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The Fragile X Mental Retardation 1 Gene (*FMR1*): Historical Perspective, Phenotypes, Mechanism, Pathology, and Epidemiology

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Abstract

Objectives—To provide an historical perspective and overview of the phenotypes, mechanism, pathology, and epidemiology of the fragile X-associated tremor/ataxia syndrome (FXTAS) for neuropsychologists.

Methods—Selective review of the literature on FXTAS.

Results—FXTAS is an X-linked neurodegenerative disorder of late onset. One of several phenotypes associated with different mutations of the fragile X mental retardation 1 gene (*FMR1*), FXTAS involves progressive action tremor, gait ataxia, and impaired executive functioning, among other features. It affects carriers of the *FMR1* premutation, which may expand when passed from a mother to her children, in which case it is likely to cause fragile X syndrome (FXS), the most common inherited developmental disability.

Conclusion—This review briefly summarizes current knowledge of the mechanisms, epidemiology, and mode of transmission of FXTAS and FXS, as well as the neuropsychological, neurologic, neuropsychiatric, neuropathologic, and neuroradiologic phenotypes of FXTAS. Because it was only recently identified, FXTAS is not well known to most practitioners, and it remains largely misdiagnosed, despite the fact that its prevalence may be relatively high.

Keywords

Fragile X tremor ataxia syndrome; FXTAS; Fragile X syndrome; cognition; executive function; trinucleotide repeat expansion; tremor; ataxia

Introduction

The fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disease with a progressive cerebellar movement disorder and a pattern of cognitive deficits that is consistent with predominantly cerebellar and white matter pathology. FXTAS was unknown

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until 1999, when it was identified in the course of a study of the extended families of individuals with fragile X syndrome (Hagerman et al., 2001).

Fragile X Syndrome (FXS) is the most common inherited cognitive developmental disability, well-known as a cause of significant neuropsychological and behavioral pathology, including features of autistic spectrum disorder (ASD). Both FXS and FXTAS are caused by mutations of the fragile X mental retardation 1 gene (*FMR1*), but they are distinctly different disorders, with onset at either end of the life span. FXS is present in earliest childhood, whereas the first signs of FXTAS typically appear around the age of 60 (Jacquemont, Hagerman, Leehey, et al., 2003). Although they have much in common, the differences between FXS and FXTAS are clear-cut. The primary similarity is the type of genetic mutation that leads in some cases to the early-onset developmental syndrome, and in other cases to the late-onset movement disorder. In a very small percentage of cases, both may be observed in the same individual (Santa Maria et al., 2013).

The focus of this review is on the phenotypes, genetics, neuropathology, and epidemiology of FXTAS, which, despite a relatively high prevalence, is unfamiliar to neuropsychologists, and to many neurologists who do not specialize in movement disorders. As a consequence, even 17 years after its discovery, the diagnosis of FXTAS is often missed. Therefore, the purpose of this paper is to clarify the different fragile X-related disorders, and to address the epidemiologic, genetic, and other factors that can facilitate diagnosis, treatment, management, and appropriate referral for genetic counseling. The paper begins with a brief discussion of FXS, as it was the first disorder associated with the relevant gene.

Fragile X Syndrome (FXS)

Fragile X syndrome, which has its onset in earliest development, tends to involve moderate to severe intellectual deficits, especially among males, although a small percentage of boys and men with FXS shows mild impairment of general intellect, often in association with certain specific cognitive deficits such as dyscalculia (e.g., Grigsby et al., 1987). On the other hand, a pattern of relatively mild cognitive impairment is characteristic of affected females, a majority of whom have a low average or borderline IQ (Cronister et al., 1991; de Vries et al., 1996) and specific cognitive deficits, including executive function disorders, dyscalculia, dysgraphia, and constructional dyspraxia (Grigsby et al., 1990). Psychiatric disorders are prevalent in FXS, including autistic spectrum behaviors (affecting about 50% to 65% of males, and about 20% of females) and attention deficit hyperactivity disorder (ADHD in up to 80% of males and about 30% of females) (Garber et al., 2008; Hagerman & Harris, 2008; Hatton et al., 2006; Hessel et al., 2005; Rogers et al., 2001). Shyness, anxiety, and depression are common (Cordeiro, Ballinger, Hagerman, Hessel, 2011; Hessel, Dyer-Friedman, Glaser, 2001; Hessel, Glaser, Dyer-Friedman, 2006; Yu & Berry-Kravis, 2014).

FXS was probably first identified in 1943 by J.P. Martin and J. Bell (Opitz et al., 1984; Richards et al., 1981). Their paper discussed two generations of a family in which 11 males had significant cognitive impairment. Because of the differences observed between males and females with respect to penetrance and expression, Martin and Bell concluded that the disorder was associated with “a sex-linked recessive gene.” However, they didn’t understand

the sex-linkage, and hypothesized that “some controlling factor caused suppression of the disease” in the two brothers who were thought to have been the source of the disorder, and suggested that two females were affected because, in their case, “the causal gene was incompletely recessive.” A somewhat similar pattern of inheritance was subsequently reported by other authors regarding apparently sex-linked developmental disorders (e.g., Renpenning et al, 1962), who considered FXS a “sex-linked recessive” condition (p. 956). Until the 1990s, precise genetic diagnoses were not yet possible, and hence it was necessary to rely on the clinical features of syndromes that might show considerable variability, often with little more to go on than the presence of an ill-defined cognitive developmental disability.

The Responsible Gene: *FMR1*

The discovery by Lubs (1969) of the Fragile X mental retardation 1 gene (*FMR1*) brought some clarity to the genetics of the fragile X. Lubs obtained data on three generations of a family in which four males had significant intellectual disability. Examining the chromosomes using karyotyping, Lubs found what he described as a “secondary constriction” on the long (q) arm of the X chromosome, which was subsequently localized to a site identified as Xq27.3. This constriction of the X was referred to as a “fragile site” because of its appearance under the microscope, and hence the name fragile X.

FMR1 was first sequenced by Verkerk et al. (1991), and related work was published by Yu et al. (1991). Even before the sequencing of *FMR1*, it was thought that the type of mutation causing FXS might be unusual, because, according to Verkerk and associates (1991, p. 912), it had “long been speculated that the fragile X site is a repeat of variable length” (e.g., Warren et al., 1987). This expectation proved to be correct, and while a very small percentage of people with FXS may have a point deletion, FXS turned out to be the first genetic disorder discovered that was caused by a newly-identified class of mutations, known as *trinucleotide repeat expansions*. Another member of this class of mutations is the better-known, but rarer, Huntington disease (Pringsheim, Wiltshire, Day, et al. 2012).

FMR1 Expansion and the *FMR1* Protein (FMRP)

DNA consists of a string of *nucleotides*, each of which consists of a sugar (*deoxyribose*), a phosphate group (PO_4^-), and one of four bases—adenine (A), cytosine (C), guanine (G), and thymine (T). In most cases, each sequential set of three consecutive nucleotides (i.e., a *trinucleotide* or *triplet*) contains the code needed to synthesize an amino acid, and the resulting amino acids are linked together in order to form proteins. Some triplets, instead of carrying the code for protein synthesis, are involved in initiating or terminating the process of replication. The sequence of nucleotides in DNA is copied into messenger RNA (mRNA) in a process called *transcription*, following which the mRNA is actively transported from inside the cell’s nucleus to the cytoplasm outside, where it has an affinity for ribosomes. Ribosomes read the mRNA sequence, and they produce and string together the amino acids required to make a protein. This process is called *translation*.

Thus, when *FMR1* is activated, the strand of mRNA that is produced is transported from the nucleus to cytoplasm, where it associates with ribosomes and provides the instructions for synthesizing FMRP. If *FMR1* is missing or sufficiently abnormal, neither transcription nor translation occurs, and the cell is unable to produce FMRP. The result is FXS (Tassone et al., 1999). This is what happens to most people who have a *full mutation* (FM) of *FMR1*. The FM usually causes FXS by disturbing a number of developmental processes requiring FMRP. *FMR1* also may be silenced by *methylation*, which in this case is an epigenetic inactivation of the *FMR1* gene. Methylation occurs commonly in individuals with an FM, preventing transcription. In some cases, however, there may be an *unmethylated* full mutation, and transcription can take place. Because these individuals are able to produce some FMRP, they are typically less severely affected. An *FMR1* knock-out mouse, which lacks a functional copy of *FMR1*, makes no FMRP and hence is a good model for understanding the action of the protein (Berman et al., 2014; Dutch-Belgian Fragile X Consortium, 1994).

FXS is a trinucleotide repeat expansion disorder. That is, the *FMR1* gene contains too many triplet repeats composed of the bases cytosine, guanine, and guanine (CGG), and this may interfere with normal functioning of the gene. The data suggest that a certain number of CGG repeats is necessary for the normal functioning of *FMR1*; the modal number of CGG repeats in *FMR1* in the general population is 29 or 30, and the normal range is considered to be from 6 (CGG CGG CGG CGG CGG CGG) to 44 repeats.

But under certain conditions that are not yet fully understood, there may be an increase in the number of consecutive CGG triplet repeats in *FMR1*, sometimes punctuated by one or more *AGG* triplet *interruptions* (Yrigollen et al., 2014). Such expansions are generally stable when the number of CGG repeats is low, but with increased repeat size, the gene becomes increasingly unstable, and *FMR1* is likely to undergo further expansion in subsequent generations (Oberlé et al., 1991). This is associated with the phenomenon of *anticipation*, or the *Sherman paradox* (Fu et al., 1991; Sherman et al., 1984, 1985), in which the manifestations of the disorder become more marked with successive generations. In general, trinucleotide repeat disorders are characterized by a relationship between the number of repeats and both age of onset and severity of illness.

Some triplet repeat disorders affect a part of a gene that codes for a protein. Huntington disease (HD), for example, involves a CAG repeat expansion; when present, a defective form of the protein huntingtin is produced. In contrast to HD, *FMR1* does not affect the code for production of FMRP. Instead, the expansion occurs in the 5' (five prime) end of *FMR1*, in the *untranslated promoter region* (UTR), just downstream of which is found a triplet (or *codon*) that initiates transcription. Hence, any FMRP that is produced is normal; other basic cellular processes, however, are adversely affected.

CGG Repeat Expansion Sizes and Associated Phenotypes

An *FMR1* expansion of 200 or more CGG repeats—a full mutation—is likely to produce fragile X syndrome, and the number of repeats may range anywhere from 200 to several thousand. In this case, it is likely that no FMRP will be produced. However, if *FMR1* has a

somewhat smaller expansion—between about 55 and 200 CGG repeats—the gene is functional, but transcribes mRNA that reflects the mutant DNA's pathological blueprint (i.e., too many CGG repeats). If *FMR1* has a repeat expansion in this range, it is referred to as a *premutation* (PM), and is associated with a risk of developing the fragile X-associated tremor/ataxia syndrome (FXTAS). People with 45 to 54 repeats are referred to as being in the *intermediate* or *gray zone*, which is of uncertain clinical significance. There have been reports suggesting a modest association between alleles in the intermediate range and fragile X primary ovarian insufficiency (FXPOI), Parkinson disease, ataxia, multiple system atrophy, and even a few cases of a mild form of FXTAS (Hall, 2014a). For individuals with the PM, the number of CGG repeats is fairly consistently inversely related to age of onset of FXTAS, as well as the integrity of motor, cognitive, and psychiatric functioning (Grigsby, Brega, Jacquemont, et al., 2006; Hessler et al., 2007; Leehey et al., 2008).

Toxic Gain-of-Function Mechanism of FXTAS

Among carriers of the PM, the efficiency of *FMR1* transcription is *increased*, as opposed to the transcriptional silencing observed with the FM and FXS. One result is significantly greater than normal *FMR1* mRNA levels, and much of this excess RNA binds to proteins in the nucleus. Other proteins may in turn bind to these aggregates. Because proteins necessary for the cell's functioning are thus encumbered, translation becomes less efficient, and although there may be a 2- to 10-fold increase in the level of mRNA in the cell, FMRP levels in tissue are typically somewhat decreased. However, it is thought that the cause of FXTAS is not the decreased level of FMRP itself, but rather a *toxic gain of function*, which means that the excess *FMR1* mRNA itself is toxic to the cell. In particular, research is focused on the hypothesis that the mRNA binds to intracellular proteins, especially RNA-binding proteins, with the resultant sequestration of those proteins and their unavailability for normal cellular functioning (Greco et al., 2006; Sellier et al., 2014; Tassone, Beilina, Carosi, et al., 2007; Tasone, Iwahashi, Hagerman, 2004). These aggregations of mRNA and protein appear to become the *inclusion bodies* that are found in neurons and astrocytes throughout much of the brain and spinal cord, and in the thyroid, heart, testes, and possibly other organs (Greco et al., 2002, 2006; Iwahashi et al., 2006). These inclusion bodies, a neuropathologic hallmark of FXTAS, are eosinophilic, ubiquitin-positive, tau-negative, alpha-synuclein-negative, intranuclear aggregations containing 20 to 30 different proteins, as well as *FMR1* messenger RNA (Greco et al., 2002; Iwahashi, Yasui, Greco, et al., 2006; Tassone, Iwahashi, Hagerman, 2004).

A gain-of-function mechanism has not yet been definitively established, and other variables (e.g., secondary genes, mitochondrial disorders, environmental factors) also may play a role in the development and progression of FXTAS. One possible contributor is inflammation, as neuropathological studies have found activated microglia in postmortem tissue (Greco 2002, 2006). Nevertheless, it is unclear whether inflammation might be a primary cause of neurodegeneration, or a secondary phenomenon in reaction to intracellular debris caused perhaps by the hypothesized gain of function mechanism. Mitochondrial dysfunction also has been implicated in FXTAS (Hagerman, 2013; Kaplan et al., 2012; Napoli et al., 2011).

Fragile X-Associate Tremor/Ataxia Syndrome: The Basic Phenotype

Neurology

The fragile X-associated tremor/ataxia syndrome was unknown until 1999, when it was identified in the course of a study of the extended families of individuals with fragile X syndrome (Hagerman et al., 2001). The FXTAS phenotype is distinct from that of FXS, and is characterized in particular by the movement disorder from which it derives its name. The primary signs are cerebellar in nature (Leehey, Hagerman, Landau, et al., 2002; Leehey, Munhoz, Lang, et al., 2003). The mean age of onset is in the early 60s, with appearance of action tremor (both intention and postural tremor) and/or gait ataxia. Signs of parkinsonism, including bradykinesia, resting tremor, and rigidity, affect approximately 30% of patients (although in a small sample, Apartis, Blancher, Meissner, et al. (2012) detected parkinsonism in 60% of their patients), and lower extremity neuropathy is common, especially diminished deep tendon and postural reflexes, and vibration sense (Berry-Kravis et al., 2007; Niu, Yang, Hall, et al., 2014). The severity of the motor deficit is correlated with the CGG repeat size (Leehey, Berry-Kravis, Goetz, et al., 2008).

Dysautonomia is also often observed, the primary signs and symptoms of which include orthostatic hypotension, constipation, erectile problems, and fecal/urinary incontinence (Jacquemont et al., 2003). Although comorbid Parkinson disease may be present on occasion, parkinsonism is common (affecting 30% to 60%), but tends to be a less debilitating component of FXTAS than the cerebellar signs. Niu et al. (2014) suggest that individuals with parkinsonian bradykinesia associated with gait ataxia or postural instability and intention tremor, but not diagnosed with FXTAS, may in fact have the *FMR1* premutation.

Neuropsychology

Neuropsychological disorders appear to be ubiquitous in FXTAS, and in many respects they are similar to the cognitive features of certain Parkinson-like disorders (especially multiple system atrophy), and a number of the spinocerebellar ataxias (SCAs). The timing of their onset in relation to the neurologic signs and symptoms of FXTAS has not been reliably established, although they may precede both tremor and ataxia.

Cognition is characterized in particular by impairments of processing speed, working memory, and executive functioning (Grigsby et al., 2014), and the deficient performance on measures of declarative memory that appears over time seems, at least in the early-to-intermediate stages, to be secondary to dysexecutive syndrome (Brega et al., 2008). The measures of executive functioning that have been found to be most sensitive to the deficits of FXTAS include the Behavioral Dyscontrol Scale (BDS; Grigsby, Kaye, Robbins, 1992), Controlled Oral Word Association Test (COWAT, Spreen & Benton, 1977), and the Hayling Sentence Completion Test (Burgess & Shallice, 1997). Men with FXTAS appear to have particular trouble on go/no-go tests of the capacity for inhibition. In general, it appears that the most severely affected subcomponents of executive functioning are inhibition, initiation of purposeful activity, and self monitoring/error detection. In individual cases, one or more of these components of executive ability may be strikingly spared, as in the case of one man

in his late 70s with severe motor disorder and difficulty with inhibition/initiation, but unusually good insight (Grigsby et al., 2008).

Wechsler IQ scores remain in the average range even in moderately advanced disease, although verbal (VIQ) and performance (PIQ) scores are typically about a standard deviation or more below those of age- and education-matched controls with a normal *FMR1* allele. On the nonverbal subtests of the WAIS, where those with FXTAS typically score worse than on the verbal scale, the discrepancy is to a large extent accounted for by deficient executive functioning, processing speed, and the effects of tremor on subtests requiring the individual to manipulate the stimuli (e.g., Block Design and Object Assembly) (Brega et al., 2008).

Language and naming typically remain intact until very late in the trajectory, although there may be dysarthria and some slowing of speech as the disease advances. The overall pattern of impairment is quite different from what is observed in Alzheimer disease, but similar to the deficits seen in cerebellar and white matter disease (Filley, this issue; Filley, Brown, Onderko, et al., 2015; Schmahmann, 2004; Schmahmann, Smith, Eichler, et al., 2008). This is consistent with extensive white matter pathology, and the widespread Purkinje cell loss and frequent involvement of the dentate nucleus of the cerebellum (Aparts et al., 2012; Brunberg et al., 2002; Greco et al., 2002, 2006; Tullberg et al., 2004; Wang et al., 2012).

In late-stage FXTAS, frank dementia, primary memory deficits, and signs of cortical impairment, are often observed (Seritan et al., 2013). Emotional and behavioral symptoms are common, and include apathy, anxiety, agitation, and depression, as well as obsessive-compulsive symptoms (Birch et al., 2014; Bourgeois et al., 2009; Grigsby et al., this issue; Hessel et al., 2005). Behavior becomes increasingly dysexecutive, with disinhibition, and difficulty initiating goal-directed activity (Grigsby, Leehey, Jacquemont, et al., 2006). The neuropsychological phenotype is thought to be more severe among males than females, presumably reflecting the fact that most heterozygous women possess an X chromosome with a normal allele in a significant percentage of cells. More thorough, systematic study of the female phenotype is needed.

The neuropsychological impairment that accompanies FXTAS goes hand-in-hand with impairment of functional status. Brega et al. (2009) studied physical functioning, activities of daily living (ADLs), and instrumental activities of daily living (IADLs) in a sample of 42 men with FXTAS, and observed that those with FXTAS were significantly more impaired than unaffected carriers and controls on all dependent measures. Disability in tasks of daily living was associated in particular with deficits in motor and executive functioning. Action tremor, for example, may become extremely debilitating, making such basic ADLs as fastening buttons, drinking from a glass, or using silverware difficult or impossible. The gait disorder significantly increases the likelihood of injuries from falls while walking. Functional independence is eventually greatly compromised, although in early stages of FXTAS, an individual may still be able to perform basic tasks by modifying the frequency with which they are done, or the method of doing them (Brega et al., 2009).

The neuropsychological presentation in early FXTAS is frequently subtle, often described by spouses and family as “personality change.” However, the data suggest that at least a subset

of asymptomatic carriers shows a mildly impaired capacity for inhibition, and perhaps subtle deficits in some other cognitive abilities as well (e.g., Goodrich-Hunsaker, Wong, McLennan, et al., 2011). An important but unresolved issue at this stage is whether these mild deficits reflect a neurodevelopmental characteristic of the premutation, are early signs of FXTAS, or both (Hunter, Sherman, Grigsby, et al., 2011; Hippolyte, Battistella, Perrin, et al., 2014; Moore, Daly, Schmitz, et al., 2004; Moore, Daly, Tassone, et al., 2004). Cornish and her colleagues reported a subtle age-related decline in inhibitory control using the Hayling Task (Burgess & Shallice, 1997), and of working memory on Letter-Number sequencing, beginning in early adulthood and continuing throughout the lifespan (Cornish, Hocking, Moss, et al., 2011; Cornish, Kogan, Li, et al., 2009; Cornish, Li, Kogan, et al., 2008). They suggested that male carriers of the premutation with more than 100 CGG repeats may be especially at risk for such cognitive difficulties. In another study, two male subjects with the premutation who had no evidence of FXTAS, and no cognitive impairment, nevertheless had white matter hyperintensities in the middle cerebellar peduncles on FLAIR/T2 MRI (Grigsby et al., 2008). It remains unclear whether mild executive deficits are cognitive features of a premutation phenotype (i.e., neurodevelopmental phenomena) or early manifestations of a neurodegenerative process.

In addition to cognitive neuropsychological impairment, the premutation phenotype is often marked by emotional and behavioral problems, including shyness, anxiety, and depression (Hessl et al., 2005). These are common among asymptomatic carriers, although perhaps less problematic than among those who have FXTAS. These symptoms may be associated with decreased amygdala activity, as well as lower levels of FMRP (Hessl et al., 2007; Hessl et al., 2011).

Diagnosis of FXTAS

Diagnostic criteria for FXTAS, first discussed by Jacquemont, et al. (2003) and revised slightly in Hagerman & Hagerman (2007), are shown in Table 1 below. They have been criticized on several counts, and proposals have been made for their revision. When FXTAS was first identified, it was thought that the prevalence of the MCP sign was more common, but it since has been found to be present in only about 60% of males with FXTAS, and perhaps a smaller percentage of females. Apartis, et al. (2012) suggested that because of this, white matter hyperintensities in the splenium of the corpus callosum (present in about 64% of their own patients) should be added as a major radiological sign, and peripheral neuropathy as a minor clinical sign. In addition, there have been a few cases of persons with gray zone alleles who developed FXTAS, and at the low end of the full mutation range, some individuals with an unmethylated allele or mosaicism have also been affected (Hagerman & Hagerman, 2015).

In general, the neurologic signs of action tremor and gait ataxia, in the context of CGG repeat expansions in the premutation range, are probably weighted most heavily in making a diagnosis of FXTAS. Executive disorders are considered a minor clinical sign of the disorder. The existence of subtle executive function deficits among apparently unaffected carriers of the premutation, and a lack of certainty concerning whether such impairment is neurodevelopmental or neurodegenerative (as well as a relatively high base rate of mild

executive impairment in the general population), make it unlikely that a diagnosis of FXTAS would be made based primarily on the presence of subtle executive dysfunction. A diagnosis of *probable* FXTAS might be made if the MCP sign were present, especially if other minor radiologic criteria (e.g., generalized atrophy, white matter hyperintensities in the cerebrum and/or corpus callosum) were also observed.

Comorbid Conditions: The Non-Neurologic Phenotypes

FXTAS may be complicated by the presence of certain comorbid conditions, especially among women. Approximately 20% of females with the premutation (both with and without FXTAS), for example, develop *fragile x primary ovarian insufficiency* (FXPOI), with irregular menses, problems with fertility, and menopause frequently occurring by the age of 40 (Allingham-Hawkins, et al., 1999; Sherman et al., 2014; Sullivan et al., 2011). The relationships are complex and the findings do not apply to all women, but early onset of estrogen deficiency may contribute to a number of disorders (e.g., osteopenia, osteoporosis), including cognitive deficits and mood disturbances (Duka, Tasker, McGowen, 2000; Hlatky, M.A., Boothroyd, D., Vittinghoff, E., et al., 2002; Sherwin, 2005), and 17 β -estradiol also appears to have anti-inflammatory and neuroprotective properties (Stice, Chen, Kim, et al. 2011, Strehlow, Rotter, Wassman, et al., 2003; Zandi, Carlson, Plassman, et al., 2002). These may further complicate the picture in FXTAS.

High rates of certain autoinflammatory and autoimmune disorders have been reported among female carriers of the premutation, most notably Hashimoto's thyroiditis and fibromyalgia (Coffey, Cook, Tartaglia, et al., 2007; Hunter, Sherman, Grigsby, et al., 2010; Leehey, Legg, Tassone, et al., 2011; Rodriguez-Revenge, Madrigal, Pagonabarraga, et al., 2009; Winarni, Chonchaiya, Sumekar, et al., 2012). One study found an anomalous cytokine profile in the blood of males with FXTAS (Marek, Papin, Ellefsen, et al., 2012), while another found that 72% of women with FXTAS had at least one immune disorder, compared with 46% of APCs and 31% of age-matched controls (Winarni, et al., 2012).

Neuropathologic studies of FXTAS have found post-mortem evidence of inflammation in the brains of several individuals with FXTAS. Most notably, Greco and her associates (Greco, Hagerman, Tassone, et al., 2002; Greco, Berman, Martin, et al., 2006) reported finding activated microglia, indicative of neuroinflammation. The role of inflammation in FXTAS, however, is not well understood. It could be a primary etiologic mechanism, it might represent a response to the presence of debris associated with neurodegeneration, or it could have nothing to do with the mechanism itself. A better understanding of the immune system among premutation carriers, and of the relationship of these autoimmune and inflammatory disorders with FXTAS is of considerable importance.

While such immune disorders are often present among asymptomatic premutation carriers, it is not known if or how they affect the development of FXTAS. Carreaga, Rose, Tassone, et al. (2014) recently reported a decreased immune response and impaired cellular immunity in women with the premutation, as well as in the premutation knock-in mouse model. There also was an association between CGG repeat size and decreased cytokine production, particularly for the inflammatory cytokines GM-CSF and IL-12(p40), and IFN γ and IL-1 α .

An interesting and important question is whether the FX-related immune dysregulation increases both the likelihood of autoimmune/inflammatory disease, and the pathogenesis and progression of FXTAS.

This issue of comorbid immune and endocrine dysfunction is of considerable interest for the neuropsychological phenotype. Both fibromyalgia and autoimmune hypothyroidism may impair certain aspects of cognition, as is the case for chronic inflammation itself (e.g., Tarr et al., 2011). In addition to immunologic dysregulation, carriers of the premutation may be at an increased risk of migraines (Au, Akins, Berkowitz-Sutherland, et al., 2013) and hypertension (Coffey et al., 2008).

Neuropathology and Neuroradiology of FXTAS

In a recent review of the neuropathology of FXTAS, Paul Hagerman (2013) summarized the major features of the disorder. Primary signs of the disease include cerebellar and white matter disease, astrocytic pathology, and the widespread distribution of the typical intranuclear inclusion bodies in both neurons and astrocytes. The inclusion bodies appear to be especially common in the hippocampus, while they are considerably less dense (< 10% of cells) in the neocortex. They have been found in both neurons and astrocytes, but not in oligodendroglia or cerebellar Purkinje cells. There is typically an extensive dropout of Purkinje cells that may range from mild to severe, but despite considerable pontine and cerebellar volume loss, inclusions are rarely noted in either the cerebellum or pontine nuclei (Greco, 2002, 2006, 2007). Grossly, considerable atrophy and volume loss throughout the brain is observed both on neuropathologic examination and on T2-weighted FLAIR (fluid-attenuated inversion recovery) magnetic resonance imaging. To a large extent, this is associated with widespread white matter and cerebellar disease. White matter degeneration appears to begin in the vicinity of the frontal pole, spreading posteriorly with progression (Wang, Hessler, Hagerman, et al., 2012).

In approximately 60% of cases, white matter hyperintensities (WMHs) are apparent in the middle cerebellar peduncles (MCPs) on T2/FLAIR imaging (Brunberg et al., 2002; Brown & Stanfield, 2015), a finding known as the MCP sign, but even when this marker is not present, spongiform changes in the peduncles may be observed on postmortem dissection. Although the MCP sign has been considered an important marker of FXTAS since the paper by Brunberg and his colleagues in 2002, it is significant that Apartis et al. (2012) reported that WMHs were more common in the splenium of the corpus callosum than in the MCPs.

Diffusion tensor imaging (DTI) has been used by several investigators to study white matter pathology in FXTAS, and reduced fractional anisotropy (FA) has been found in many areas, including the genu as well as the splenium of the corpus callosum (Filley, Brown, Onderko, et al., 2015; Hashimoto, Srivastava, Tassone, et al., 2011; Renaud et al., 2015). A particularly noteworthy paper by Wang, Hessler, Hagerman, et al. (2012) reported widespread disruption of structural connectivity in persons with FXTAS, but minimal changes among unaffected individuals with the premutation.

Although to a large extent FXTAS is a disease of the cerebellum and white matter (Filley, 2016, this issue), both cortical and subcortical (thalamus and basal ganglia) gray matter volume loss is noted (Cohen et al., 2006; Wang et al., 2013). Some data suggest that in the early stages of FXTAS, white matter disease predominates, while cortical and gray matter degeneration occur later (Battistella et al., 2012). This is consistent with neuropsychological data concerning the course of FXTAS, discussed above. Rivera's group at UC Davis has been especially active in studying the neuroradiologic features of FXTAS (Hashimoto, Javan, Tassone, et al., 2011; Hashimoto, Srivastava, Tassone et al., 2011; Wang et al., 2012, 2013).

Epidemiology of *FMR1* Mutations

FMR1, or some analogous gene, appears to have been widely conserved across evolution. The results of one study of 44 species of mammals suggested that *FMR1* has been present for at least 150 million years of mammalian descent (Eichler et al., 1995). A homolog of *FMR1*, called *dFMR1*, has been identified in *drosophila melanogaster* (fruit flies), and it has functions similar enough in many respect to those in mammals (Wan et al., 2000) that the drosophila model has been useful for studying FX-related disorders (Tessler & Broadie, 2012).

Evolutionary conservation of *FMR1* suggests that the gene is of fundamental importance for development and physiological functioning (Oostra & Chiurazzi, 2001). This is also supported by the often severe developmental phenotype associated with the fragile X-associated disorders. *FMR1*, and its protein product FMRP, are active early in fetal development (Abitbol et al., 1993), in brain, retina, liver, gonads, and cartilage. *FMR1* expression also affects mature spermatogonia. Among other things, it has been found that FMRP is involved in RNA binding, in shuttling mRNA from nucleus to cytoplasm, in associating groups of ribosomes with a single strand of mRNA during protein synthesis, and in DNA repair (Shi et al., 2012).

As a rule, the greater the number of trinucleotide repeats, the greater is the probability of expansion of the gene to a premutation or full mutation allele. These expansions are most likely to occur during female meiosis, and hence women who are carriers of the premutation have an increased likelihood of passing the full mutation to their children.

Estimating the prevalence of the different *FMR1* genotypes (normal, intermediate, premutation, and full mutation) has been a relatively slow process because short of newborn genomic screening, identifying individuals with *FMR1* mutations, especially premutations and gray zone alleles, is difficult. Hence, estimates vary by a factor of two to four. Variables affecting the measurement of the various FX alleles include ethnicity, small samples, ascertainment bias, and the precise definition of the different ranges (e.g., the gray zone is defined in different ways), but in her review of gray zone (intermediate) *FMR1* alleles, Hall (2014) noted that the findings of 15 studies yielded values from 0.3% to 3.8% of the total population.

Diagnostic criteria for FXTAS have been established (Jacquemont et al., 2003), although some modifications may be in order given the current understanding of the disorder (Hall, Birch, Anheim, et al., 2014). Modern molecular methods, including polymerase chain reaction (PCR) and Southern blot (Filipovic-Sadic et al., 2010; Rousseau et al., 1991, 1994; Tassone et al., 2008), have simplified and improved the diagnosis of FXS, but until the early 90s cytogenetic testing was typically used. Until then, variations in research design and less accurate diagnostic methods led to variable estimates of the prevalence of FXS, but by about 2000, it was thought that FXS affected about 1 male in 4,000 and about 1 in 8,000 females. A more recent analysis of aggregated data from studies involving over individuals from the total population (i.e., with no ascertainment bias against individuals having an intellectual disability) (Hunter et al., 2014) estimated the frequency of the full mutation at approximately 1 per 7,000 among males, and 1 per 11,000 among females. Similarly, the prevalence of the premutation in the total population has been unclear, but Hunter and her colleagues (2014) examined the data from studies that involved nearly 135,000 individuals and reported that the prevalence of the PM was about 1 per 855 males and 1 per 291 females—both lower than generally thought, but as this estimate uses aggregate data, it may be more reliable.

While most males with the full mutation will develop the features of FXS, the majority of FM females have a considerably milder phenotype. This is because unless they are homozygous (i.e., inheriting the full mutation from both parents), women have both the FX allele on one X, and a more typical allele on the other. In each of a female's cells, one or the other X chromosome is inactivated and becomes what is known as a *Barr body*. The percentage of activated genes in a tissue such as brain is known as the *activation ratio* (AR), and the lower the AR, the more likely a female is to have a decreased level of FMRP. A very low AR may result in low levels of FMRP and a severe FXS phenotype, while a high AR may result in a very high functioning individual of average or even high average intelligence in some cases. This process of inactivation is in theory basically stochastic, so that there is a wide and essentially Gaussian distribution of ARs.

The determinants of penetrance of FXTAS among carriers of the PM are somewhat less straightforward, as are the prevalence and penetrance estimates themselves. With respect to the penetrance of the disorder, it is currently thought that FXTAS will eventually affect approximately 40% of male PM carriers (Jacquemont et al., 2004) and about 16% of female carriers (Coffey et al., 2007; Rodriguez-Revenga, 2009) over the age of 50. Given that the mean age of onset of FXTAS appears to be about 62, age-adjusted penetrance and prevalence are somewhat higher in older members of the population.

Conclusion

Although we now understand a good deal about FXTAS, the disorder remains mostly unknown or is infrequently seen among neurologists and neuropsychologists who work outside the specialty area of movement disorders. Until about fifteen years ago, it was always misdiagnosed because it had not yet been identified as a distinct condition (Hall et al., 2005). Yet it is relatively common, and it's important that it be recognized clinically, as the management of FXTAS differs from that of the movement disorders with which it is

sometimes confused. At least one individual with FXTAS was treated with deep brain stimulation before the disorder was known, with no benefit, and medications with some efficacy in treating other movement disorders are generally ineffective with FXTAS.

Moreover, the recognition of FXTAS is important so that those at risk of inheriting either the FM or PM might receive appropriate genetic counseling. Assuming that the prevalence estimates for the premutation are reasonably accurate, and that penetrance rates of 16% and 40% among females and males, respectively, are approximately correct, the crude lifetime prevalence of FXTAS is roughly 55 per 100,000 women and 47 per 100,000 men—in the same range as some other movement disorders, and significantly more prevalent than the spinocerebellar ataxias (SCAs) taken as a group (Ruano et al., 2014). There currently is no treatment for FXTAS, although symptom management is sometimes feasible with an empirical approach to medications that might improve the movement disorder or cognition.

Diagnosis requires appropriate assays for detection of the *FMR1* premutation, in association with intention tremor and/or gait ataxia, parkinsonism, neuropathy, impaired executive functioning and processing speed, and deficits in memory. Family history is frequently a crucial aspect of making an accurate diagnosis. Fragile X syndrome is the most common heritable cause of developmental disabilities, and it shows an X-linked pattern of transmission. The presence of developmental disorders and learning disabilities in the family history is often an indicator that one should consider fragile X as part of the differential diagnosis, especially if more than one family member is affected. For example, a man with progressive action tremor and ataxia, who is the grandfather of two children with significant cognitive impairment or autistic spectrum disorders, should rouse one's suspicion regarding possible *FMR1* mutations. The same is true for a woman with two affected children, or families with two or more sisters who have intellectually disabled children. Early FXTAS may resemble essential tremor, which is sometimes familial and is much better known, and the two can be confused. The comorbidities associated with the premutation among women—autoimmunity, autoinflammation, and early menopause—likewise should increase one's consideration of *FMR1* involvement. If imaging has not yet been done, it should be recommended to allow one to determine whether there are FXTAS-consistent neuroimaging findings.

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Table 1

FXTAS Diagnostic Criteria (adapted from Hagerman & Hagerman, 2007)

CATEGORY	SIGNIFICANCE	FEATURES
Genetic (<i>FMRI</i> CGG repeats)	Required for Diagnosis	55 to 200 CGG repeats in <i>FMRI</i>
Clinical Signs	Major	Gait ataxia
	Major	Intention tremor
	Minor	Parkinsonism
	Minor	Memory and/or executive function deficits
MRI	Major	White matter hyperintensities in middle cerebellar peduncles
	Minor	Cerebral white matter hyperintensities on T2/FLAIR MRI
	Minor	Moderate to severe generalized atrophy
Neuropathology	Major	Presence of characteristic intranuclear inclusions

Definite FXTAS: 1 Major Clinical sign *and* 1 Major Radiologic sign *and/or* FXTAS inclusions on autopsy **Probable FXTAS:** 2 Major Clinical signs *or* 1 Major Radiologic sign *and* 1 Minor Clinical sign

Possible FXTAS: 1 Major Clinical sign *and* 1 Minor Radiologic sign