imaging study of girls with FXS, combined with girls and boys who show mosaicism for FXS (a condition in which either an individual has some cells that have a full mutation and some cells that have a premutation, or in which all cells have a full mutation, but the methylation pattern is not the same in all cells). Brain responses to fearful faces was examined, and in this group of individuals on the fragile X spectrum, all of whom had some level of FMRP production, fear-specific amygdala activity was positively related to FMRP levels.

Far less work has been done examining children and adolescents with the fragile X premutation. Although their cognitive profiles tend to be in the typical range, patterns (relative to the general population) of increased attention deficits (including diagnoses of attention-deficit/hyperactivity disorder), increased autism symptomology, and higher rates of anxiety disorders have been documented.

Adulthood and Aging

In adults with FXS, in which varying levels of intellectual disability are seen, the documented cognitive profile has included relative weaknesses in abstract reasoning and overall executive control (including verbal short-term memory, problem-solving, and planning) along with relatively stronger performance on measures of visuo-perceptual recognition and vocabulary. Psychiatric issues that are prevalent in childhood, including high levels of anxiety, continue to be present for full mutation individuals into adulthood.

There is now a large and growing literature on adults with the fragile X premutation. Some of this work has focused on individuals who are younger adults and asymptomatic for the neurodegenerative disease FXTAS. For these young, asymptomatic adults, who have overall IQs in the normal (and sometimes above normal) range, only subtle weaknesses in cognitive function have been documented. These include inhibitory control, orienting of spatial attention, motion perception, visuo-motor coordination, and visuo-spatial working memory. Although these deficits are detectable in premutation carriers, they represent a much milder form than those seen in FXS and typically have little, if any, effect on their everyday cognitive functioning.

Using magnetic resonance imaging methodology, a number of studies have shown differences in brain activation in premutation carriers, including in the domains of numerical magnitude estimation, temporal working memory, memory retrieval (recall) and encoding, and processing of emotional faces. In many cases, this altered neural activity is correlated with molecular measures such as CGG repeat size, *FMRP* expression, and elevated levels of *FMR1* mRNA, or with psychiatric symptoms.

Other investigations in adults with the premutation have focused on individuals diagnosed with the neurodegenerative disease FXTAS. Much work has focused on structural differences in the brains of those with the disease, showing patterns of cortical and subcortical gray matter loss and declines in white matter connectivity (in motor fiber tracts, cerebellar and medial temporal areas of the brain). Behavioral and a few functional (i.e., task based) brain

imaging studies of individuals with FXTAS have documented a pattern of impairment on executive function (including impulse control, flexible thinking, working memory, planning, and organization), information processing speed, and fine motor control. In many cases, these findings in individuals with FXTAS are also accompanied by results that show dysfunction worsens as the disease progresses and that are often modulated by *FMR1* gene expression indices such as elevated mRNA levels.

See also [Anxiety](#); [Autism Spectrum Disorders](#); [Developmental Disturbances](#); [Executive Functioning](#); [Intellectual Disabilities](#)

- Fragile X syndrome
- intellectual disability
- mutation
- syndromes
- ataxia
- genes
- brain

Susan M. Rivera

<http://dx.doi.org/10.4135/9781506307633.n335>

10.4135/9781506307633.n335

Further Readings

Bourgeois, J. A., Coffey, S. M., Rivera, S. M., Hessler, D., Gane, L. W., Tassone, F., ... & Hagerman, R. J. (2009). A review of fragile X premutation disorders: Expanding the psychiatric perspective. *Journal of Clinical Psychiatry*, 70(6), 852–862. doi:10.4088/JCP.08m04476

Farzin, F., Rivera, S. M., & Whitney, D. (2011). Resolution of spatial and temporal visual attention in infants with fragile X syndrome. *Brain*, 134(11), 3355–3368. doi:10.1093/brain/awr249

Hagerman, R., Hoem, G., & Hagerman, P. (2010). Fragile X and autism: Intertwined at the molecular level leading to targeted treatments. *Molecular Autism*, 12. doi:10.1186/2040-2392-1-12

Kim, S. Y., Burris, J., Bassal, F., Koldewyn, K., Chattarji, S., Tassone, F., ... & Rivera, S. M. (2012). Fear-specific amygdala function in children and adolescents on the fragile X spectrum: A dosage response of the *FMR1* gene. *Cerebral Cortex*, 11. doi:10.1093/cercor/bhs341