

13

FRAGILE X SYNDROME

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Fragile X syndrome (FXS) is the most common inherited cause of mental retardation, occurring in approximately 1 in 3,200 individuals in the general population (Sherman, 2002). It is also a significant cause of autism; approximately 3–6% of individuals with autism will have the fragile X mutation (Hagerman, 2002b). FXS is caused by an expansion of a trinucleotide repeat (cytosine–guanine–guanine, or CGG), which occurs at the front end of the fragile X mental retardation 1 (*FMR1*) gene. This gene is at the bottom end of the X chromosome, at Xq27. In cytogenetic studies, when the appropriate tissue culture medium is used, a fragile site will appear at this location. Since 1991, diagnostic DNA testing has been available, which demonstrates the expansion of the CGG repeat. Unaffected individuals normally have fewer than 40 repeats. Individuals carrying a premutation, who are usually cognitively unaffected, have between 55 and 200 CGG repeats. Individuals significantly affected by FXS have a full mutation, which is considered to be more than 200 CGG repeats. When the premutation is passed from father to daughter, it remains a premutation. However, when a premutation is passed to the next generation by a female, it often expands to a full mutation. Therefore, most mothers of children with FXS have the premutation.

We now take a genomics approach to understanding the great variability that can occur in both children and adults affected by this syndrome. The *FMR1* gene normally produces a protein, FMRP, which is a regulator for the translation of many other gene messages (messenger RNAs, or mRNAs). When FMRP is absent or deficient, as in individuals with the full mutation, both over- and undertranslation of other gene messages occur. There can also be significant variability within the expression of the *FMR1* gene and levels of FMRP. Mosaic patterns can occur, in which some cells have the premutation and other cells have the full mutation. Cells with the premutation are producing significant levels of FMRP, so that individuals with mosaicism are typically less affected than individuals with the full mutation who are not producing any FMRP (Loesch et al., 2003a, 2003b; Loesch, Bui, et al., 2003; Merenstein et al., 1996). Individuals carrying the premutation have recently been shown to produce elevated mRNA levels from the *FMR1* gene, ranging from 2 to 10 times normal levels, and to produce varying levels of FMRP. Elevated mRNA levels are now thought to cause central nervous system (CNS) toxicity over time, particularly in older males with the premutation; this results in the development of the fragile-X-associated tremor ataxia

syndrome (FXTAS), described below (Hagerman et al., 2001; Jacquemont et al., 2003). The discovery of FXTAS has led to a new appreciation of problems associated with aging in individuals with the FMR1 mutation.

Our aim in this chapter is to describe the physical, behavioral, and cognitive phenotypes of individuals affected by the FMR1 mutation in adulthood. Although our primary focus is on those with the full mutation, we also discuss those with the premutation. Finally, we address treatment issues.

PHYSICAL PHENOTYPE

General Physical Characteristics

Few well-controlled studies exist regarding aging in individuals with FXS. The connective tissue abnormalities found in children (flat feet, hyperextensible finger joints, double-jointed thumbs) tend to be less dramatic in adults, because the ligaments tighten with age. However, occasional joint dislocations, a higher frequency of hernias, and development of mitral valve prolapse continue as manifestations of atypical connective tissue. Gastroesophageal reflux may also continue to be a problem in adolescents and adults with FXS, and may be the etiology of feeding and behavior problems (Hagerman, 2002b). Individuals should be closely monitored for both acute and serous otitis media (middle-ear infections), which again may present as irritability and behavioral changes in nonverbal individuals with FXS. Strabismus is common in children with FXS, and this problem will often persist into adulthood without treatment. Adolescents and adults with FXS need to be monitored for late-onset seizures as well. Overall, about 20% of individuals with FXS have seizures, most commonly generalized and complex partial seizures (Musumeci et al., 1999). Macroorchidism is the most remarkable physical feature in male adolescents or adults with FXS. It begins to develop at age 8 or 9 years, and the testicles reach their peak in size by age 16 or 17 years. Macroorchidism can be documented by a testicular volume of 30 ml or larger, and it occurs in 80–90% of adult males with FXS (Hagerman, 2002b).

A long face and/or prominent ears occur in the majority of adult individuals with FXS (see Figure 13.1), but approximately 30% may not have either feature. The lack of typical features should not preclude FMR1 DNA testing. This testing should be done for any individual who presents with mental retardation or autism of unknown etiology.

Neuroimaging Findings

Early neuroimaging studies of FXS found significant ventriculomegaly in approximately 40% of children and adults with the syndrome (Musumeci et al., 1991; Wisniewski, Segan, Mizejeski, Sersen, & Rudelli, 1991). Reiss, Mazzocco, Greenlaw, Freund, and Ross (1995) confirmed this finding by documenting an inverse correlation between the size of the ventricles and IQ, and a positive correlation with age. As patients aged, the size of the ventricles increased, although this was only followed into adolescence and early adulthood. Reiss and colleagues have suggested that mild frontal and parietal atrophy occurs with age, and have hypothesized an enhancement of apoptosis in FXS (Reiss, Lee, & Freund, 1994; Reiss, Mazzocco, et al., 1995).

An important finding that has been consistently observed in FXS is a smaller cerebellar vermis in both males and females than in nondisabled controls, and in the males than in age-matched developmentally disabled controls (Mostofsky et al., 1998; Reiss, Aylward,

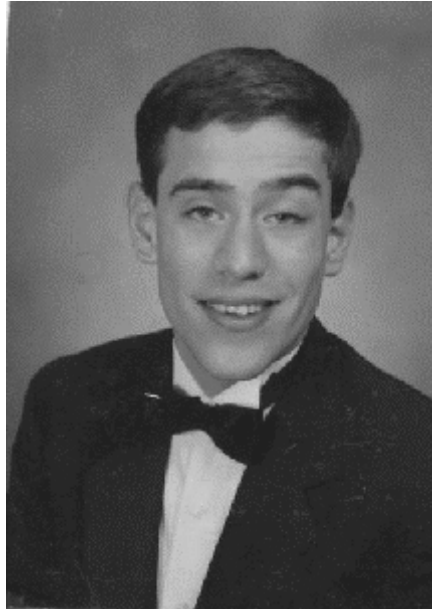


FIGURE 13.1. A 25-year-old male with FXS. Note the long face, mildly prominent ears, and ptosis of the left eye.

Freund, Joshi, & Bryan, 1991; Reiss, Freund, Tseng, & Joshi, 1991). The size in females appears to be intermediate between those of the males with FXS and controls, and the decrease correlates inversely with the activation ratio in females (Mostofsky et al., 1998; Reiss, Freund, et al., 1991). Mostofsky and colleagues (1998) found significant correlations between the size of the posterior cerebellar vermis (lobules VI–X) on the one hand and IQ, executive function, and visual–motor coordination measures on the other, demonstrating the importance of this structure for many aspects of cognition. Mazzocco and colleagues (1997) studied 28 school girls with FXS and found that the parental ratings of the frequency and severity of autistic behaviors, particularly social communication impairments and stereotypies, correlated inversely with the size of lobules VI and VII of the posterior cerebellum. These mannerisms, part of the behavioral phenotype of FXS, are uniquely correlated with the CNS structural changes and vary with the severity of these changes.

In contrast to the cerebellar findings, Reiss, Lee, and Freund (1994) reported that the right and left hippocampal volumes were increased by about 20% in both males and females with FXS (age range 6–27 years). In a follow-up study of five boys and girls with FXS, the hippocampal enlargement was less dramatic (7% left and 13% right, compared to controls) (Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997). Reiss, Mazzocco, and colleagues (1995) have also reported an increase in the volume of the caudate in both males and females with FXS compared to controls, and an increase in the volume of the thalamus in females compared to sex- and age-matched controls.

Typically, individuals with FXS have large heads and brains in childhood compared to controls, both by clinical measurement and in magnetic resonance imaging (MRI) studies (Butler, Brunschwig, Miller, & Hagerman, 1992; Hagerman, 2002b; Reiss, Abrams, Greenlaw, Freund, & Denckla, 1995; Schapiro et al., 1995). Jakala and colleagues (1997) studied 10 males with fragile X (mean age 29 ± 11 years) and 10 females with fragile X (mean age 34 ± 15 years). Both individuals with the full mutation and persons with the

premutation were included in this study. The researchers found that although the males with the full mutation had larger brains than controls, the size of their hippocampus when normalized for brain size did not differ from that of males with a premutation or controls. In addition, they found that those with a full mutation had enlargement of the ventricles and perivascular spaces, atrophy relative to age, white matter changes and perivascular changes in the temporal regions, and subjectively atypical morphology of the hippocampus compared to those with the premutation. They also found that the length of the CGG repeat in males with the full mutation correlated positively with brain volume and negatively with Verbal and Performance IQ. The study by Jakala and colleagues emphasizes the importance of the MRI in detecting abnormalities in adults with fragile X.

In a study of children and adolescents with FXS, Reiss, Kazazian, and colleagues (1994) found that the size of the superior temporal gyrus decreased more significantly with age in males with FXS than in controls. Kates and colleagues (2002) also found smaller temporal lobes in boys with FXS than in nondisabled controls. In addition, the Kates and colleagues study separated boys with the fully methylated full mutation ($n = 21$) from boys with a mosaic pattern ($n = 12$), and found that those with mosaicism had significant reductions in the volume of parietal white matter, compared to boys with the full mutation. This last result is particularly germane to the RNA toxic “gain-of-function” hypothesis that is described below and thought to be responsible for FXTAS, since parietal volume loss is particularly evident in individuals with the premutation and FXTAS. Thus it is possible that the reduced parietal volumes in boys with mosaicism is a very early sign of neurological involvement as a consequence of continued production of *FMR1* mRNA.

Additional neuroimaging modalities (e.g., single-photon emission computed tomography) have shown hypofunction of the frontal-subcortical regions in FXS. Hjalgrim and colleagues (1999) studied five males and one female with FXS and found hypoperfusion of the right frontal lobe and right thalamus compared to nondisabled controls. Guerreiro and colleagues (1998) reported frontal hypoperfusion in six patients with FXS, and parietal or cerebellar hypoperfusion in two of these patients. Functional MRI studies have shown a decrease in activation of the neural network on math tasks (Rivera, Menon, White, Glaser, & Reiss, 2002) and working memory tasks, which correlates with the deficit in FMRP (Menon, Kwon, Eliez, Taylor, & Reiss, 2000). Although the sophistication of the neuroimaging studies has advanced dramatically in the last few years, there has not been a focus on aging or longitudinal studies in FXS.

BEHAVIORAL PHENOTYPE

The behavioral phenotype of FXS in childhood includes hyperactivity and hyperarousal to sensory stimuli (Hagerman, 2002b; Miller et al., 1999). The hyperactivity typically improves with age and is usually not a problem in adulthood. However, the hyperarousal often continues into adulthood and is manifested by mood instability and outburst behavior. Approximately 30% of males have problems with physical or verbal aggression (Hagerman, 2002b). Treatment options include counseling, described in Epstein, Riley, and Sobesky (2002) and Braden (1997), and medications, described below.

Approximately 30% of individuals with FXS have autism (Bailey, Hatton, Skinner, & Mesibov, 2001; Rogers, Wehner, & Hagerman, 2001). Some of these individuals with autism are avoidant of social interactions; others are interested in people, but their significant sensory integration problems and severe anxiety interfere remarkably with social interactions. Those individuals with autism and FXS together have a lower IQ and more

severe receptive and expressive language deficits than those with FXS alone (Bailey et al., 2001; Philofsky, Hepburn, Hayes, Hagerman, & Rogers, 2004; Rogers, Wehner, & Hagerman, 2001). Additive effects from genes that interact with FMRP may lead to autism in FXS, and this is an area that is being intensively researched. Einfeld, Tonge, and Turner (1999) carried out a 7-year follow-up study of 46 individuals with FXS from adolescence into young adulthood (mean age 22.4 ± 5.47 years), and found improvements in disruptive behavior but an increase in antisocial behavior. This finding is similar to the longitudinal studies of adults with FXS by Das and Turk (2002), which found a dramatic increase in symptoms of autism as these individuals aged. Over 60% met diagnostic criteria for autism in adulthood, with a significant increase in reclusive behavior and echolalic language with age. These investigators used the Diagnostic Instrument for Social and Communicatory Disorders to evaluate behavioral problems and autism. A more detailed analysis of psychopathology is needed to clarify and expand these early findings.

In general, psychopathology in aging, intellectually disabled adults remains understudied. A few studies suggest that the intellectually disabled population of children and adults suffers from much higher rates of psychopathology than the general population (Einfeld & Tonge, 1996; Hardan & Sahl, 1997; Taylor, Hatton, Dixon, & Douglas, 2004). One study, using a structured screening instrument, estimated the prevalence of psychotic disorders at 10.2% (Taylor et al., 2004). Most researchers, however, recognize that these screening instruments overestimate the prevalence of psychopathology in disabled populations. Therefore, any attempts to characterize the prevalence of psychopathology in FXS require a reference population with similar intellectual abilities. Only limited anecdotal information is available regarding clinical experience in older individuals who have FXS.

COGNITIVE PHENOTYPE

Declines in IQ scores have been documented in the majority of males and in some females with FXS throughout childhood and into adolescence (Fisch et al., 1992; Fisch, Simensen, Arinami, Borghgraef, & Fryns, 1994; Fisch, Simensen, & Schroer, 2002; Hagerman et al., 1989; Hodapp, Dykens, Ort, Zelinsky, & Leckman, 1991; Lachiewicz, Gullion, Spiridigliozzi, & Aylesworth, 1987; Wright-Talamante et al., 1996), but no study of more than 10 patients with FXS has been conducted regarding IQ changes with aging into late adulthood. It was formerly thought that IQ remains stable throughout adulthood, but the limited work of Borghgraef and colleagues (2002) suggests that this is not the case. Borghgraef and colleagues presented a 10-year follow-up study of 10 males with FXS, whose initial ages ranged from 33 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. Borghgraef and colleagues summarized that the declines were most remarkable in the verbal area, with the use of language decreasing over time. Detailed molecular data, including the percentage of methylation and mRNA levels, were not available. These investigators reported only that 9 of the 10 patients had a full mutation, and that the remaining patient had a premutation but also had mental retardation.

Wieggers, Curfs, Vermeer, and Fryns (1993) also found IQ declines in 39 males with FXS (initial ages 4–26 years). However, on a Dutch adaptive behaviors scale, self-help skills improved with age, although the social skills did not; the latter constituted the lowest area

of functioning. This emphasizes the problems of social relatedness in FXS and demonstrates the need for further study in aging individuals.

CHARACTERISTICS OF INDIVIDUALS CARRYING THE FRAGILE X PREMUTATION

Although early studies demonstrated the absence of intellectual deficits in individuals with the fragile X premutation (Mazzocco, Pennington, & Hagerman, 1993; Reiss et al., 1993), these studies were carried out typically on mothers who had children with FXS. More recently, some young children with the premutation have been found with cognitive deficits and autism spectrum disorders (Aziz et al., 2003; Goodlin-Jones, Tassone, Gane, & Hagerman, 2004; Tassone, Hagerman, Chamberlain, & Hagerman, 2000), suggesting that some individuals with the premutation may be at risk for developmental problems. The study of these patients led to the discovery of elevated mRNA levels in patients with the premutation (Tassone, Hagerman, Chamberlain, & Hagerman, 2000; Tassone, Hagerman, Taylor, Gane, et al., 2000). Subsequently, older men with the premutation who had grandchildren with FXS were found to have neurological problems, including intention tremor and ataxia (Hagerman et al., 2001). Further evaluation of these grandfathers demonstrated the same phenotype, which includes not only the tremor and ataxia, but a “stocking distribution” neuropathy in the lower extremities, cognitive deficits that begin as memory problems, autonomic dysfunction (including hypertension and impotence), and brain atrophy on MRI (Jacquemont et al., 2003; Jacquemont, Farzin, et al., 2004).

Jacquemont, Hagerman, and colleagues (2004) completed an epidemiological study to better understand the prevalence of FXTAS in older males and females with the premutation; this study was conducted in the state of California and involved 192 families. An increased incidence of tremor and ataxia was seen in males over age 50 carrying the premutation, compared to controls and to females carrying it. Among males with the premutation, 17% of those in their 50s were affected with tremor and ataxia, 38% of those in their 60s, 47% of those in their 70s, and 75% of those in their 80s (Jacquemont, Hagerman, et al., 2004). This study has dramatically raised awareness regarding FXTAS around the world, leading to the initiation of many other screening studies among neurological populations with movement disorders. Many children are now being diagnosed with FXS after their grandfathers are diagnosed with FXTAS. This wide recognition of FXTAS has led to the identification of rare females with FXTAS, although none have experienced dementia (Hagerman, Leavitt, et al., 2004). Perhaps the extra X chromosome and/or hormonal differences protect the females generally from FXTAS and dementia.

Older males with FXTAS show signs of dementia as well as tremors and ataxia. The neuroradiological sign most closely associated with FXTAS is a white matter change, manifested by hyperintensities on T2-weighted imaging in the middle cerebellar peduncles (Brunberg et al. 2002). In addition, there are findings characteristic of periventricular and subcortical white matter disease (Brunberg et al., 2002; Greco et al., 2002). Also, FXTAS is associated with significant brain atrophy; one study demonstrated significant differences in brain size, in addition to the white matter changes, in individuals with the premutation and FXTAS ($n = 17$), compared to age-matched controls (Brunberg et al., 2002). The presence of eosinophilic intranuclear inclusions has been documented throughout the cerebrum, with the highest density in the hippocampus, followed by frontal and temporal regions (Greco et al., 2002). A total of 10 brains of males who have died from FXTAS have been studied. All of these brains possessed numerous inclusions. Preliminary antibody studies

have demonstrated that these inclusions are tau-negative, synuclein-negative, and ubiquitin-positive (Hagerman & Hagerman, 2004a, 2004b).

Patients with the fragile X premutation and FXTAS have psychiatric problems, including irritability, anxiety, outbursts, and delusional thinking (Hagerman & Hagerman, 2004a; Jacquemont et al., 2003; Jacquemont, Farzin, et al., 2004), in addition to tremor and ataxia. Elevated mRNA levels have been documented in those carrying the premutation, with a positive correlation between the size of the premutation and the level of mRNA (Tassone, Hagerman, Chamberlain, & Hagerman, 2000; Tassone, Hagerman, Taylor, Gane, et al., 2000; Tassone, Hagerman, Taylor, Mills, et al., 2000). These findings have led to the hypothesis of an RNA toxic “gain-of-function” model, in which the elevated mRNA leads to sequestration of protein, important for neuronal function. The mRNA and the sequestered proteins form inclusions in neurons and astrocytes. This process eventually leads to enhanced cell death and brain atrophy. The toxic RNA gain-of-function model is similar to myotonic dystrophy (Hagerman & Hagerman, 2004b). It is hypothesized that the toxic gain-of-function mechanism is also leading to enhanced psychopathology in individuals with the premutation and elevated mRNA. Inclusions have not been detected in neuropathological studies of individuals with the full mutation who have FXS (Hinton, Brown, Wisniewski, & Rudelli, 1991; Rudelli et al., 1985; Sabaratnam, 2000).

INTERVENTIONS

The treatment of both children and adults with FXS involves multimodality interventions. Those who are in an educational setting require the services of special education professionals, including speech and language pathologists, occupational therapists, and special education teachers. Whenever possible, inclusion in a regular classroom is helpful for children with FXS because they imitate the behavior of the children who surround them, and nondisabled models can be very beneficial. Likewise, inclusion of adults in supervised settings that provide them with typical social and language models is important. The services of a psychologist to provide behavioral interventions and family counseling can also be extremely helpful, and descriptions of specific behavioral intervention programs have been published (Braden, 2002; Epstein, Riley, & Sobesky, 2002).

Both children and adults with FXS can be extremely sensitive to sensory stimuli, including visual, auditory, tactile, and olfactory stimuli in their environment. They can be easily overwhelmed in a crowded setting such as a shopping mall or concert, and sometimes such stimuli can precipitate a behavior outburst. Counseling in childhood and adulthood can help individuals learn calming techniques for the autonomic dysregulation that occurs in overstimulating situations. In addition, the use of medication can be quite helpful in calming behavior, decreasing aggression, decreasing anxiety, stabilizing mood, and improving attention.

The use of stimulant medication has demonstrated efficacy in children with FXS (Hagerman, Murphy, & Wittenberger, 1988). Stimulant medication is usually not needed in adulthood, because hyperactivity improves over time. Occasionally stimulants can be useful for impulsivity in adulthood. Clonidine can also be utilized to calm behavior and decrease aggression in both children and adults. Clonidine and guanfacine are alpha-2-adrenergic agonists, which also lower high blood pressure (this is often a helpful side effect in adults with FXS). Clonidine is also available as a patch preparation (Catapres-TTS-1, 2, or 3) (Hagerman, 2002a).

The most serious problem in adult behavior is intermittent aggression. This can be related to anxiety or sensory overstimulation, although there often seems to be a component of mood instability, which can exacerbate the aggression or outburst episodes. The anxiety can be treated by a selective serotonin reuptake inhibitor (SSRI), but approximately 20% of patients with FXS can have significant activation, leading to more aggression. Citalopram is the least activating of the SSRIs and can be often efficacious for decreasing anxiety (Hagerman, 2002a). Often adults with FXS who have problems with aggression will benefit from an atypical antipsychotic medication, such as risperidone or aripiprazole. This medication may be helpful in stabilizing mood in addition to decreasing psychotic thinking, which may be a problem for approximately 10% of individuals with FXS. Additional mood stabilizers include anticonvulsant medications, such as valproic acid, carbamazepine, or oxycarbazone. Older mood stabilizers (e.g., lithium) can also be helpful in patients with FXS.

Sleep disturbances are often a problem in childhood and occasionally in adulthood. The use of melatonin, a natural sleep hormone that can be purchased over the counter, is efficacious in approximately 50% of children with FXS and can also be helpful in adults. An alternative to melatonin would be clonidine at bedtime.

Recent studies regarding the genomic effects of the lack of FMRP have demonstrated that there is enhanced long-term depression (LTD) of synaptic connections, particularly in the hippocampus, related to enhanced stimulation of the group 1 metabotropic receptors (particularly the mGluR5 receptor). This receptor leads to protein synthesis that controls LTD at the synapse. This particular protein synthesis process is regulated by FMRP. When FMRP is absent, LTD is enhanced, which leads to the weak and immature synapses typically seen in fragile X neuropathology studies (Bear, Huber, & Warren, 2004). Research is in process to develop mGluR5 antagonists that will be a specific intervention for individuals with FXS. One available mGluR5 antagonist, MPEP, has been shown to reverse some symptoms of FXS (including seizures and cognitive deficits) in the knockout mouse model (Bauchwitz, personal communication, April 2004). The enhanced LTD in FXS leads to a depletion of AMPA receptors, another glutamate receptor system important for cognition. Experimental ampakine medication, which enhances AMPA receptor activity and stimulates glutamate systems in the brain, is currently being tested in adult individuals with FXS at the University of California–Davis and at Rush University Medical Center in Chicago. Results are not yet available regarding the efficacy of these new medications, but the future looks bright for specific psychopharmacological interventions that will be generally available for both children and adults with FXS.

Families identified as having a child or adult member with FXS should be referred to the National Fragile X Foundation at (800) 688-8765, so that they can receive further parent-oriented information and information to disseminate to the professionals working with the individual with FXS. They can also be linked to parent support groups throughout the United States and internationally. Information is also available and can be downloaded from the National Fragile X Foundation website at www.fragilex.org.

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