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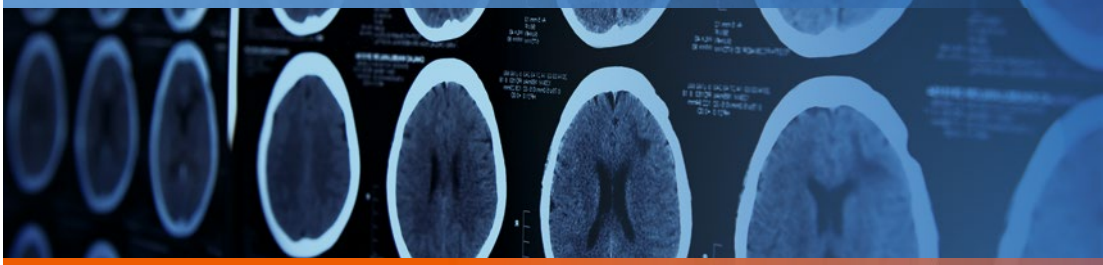

FXTAS, FXPOI, and Other Premutation Disorders

Second Edition

Springer

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Chapter 1
Clinical Neurological Phenotype of FXTAS

Maureen A. Leehey, Deborah A. Hall, Ying Liu, and Randi J. Hagerman

Abstract The classic presentation of fragile X-associated tremor/ataxia syndrome (FXTAS) is an aging man with progressive cerebellar gait ataxia, kinetic tremor, mild parkinsonism, cognitive decline, especially executive dysfunction and short-term memory deficiency, and peripheral neuropathy. Autonomic dysfunction and mood/anxiety disorders may be present. MR imaging often reveals global brain atrophy and white matter changes, including hyperintensities of the middle cerebellar peduncles, termed the "MCP sign," and of the splenium of the corpus callosum, and pathology shows intranuclear inclusions, especially in brain. Recent studies, however, have shown that the FXTAS clinical picture is variable, for example, affected persons may have minor or no tremor and others have predominant dementia or peripheral neuropathy. Onset of motor signs in men is typically in the early 60s, and approximately 40 % of carrier men and 8–16 % of carrier women over age 50 develop the disorder. Penetrance is age related, such that 75 % of men ≥80 years of age are affected. While less data exist regarding FXTAS in carrier women, they appear to have similar but less severe motor signs, perhaps less cognitive impairment, and some different patterns of involvement than seen in men. FXTAS, at present, is underdiagnosed largely because the presentation is often a combination of signs which are common in the elderly and because affected persons often lack insight regarding their deficits and are resistant to seeking medical care. Furthermore, the heterogeneous nature of the disorder facilitates misdiagnosis, especially in the earlier stages. Diagnosis requires *FMR1* gene testing. Accurate diagnosis is not only important for the affected person but also for their family, as immediate family members may be at risk of having progeny with fragile X syndrome or other premutation associated problems.

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Introduction

The core clinical features of fragile X-associated tremor/ataxia syndrome (FXTAS) are cerebellar gait ataxia and action tremor (Hagerman et al. 2001; Leehey et al. 2002). Cognitive dysfunction, particularly frontal executive dysfunction, is a very common and disabling manifestation (Grigsby et al. 2008; Juncos et al. 2011) (see Chap. 3). Parkinsonism (Juncos et al. 2011; Niu et al. 2014; Apartis et al. 2012; Hall et al. 2010) and neuropathy (Apartis et al. 2012) can also occur in varying degrees, and other frequent signs are mood/anxiety disorders (Birch et al. 2014; Bourgeois et al. 2011; Adams et al. 2010; Hashimoto et al. 2011a; Seritan et al. 2013a) and autonomic dysfunction (Juncos et al. 2011; Hamlin et al. 2012; Jacquemont et al. 2003). Predictable radiographic abnormalities are global brain atrophy and cerebral and cerebellar white matter changes, including involvement of the middle cerebellar peduncles (Brunberg et al. 2002) (see Chap. 4), the insula, the pons (Hagerman and Hagerman 2013), and the splenium of the corpus callosum (Apartis et al. 2012). Intranuclear inclusions are seen in many areas of the brain in individuals with FXTAS at autopsy (Greco et al. 2002, 2006, 2007) (see Chap. 5) and represent a pathological hallmark of the condition, likely mediated by a RNA toxicity mechanism proposed for this disease (Hagerman and Hagerman 2013; Hagerman et al. 2004) and/or a DNA damage repair mechanism (Hagerman and Hagerman 2015) (see Chap. 6). While these features encompass a "classic" FXTAS presentation (see Fig. 1.1), accumulating data suggest that the clinical phenotype may vary considerably among affected persons. Below is a case report of a subject with a typical presentation of FXTAS.

Case Study

Case 1. A retired geologist was brought to a clinic at age 77 by his wife although he insisted he was not having any problems and did not need to be seen. During the visit he admitted to balance difficulty starting at age 65 when he played tennis. At age 69, his wife noticed bilateral hand tremor, especially when holding up a newspaper. The tremor progressed slowly. The patient still did not appreciate any impairment from shaking nor even acknowledge the tremor. At age 71, he gave up tennis and began having occasional falls. His primary care physician started donepezil, which was not helpful. Antidepressant medication was recommended and refused. At age 74, he took levodopa, but after a year it was stopped as there was no obvious benefit. In recent years people had commented that he stumbled like a "drunken sailor." One year ago he began leaning to the right, and an MRI done for possible

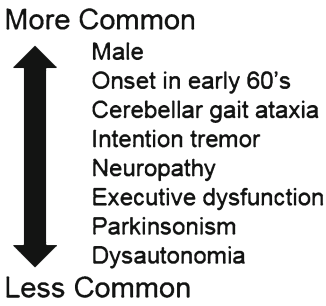


Fig. 1.1 Clinical characteristics of FXTAS

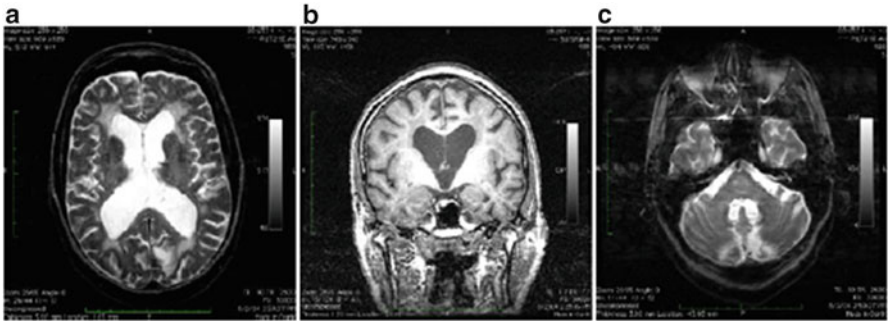


Fig. 1.2 Brain MR images of case 1. A T2-weighted axial image showing large ventricles and cerebral white matter hyperintensities (**a**), a gradient-echo T1-weighted coronal image showing large ventricles and frontal cerebral atrophy (**b**), and a T2-weighted axial image showing there is no hyperintensity in the middle cerebellar peduncles, i.e., the MCP sign (**c**). The latter, when present, is a distinctive finding in FXTAS that occurs in approximately 60 % of affected males and 13 % of affected females (Adams et al. 2007). See Chap. 4 for more details on radiological findings

stroke showed moderate generalized atrophy with very large ventricles and white matter T2 hyperintensities in the cerebral hemispheres and the pons. He was being treated for hypertension and hyperlipidemia and drank two beers per night. There was no history of alcohol abuse. One of his daughters had a son with fragile X syndrome. On examination at age 77, he had a high-average verbal IQ and significantly below-average performance IQ. Short-term memory, capacity to learn and retain new information, and speed of information processing were impaired. MMSE was 26/30. He had slightly masked facies, a mild intention tremor bilaterally in the arms, mild slowing and incoordination of rapid alternating movements, moderately increased tone of a gegenhalten quality in both arms, reduced reflexes in the legs, and no perception of vibration in his great toes. He was unable to perform or even initiate tandem gait. Casual gait was slightly wide based and mildly slow, with irregular foot placement. He leaned to the right and was somewhat stooped forward in a parkinsonian fashion. Repeat MRI showed atrophy and white matter changes (Fig. 1.2), and the radiologist felt it was consistent with normal pressure hydrocephalus. At age 80 he had moderate dementia (MMSE is 21/30), frequent falls, mild intention tremor, and occasional urinary incontinence. Venlafaxine was added for agitation. *FMR1* gene analysis showed 125 CGG repeats.

As an X-linked disorder, FXTAS mainly affects premutation carrier men (Jacquemont et al. 2004), due in part to the protective influence of a second X chromosome in women (Hagerman et al. 2004; Berry-Kravis et al. 2005; Jacquemont et al. 2005). Recently more data has been published regarding women. This data suggests that the premutation may confer different medical risks with aging than those that occur in men, due to hormonal and other, as yet unknown, factors. Chaps. 10 and 12 discuss non-FXTAS phenotypes that occur in carrier women, and a section in this chapter is specifically devoted to the current knowledge regarding carrier women with FXTAS.

The age of onset of one or both of the core motor signs of FXTAS, tremor and ataxia, in men is 61.6 ± 7.9 years (mean ± SD) (Tassone et al. 2007). Using established diagnostic criteria (Jacquemont et al. 2003), approximately 40 % of carrier men and 8–16 % of carrier women over age 50 (Jacquemont et al. 2004; Tassone et al. 2007; Coffey et al. 2008; Rodriguez-Revenga et al. 2009) develop the disorder. Penetrance, however, is age related, such that 75 % of men ≥80 years of age are affected, as shown in Fig. 1.3 (Jacquemont et al. 2004).

There appear to be two dominant phenotypic presentations of classic FXTAS: (a) a tremor-dominant subtype in which the onset of ataxia is delayed; (b) a second in which ataxia is the dominant presentation from the outset. In both subtypes, once ataxia emerges it tends to track frontal cognitive changes ($p < 0.01$) (Juncos et al. 2011).

Clinical Signs of FXTAS

Movement Disorders

The average age of onset of tremor in carrier men is 62.6 ± 8.1 years (range 39–78 years) (Tassone et al. 2007). Most have action tremor as the initial motor manifestation (Juncos et al. 2011; Apartis et al. 2012; Leehey et al. 2007), but in some cases the tremor is minor and not noticed by the patient, as in the case report. It may not be evident until late in disease. In a study of 54 premutation men with a mean age of 67 that were selected without regard to neurological signs (Leehey et al. 2008), 50 % had tremor and the mean severity was rated as slight by movement disorders neurologists. Seventeen percent (9/54) had a tremor in at least one arm that was rated as moderate or severe (unpublished data). In another study of 50 FXTAS men (21 definite, 10 probable and 9 possible, 10 indeterminate FXTAS), 88 % had tremor on neurological examination and 41 % of those were not aware of it. Voice tremor and/or titubation was present in 10 % of patients (Juncos et al. 2011). Head tremor is common. The classic FXTAS tremor is a relatively symmetric kinetic tremor that increases in amplitude at endpoint, and a milder postural tremor is often present. Rest tremor is less common than action tremor, and in at least some of the more severe cases is likely a reemergence of the postural tremor.

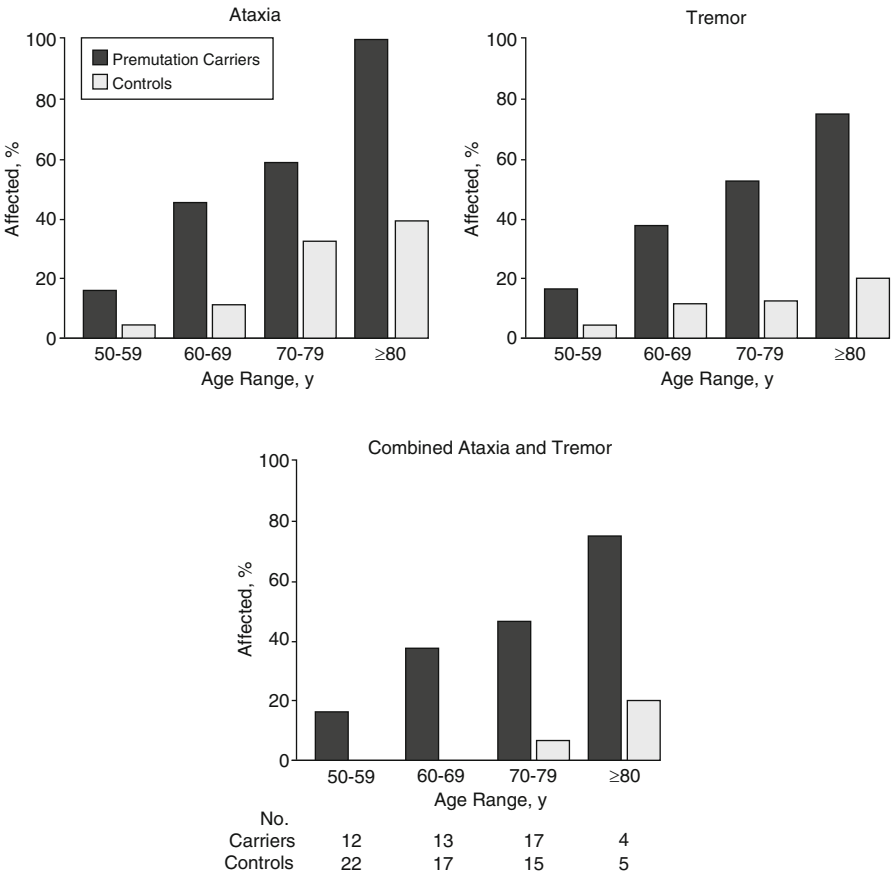


Fig. 1.3 Percentage of men with self-reported symptoms of gait disturbance, intention tremor, or combined ataxia and tremor. Reprinted with permission from Jacquemont et al. (2004); Copyright © 2004, American Medical Association. All Rights reserved

Clinical and electrophysiological characterization of tremor in 18 men and 4 women with definite or probable FXTAS showed three different tremor patterns: essential tremor-like tremor (35 %), cerebellar tremor (29 %), parkinsonian tremor (12 %), and no detectable tremor (24 %) (Apartis et al. 2012). Patients with essential-like tremor had a small amplitude bilateral and symmetric or asymmetric tremor, involving wrist and fingers only. The tremor occurred during postural maintenance and action. Patients with cerebellar tremor had a higher amplitude bilateral proximodistal tremor in the upper limbs. The tremor occurred during postural maintenance and non-goal-directed movements and worsened during target-directed movements. Parkinsonian tremor was characterized by a unilateral upper limb rest tremor. As the disease progresses, the kinetic tremor increases in amplitude and is associated with hypermetria on finger–nose testing. Large-amplitude tremor and dysmetria may interfere greatly with eating, writing, and other daily activities that require fine

motor control. Handwriting becomes large, untidy, and tremulous. Women with FXTAS have a lower frequency of tremor compared to men (Apartis et al. 2012).

The mean age of onset of cerebellar gait ataxia, another defining feature of FXTAS, is 63.6 ± 7.2 years (range 47–78 years) (Tassone et al. 2007). Progressive difficulty with tandem gait (considering normal as 10 perfectly placed consecutive steps) (Huntington Study Group, 1996) likely occurs a few years before the carrier begins falling or develops a feeling of instability. Progressive gait instability is a major source of disability in FXTAS, with falls frequently resulting in injury, such as fractures, lacerations, and even subdural hematomas. Studies using posturography show that individuals with FXTAS have greater postural sway on conditions that test cerebellar and vestibular pathways and suggest deficits in this anatomic Movement disorderspathway and those that serve sensorimotor processing (O'Keefe et al. 2015). In addition, pathology in the corticopontocerebellar loop appears to be responsible for loss of balance control, and abnormalities in the spinocerebellar tracts lead to general balance perturbations in FXTAS patients (O'Keefe et al. 2015). Slowed, poorly coordinated hand movement, i.e., dysdiadochokinesis, and abnormalities of heel–shin testing occur in later stages or in those with a predominately cerebellar presentation. Ataxia, like tremor, sometimes is not noticed by patients (Juncos et al. 2011).

Parkinsonism is another motor feature of FXTAS and has been documented in 29 to 64 % of individuals with FXTAS (Juncos et al. 2011; Niu et al. 2014; Apartis et al. 2012). The major signs are hypomimia and rigidity. Rest tremor is uncommon and is more often seen in persons with advanced disease and prominent action tremor. Some affected persons have a mildly stooped parkinsonian posture. Premutation carriers with parkinsonism had variable Unified Parkinson Disease Rating Scale (UPDRS) scores, ranging from 0 to 50 with a mean score 12.3 ± 12 (Juncos et al. 2011). Generally the parkinsonian signs are mild in FXTAS, with 24 % of premutation carriers initially diagnosed with Parkinson disease (PD) in one study (Hall et al. 2005). These persons generally have an inadequate response to levodopa (Scaglione et al. 2008). However, some carriers have a predominant parkinsonian presentation indistinguishable from primary PD. Hall et al. (2009) described four such premutation carriers, all with good levodopa response.

How the premutation plays a role in parkinsonism in FXTAS has been investigated. [^{123}I]-CIT SPECT (single proton emission computed tomography) imaging has been reported in 14 carriers, ten with FXTAS (seven definite, two probable, one possible; 90 % men) (Scaglione et al. 2008; Zuhlke et al. 2004; Ceravolo et al. 2005; Cellini et al. 2006; Madeo et al. 2013), two with alleles in the gray zone (41 and 51 repeats) and possibly FXTAS (Hall et al. 2010) and two premutation carriers without FXTAS but with cerebellar signs and mild parkinsonism (Hall et al. 2010; Ceravolo et al. 2005). Six of the fourteen had reduced putaminal uptake indicating loss of presynaptic dopaminergic terminals as occurs in idiopathic PD. Three of those six also had iodine-123 iodobenzamide (IBZM) studies of postsynaptic D2 dopamine receptor binding, all showing reduced tracer uptake. Of note, an individual (Kamm

et al. 2005) with 61 repeats whose clinical course was more consistent with multiple system atrophy (MSA) than FXTAS had reduced IBZM uptake, as expected in MSA. While functional imaging results are mixed and larger studies are needed, the current studies suggest that reduced presynaptic dopamine transporter integrity is related to more definite FXTAS diagnosis and higher motor UPDRS scores, thus more advanced disease, and that postsynaptic dopamine striatal activity is also impaired. Some individuals may manifest a complex, mixed disease process. This is supported by the finding of both Lewy bodies and FXTAS intranuclear inclusions on pathological examination of brain from a premutation carrier with a predominantly parkinsonian presentation (Greco et al. 2002).

Cognitive and Psychiatric Signs

Cognitive dysfunction and behavioral changes are a very problematic and disabling aspect of FXTAS (see Chap. 3 for more details). In part, they are likely a source of the common dichotomy between the family's recognition of tremor and other signs and the patient's lack of recognition or concern. Studies suggest that dementia occurs in about 21–50 % of men with the disorder (Juncos et al. 2011; Jacquemont et al. 2004; Bourgeois et al. 2007; Seritan et al. 2008), perhaps less often in women (Hagerman et al. 2004), and that the frequency is higher in late-stage FXTAS. Impairment of cognition in a subset of carriers without motor signs of FXTAS develops as early as middle adulthood, and progressively worsens with increasing age (Grigsby et al. 2008; Cornish et al. 2008, 2011; Hocking et al. 2012). Disturbance of executive functioning, working memory, and information processing are the primary deficits in both genders (Birch et al. 2014; Grigsby et al. 2014; Kraan et al. 2014) (as summarized by Grigsby et al. 2014; Birch et al. 2014; Kraan et al. 2013). It is not possible to localize the cognitive deficits of FXTAS to a specific brain region. Neuropathological studies in FXTAS show extensive involvement of white matter and the cognitive phenotype is consistent with a white matter dementia, in contrast to the impaired cortical function more characteristic of Alzheimer's disease and related disorders. In addition, neurophysiological and other studies implicate frontal lobe impairment, while the prominent executive function deficits along with frequent cerebellar motor signs imply cerebellar involvement (Grigsby et al. 2014).

Psychiatric symptoms are also common (Birch et al. 2014; Bourgeois et al. 2006, 2011; Adams et al. 2010; Hessl et al. 2005; Bacalman et al. 2006; Seritan et al. 2013b) Three studies (Adams et al. 2010; Bacalman et al. 2006; Hashimoto et al. 2011b) compared psychiatric symptoms in FXTAS to those of matched controls. These yielded mixed results. However, reports from the spouse/family members of apathy, irritability, depression, disinhibition, and agitation/aggression were significantly elevated in individuals with FXTAS (Bacalman et al. 2006).

Peripheral Nervous System Findings

The peripheral nervous system is involved in FXTAS and inclusions are common throughout the PNS (Hunsaker et al. 2011). Peripheral neuropathy was present in the five men that were originally described with FXTAS (Hagerman et al. 2001), in 60 % of men in a descriptive study of 20 affected men (Jacquemont et al. 2003), and in 53 % of 17 affected women (Coffey et al. 2008). However, a recent study (Juncos et al. 2011) reported that signs and symptoms of peripheral neuropathy were present in only 20 % of 50 premutation carrier men, the majority of whom had FXTAS. This was not different from age-matched controls (26 %). The frequency of peripheral neuropathy in this study may have been underestimated since it was assessed by patient report and nonquantitative examination. Another recent study found 81 % of 22 persons with FXTAS had peripheral neuropathy (Apartis et al. 2012). A large controlled study (Berry-Kravis et al. 2007) reported that carrier men had more neuropathic signs than controls ($p = 0.0014$) and that the severity of the signs correlated with CGG repeat size and with the presence of ataxia. Carrier women tended to have more neuropathic signs than controls ($p = 0.17$) and severity correlated with ataxia. Neuropathy has been reported as the presentation of FXTAS. A carrier women presented with a painful small fiber neuropathy and was found to have cerebellar signs and MRI abnormalities diagnostic for FXTAS (Chanson et al. 2015). Also, Hagerman et al. (2007) described three men and one woman with FXTAS that presented with neuropathy and a carrier man that had neuropathy and no other signs of FXTAS. Electrophysiological findings in men with FXTAS were found to be consistently abnormal in a controlled (Soontarapornchai et al. 2008) and uncontrolled study (Apartis et al. 2012). Carrier men without FXTAS had slightly but not significantly abnormal testing. CGG repeat length and mRNA level correlated with severity of some of the electrophysiological findings (Soontarapornchai et al. 2008). One study identified different electrophysiologic patterns. Fifty-six percent (9/16) had a non-length dependent sensory neuropathy and 25 % had a length-dependent sensory neuropathy (Apartis et al. 2012). Electrodiagnostic studies document a predominantly axonal sensorimotor polyneuropathy (Soontarapornchai et al. 2008). Usually neuropathic findings are not severe enough to exacerbate ataxia (Juncos et al. 2011; Apartis et al. 2012). Some affected persons have marked neuropathic pain, suggesting involvement of small fibers (Chanson et al. 2015).

Autonomic Symptoms

Autonomic symptoms are common in men with FXTAS, with case series reporting impotence (56–80 %), bowel incontinence (30 %), bladder dysfunction (35–55 %), and orthostatic hypotension (15 %) and hypertension (50–65 %) (Juncos et al. 2011; Apartis et al. 2012; Hamlin et al. 2012; Jacquemont et al. 2003). Erectile dysfunction typically begins before the onset of tremor and ataxia and bladder and bowel incontinence occur late in the course of FXTAS (Greco et al. 2007). A controlled study found that carrier men reported urinary incontinence more than controls, but

the difference was not significant ($p=0.07$) and there was no difference in women (Jacquemont et al. 2004). Another study compared scores on the Scales for Outcomes in PD-Autonomic (SCOPA-AUT) rating scale in 56 premutation men to PD, Huntington disease, and published controls. Carriers reported more urinary symptoms than published controls ($P<0.01$), but had no difference in other autonomic symptoms. The urinary symptoms were significantly correlated with tremor, ataxia, and Montreal Cognitive Assessment scores, indicating worsening with increased disease severity. Interestingly, the carriers had higher SCOPA-AUT scores than the Huntington disease subjects but lower than the PD subjects. Urinary and fecal incontinence is present in late-stage FXTAS (Greco et al. 2007; Leehey et al. 2007; Gokden et al. 2009). Autonomic dysfunction is thought to be a consequence of involvement of the peripheral nervous system (Hunsaker et al. 2011; Gokden et al. 2009). There are case reports of carriers with symptomatic orthostasis or syncope (Kamm et al. 2005; Gokden et al. 2009; Louis et al. 2006; Pugliese et al. 2004). Pugliese and colleagues (2004) reported a 73-year-old man that presented with postprandial hypotension and was found to have had bilateral hand tremor for two years and 73 CGG repeats in his *FMR1* gene. The patient had no ataxia or family history suggestive of *FMR1*-related disorders. Louis et al. also reported a 77-year-old man who met clinical and autopsy criteria for FXTAS who had episodes of syncope an hour after a meal or during a large bowel movement (Louis et al. 2006). Syncope should include a workup for bradycardia or arrhythmias since the cardiac conduction system can be involved with inclusions (Hunsaker et al. 2011; Gokden et al. 2009). Some men with FXTAS have required placement of a pacemaker. Involvement of the autonomic nervous system has been documented in neuropathological studies which showed intranuclear inclusion bodies typical of FXTAS in paraspinal sympathetic ganglia (Greco et al. 2006), myenteric ganglia of the stomach, and subepicardial autonomic ganglia (Gokden et al. 2009).

Controlled studies find that hypertension is more common in carriers with FXTAS. In a cohort of men, including 92 premutation carriers without FXTAS, 100 with FXTAS, and 183 controls, a significantly elevated odds ratio (OR) of hypertension relative to controls for premutation carriers with FXTAS (OR = 3.22, 95 % CI: 1.72–6.04; $P=0.0003$) was found among participants over 40 years old. The age-adjusted estimated odds of hypertension in premutation carriers without FXTAS in the over 40-year-old age group was higher compared to controls (OR = 1.61, 95 % CI: 0.82–3.16), but was not statistically significant ($P=0.164$) (Hamlin et al. 2012). Women with FXTAS also have hypertension more than matched controls ($p=0.002$) (Coffey et al. 2008). Further, anecdotal evidence suggests that cardiac dysfunction, e.g., congestive heart failure, may occur more frequently in men with FXTAS in the later stages, but controlled studies are needed.

Other Clinical Findings

Other disorders appear to be more common in premutation carriers and/or FXTAS. Among 50 premutation carriers, most of whom had FXTAS, 50 % reported hearing loss ($p=0.002$). Ninety-eight percent of them had previously documented

sensorineural hearing loss (Juncos et al. 2011). In the same population 20 % had spouses that reported nighttime activity suggestive of REM sleep behavior disorder; this reached significance ($p < 0.0001$) compared to a historical control. The prevalence of migraine was 54.2 % in carrier women and 26.79 % in carrier men compared to matched female, 25.3 % ($p = 0.0001$), and male controls, 15.5 % ($p = 0.041$) (Au et al. 2013). Olfactory identification capacity was measured in 41 premutation carriers and 42 controls using the University of Pennsylvania Smell Identification Test. Frequency of olfactory defects was higher in carriers compared to controls (61 % vs. 29 %, $P = 0.003$) (Juncos et al. 2012). Premutation carriers with and without FXTAS reported symptoms of restless legs syndrome 1.9 times more than controls and those affected endorsed worse symptoms than controls (Summers et al. 2014). Further, a questionnaire study suggested that persons with FXTAS have a 3.4-fold risk for sleep apnea compared to matched controls; the authors hypothesized that significant hypoxia at night may worsen FXTAS (Hamlin et al. 2011).

Eye movement abnormalities in FXTAS have been reported (Scaglione et al. 2008; Sulkowski and Kaufman 2008; Fraint et al. 2014). Three of five men with FXTAS had a vertical gaze palsy (Scaglione et al. 2008). Fraint et al. (2014) detailed eye findings in 19 persons with FXTAS, and found five had a PSP-like phenotype, including decreased optokinetic nystagmus, especially in the vertical direction, slowed vertical saccades, and square wave jerks. One of his cases, a 75-year-old woman with FXTAS had absent vertical optokinetic nystagmus, slowed vertical saccades, and square wave jerks. In this cohort other frequent findings were saccadic pursuits, lateral end gaze nystagmus, dysmetric saccades, and slowed saccades. Another study reported an 80-year man with FXTAS who had acquired diplopia, strabismus, and other oculomotor abnormalities (Sulkowski and Kaufman 2008).

Although not a clinical study of FXTAS, Seltzer et al. (2012) reported the prevalence of symptoms that occur in FXTAS in their population-based sample of 30 premutation carriers who were in their mid-60s. Compared with controls, there was a significantly higher rate of dizziness/faintness (17.9 % weekly or more often for the premutation group vs. 3.9 % for the controls, $P < 0.001$) and numbness (28.6 % weekly or more often for the premutation group vs. 13.3 % for the controls, $P < 0.05$). There have been two case reports of monoclonal gammopathy of unknown significance (Fraint et al. 2014; Sumekar et al. 2011), one of generalized cortical reflex myoclonus (Poston et al. 2010) and one of pathological crying (Van Ballaer and Vandenbulcke 2014) in FXTAS. In late-stage FXTAS, problems with swallowing, sedation in the day, and muscle weakness are common (Hagerman and Hagerman 2013; Leehey et al. 2007).

Premutation Carrier Women

Premutation carrier women have unique medical concerns not reported in men. For example they have a higher rate of primary ovarian insufficiency (POI), approximately 18 % (Coffey et al. 2008; Rodriguez-Revenga et al. 2009), compared to other

women (Cronister et al. 1991). Fragile X-associated POI (FXPOI) is discussed in Chap. 10. Having FXPOI, however, does not apparently increase the risk of FXTAS in women (Coffey et al. 2008), although prospective studies are needed.

Besides FXPOI, disorders found more often in women when collecting historical information compared to men with FXTAS include autoimmune thyroid disorders, chronic muscle pain, fibromyalgia and, as previously discussed, migraine headaches (Coffey et al. 2008; Rodriguez-Revenga et al. 2009; Au et al. 2013; Winarni et al. 2012). Approximately 50 % of women with FXTAS have thyroid dysfunction, usually hypothyroidism (Coffey et al. 2008; Winarni et al. 2012). This problem may be diagnosed in early or mid-adulthood, usually long before neurological difficulties. Chronic muscle pain is reported in 24 % (Rodriguez-Revenga et al. 2009) and 35 % (Coffey et al. 2008) of women with FXTAS, compared to 10.7 % in controls (Coffey et al. 2008; Winarni et al. 2012). Likewise, fibromyalgia is reported in 25 % (Winarni et al. 2012) and 43.8 % (Coffey et al. 2008) of women with FXTAS compared to 4.2 % (Winarni et al. 2012) and 9.4 % (Coffey et al. 2008) in controls.

Daughters of men with FXTAS are more likely to report balance problems and neurological symptoms than daughters of premutation carrier fathers without FXTAS (Chonchaiya et al. 2010). Sleep problems were the most common symptom reported for these women and this problem may be related to their anxiety and chronic worries which can be disruptive of sleep at night. (Chonchaiya et al. 2010; Besterman et al. 2014) In addition, chronic pain such as neuropathy or fibromyalgia can lead to sleep problems and exacerbate psychological problems (Jalnapurkar et al. 2015). The use of opioids or other substance abuse to treat chronic pain has the potential to exacerbate the progression of white matter disease and FXTAS, as has been reported in a few case studies (Muzar et al. 2014, 2015).

Cognitive decline has been found to be less frequent in women compared to men with FXTAS (Seritan et al. 2008). However, carrier women without FXTAS have visuospatial deficits (Goodrich-Hunsaker et al. 2011), attention problems (Hunter et al. 2008), and language dysfluencies that progress with age (Sterling et al. 2013). Women with FXTAS demonstrated lower performance in verbal learning and executive function and a significant reduction of the N400 congruity effect in ERP analyses (Yang et al. 2014). Karmon and Gadoth (2008) reported that a 62-year-old women with 75 repeats had classic FXTAS including severe dementia. In a clinical-neuropathological cases series of eight autopsied premutation carrier women, four had dementia; of the four, three had FXTAS diagnosed before death. Postmortem examination revealed the presence of intranuclear inclusions in all eight cases. Among the four subjects with dementia, three also had neuropathological findings of Alzheimer's disease in addition to their FXTAS (Tassone et al. 2012). Thus dementia in FXTAS occurs from FXTAS alone but may also be from or potentiated by coexistent Alzheimer's disease.

The most common problems of women with the premutation in mid-adulthood are anxiety and depression (Franke et al. 1996, 1998; Sobesky et al. 1996; Roberts et al. 2009). This is addressed in Chap. 12.

The following case history demonstrates how a woman with FXTAS may present differently than an affected man.

Case Study

Case 2. A 79-year-old woman presented with weakness and inability to walk. Her neurological symptoms began at age 67 with pain in her legs and a feeling of tightness in her feet as if she was wearing tight boots. She also developed pain in the muscles of her low back. She was treated with hydrocodone and required higher doses as the pain became chronic. She developed hypertension and swelling in her legs. Electrodiagnostic studies documented a length-dependent polyneuropathy. At age 75, she was diagnosed with fibromyalgia by her rheumatologist and chronic inflammatory demyelinating polyneuropathy by her neurologist. She was treated with intravenous gamma globulin and prednisone but her symptoms worsened. By age 76, she needed a four-pronged cane due to weakness in her legs and gait ataxia; 2 years later she was dependent on a wheelchair. Her family noticed an intention tremor at age 78, but the patient denied any tremor. When examined at age 79, she had marked weakness and severe edema in the lower extremities with absent ankle reflexes. She had no vibration sense and decreased cold and pinprick sensation in her distal lower extremities. She was unable to walk or stand, even with full support. An action tremor was present in the right hand. Cognition was normal for age but she appeared depressed. Brain MRI demonstrated moderate brain atrophy and widespread subcortical and periventricular white matter disease without a clear MCP sign. *FMR1* gene analysis showed her CGG repeat sizes to be 30 and 73. She has ten children, many of whom are carriers, and multiple grandchildren with fragile X syndrome.

Natural History of FXTAS

Formal study of the natural history of FXTAS consists of only one retrospective chart review study (Leehey et al. 2007). This report studied the progression of tremor and ataxia in 55 men with FXTAS. After the initial motor sign, usually tremor, median delay of onset of ataxia was two years, onset of falls six years, dependence on a walking aid 15 years, inability to do most daily activities 16 years, and death 21 years. However, life expectancy ranged from 5 to 25 years, and several cases of death within 5–7 years after seeking medical care have been reported (Greco et al. 2006; Kamm et al. 2005; Gokden et al. 2009; Louis et al. 2006). Cause of death is usually due to cardiopulmonary problems, including pneumonia often secondary to aspiration, cardiac arrest, congestive heart failure, and progression of neurological disease. In the months before death, patients are bedridden, dysarthric, dysphagic, without bladder or bowel control, rigid, and bradykinetic (Greco et al. 2007; Leehey et al. 2007; Louis et al. 2006).

Diagnosis of FXTAS

While tremor and ataxia are the core motor signs in FXTAS, accumulating literature documents the wide variation in clinical presentation. Some persons present with predominant dementia (Bourgeois et al. 2006; Goncalves et al. 2007), neuropathy (Chanson et al. 2015; Hagerman et al. 2007), parkinsonism (Hall et al. 2010; Louis et al. 2006), dysautonomia (Pugliese et al. 2004), or action tremor without much ataxia (Leehey et al. 2003). Some have spasticity in the legs and other pyramidal tract signs (Jacquemont et al. 2005; Cellini et al. 2006; Kamm et al. 2005). A retrospective study of diagnoses given to persons with FXTAS ($n=56$) before FXTAS was a known clinical entity demonstrates the heterogeneity of presentations: 24 % were diagnosed with parkinsonism, 20 % with tremor, 17 % with ataxia, 13 % with dementia, 10 % with cerebrovascular disease, and 16 % with other miscellaneous disorders (see Chap. 2). The latter included multiple sclerosis, benign positional vertigo, peripheral neuropathy, and normal pressure hydrocephalus (Hall et al. 2005). Moreover, affected persons within the same family may present with different neurological features (Peters et al. 2006; Capelli et al. 2007). The heterogeneity in clinical signs is probably due to the widespread pathological involvement of both the central and the peripheral nervous systems. In addition, some of this variability is likely due to the size of the CGG repeat, since age of onset (Tassone et al. 2007) and death (Greco et al. 2006) correlate negatively and the severity of motor signs (Leehey et al. 2008) and degree of brain atrophy (Loesch et al. 2005) correlate positively with repeat size.

The protean presentation of FXTAS makes diagnosis difficult and the differential diagnosis broad. Other disorders that can have presentations similar to FXTAS are listed in Table 1.1. The diagnosis of multiple system atrophy is made when established diagnostic consensus criteria (Gilman et al. 2008) of autonomic, parkinsonian, and cerebellar dysfunction are met. In one study (Kamm et al. 2005), less than 1 % of persons meeting previously established but still stringent diagnostic criteria (Gilman et al. 1999) had FXTAS, but approximately 4 % of persons with the cerebellar subtype had FXTAS. The presence of unusual features in a person meeting diagnostic criteria for multiple system atrophy, e.g., a prolonged course or a prominent tremor, should prompt *FMR1* gene testing (Kamm et al. 2005). Another area of FXTAS diagnostic overlap is late-onset cerebellar ataxia. Studies screening populations with cerebellar ataxia report that approximately 2 % of cases were *FMR1* carriers (see Chap. 2) (Jacquemont et al. 2006). This frequency is comparable to the frequency of any of the individual spinocerebellar ataxias, and yield would be increased if the patient is male and has onset over age 50. Ataxia that is assumed to be from strokes or cervical spine stenosis in an older male may instead be from FXTAS (Hall et al. 2005), particularly if there are concomitant signs consistent with FXTAS. A further area of FXTAS diagnostic overlap is dementia. Alzheimer's disease can be distinguished from FXTAS because persons with Alzheimer's have deficits in encoded memory and language, while persons with FXTAS have relative

preservation of these but have deficits in retrieval and executive function (Seritan et al. 2008). White matter MRI changes, mild parkinsonism, and dementia occur in both vascular dementia and FXTAS, but these two disorders may be distinguished because of the prominent executive dysfunction in FXTAS and other concomitant FXTAS signs.

Diagnostic Criteria for FXTAS

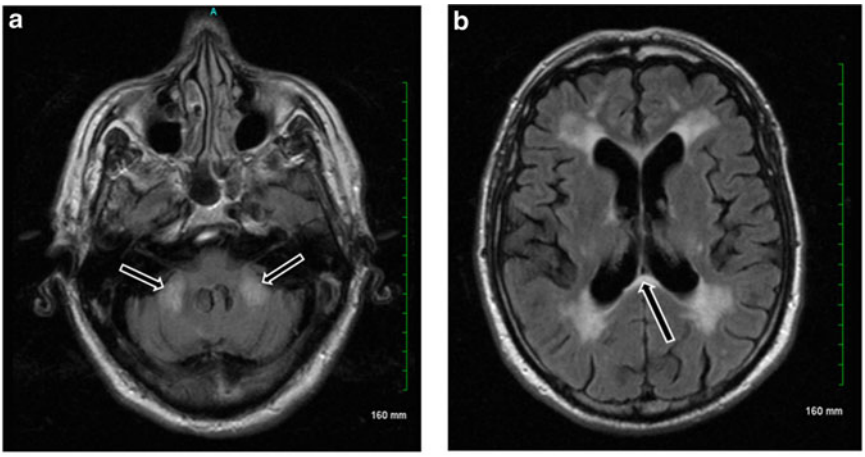
When FXTAS is suspected, diagnostic evaluation requires *FMR1* gene testing, and MR imaging is useful in documenting the degree and type of brain involvement. Additional studies may be warranted when patients have specific signs, such as testing for reversible causes of dementia and electrodiagnostic studies to characterize neuropathy. Diagnostic criteria for FXTAS were established in 2003 (Fig. 1.4) (Jacquemont et al. 2003; Hagerman and Hagerman 2004) and later revised (Hall et al. 2014). The initial description of FXTAS consisted of a neurodegenerative disorder in premutation carriers, mostly in men over age 50, characterized by intention tremor, cerebellar gait ataxia, and parkinsonism, as well as brain atrophy and often middle cerebellar peduncle hyperintensities (the "MCP sign") on magnetic resonance

Table 1.1 Differential diagnosis of FXTAS

Multiple system atrophy, especially the cerebellar subtype
Late-onset cerebellar ataxia
Essential tremor
Parkinsonism, especially atypical presentations
Spinocerebellar ataxia[a]
Secondary ataxia
Alzheimer's disease
Peripheral neuropathy[b]
Vascular dementia
Multiple sclerosis
Normal pressure hydrocephalus
Progressive supranuclear palsy (PSP)
Frontotemporal dementia
Alcoholic tremor/ataxia

[a]Spinocerebellar ataxia (SCA) type 12 is particularly similar to FXTAS since it is characterized by cerebellar gait ataxia, action tremor, and dementia. However, onset of SCA 12 is usually in the fourth decade

[b]The hereditary neuropathies, Charcot–Marie–Tooth disease, should also be considered in the differential diagnosis of FXTAS



c

Diagnostic Criteria		
Molecular	Required	*FMR1* mutation including gray zone
Clinical	Major	Intention Tremor
	Major	Cerebellar gait ataxia
	Minor	Parkinsonism
	Minor	Neuropathy
	Minor	≥ Moderate short term memory deficit
	Minor	Executive function deficit
Radiological	Major	MRI white matter lesions in MCPs or brainstem
	Minor	MRI white matter lesions in the splenium of the corpus callosum
	Minor	MRI cerebral white matter lesions
	Minor	≥ Moderate generalized brain atrophy
Neuropathology	Major	Ubiquitin-positive intranuclear inclusions
Diagnostic Categories		
Definite	One clinical major + [one radiological or pathological major]	
Probable	Two clinical major or [one clinical minor + one radiological minor]	
Possible	One clinical major + one clinical minor	

Fig. 1.4 Diagnostic criteria for FXTAS. Radiological criteria are shown on axial flair T2-weighted MR images, bilateral hyperintensities of the middle cerebellar peduncles (**a**) and hyperintensities of the splenium of the corpus callosum (**b**). The diagnostic criteria required for each diagnostic category is listed in (**c**). The molecular criterion has been amended to allow for the diagnosis in individuals carrying gray zone or full mutation with a lack of methylation or mosaic alleles

imaging (MRI) scans (Hagerman et al. 2001; Leehey et al. 2002; Apartis et al. 2012; Jacquemont et al. 2003). Diagnostic criteria (Jacquemont et al. 2003; Hagerman and Hagerman 2004) were proposed based on this, with the addition of the neuropathological hallmark, intranuclear inclusion bodies (Hagerman and Hagerman 2004), soon after. There has been an enormous amount of literature suggesting that the disorder has additional features (Hall et al. 2014), including peripheral neuropathy and MRI T2 hyperintensities in the splenium of the corpus callosum (CCS) (Apartis et al.

2012). Neuropathy is common enough to be a minor clinical diagnostic criterion, but too nonspecific and common in the aging population to be classified as a major criterion (Hall et al. 2014). CCS hyperintensities were as frequent as MCP hyperintensities, and were useful in identifying patients who had no MCP sign (Apartis et al. 2012). Thus, Hall et al. (2014) proposed these be added as a major criterion for FXTAS. However, the CCS hyperintensities are not unusual in the aging population so here, in Fig. 1.4, it has been added as a minor MRI diagnostic criterion.

FXTAS was initially described in *FMR1* premutation carriers. Recent reports, however, have shown that some individuals carrying a gray zone expansion (41–54 *FMR1* CGG repeats) have a classic FXTAS picture (Hall et al. 2012; Liu et al. 2013). The reason that gray zone carriers may develop clinical disorders is because molecular changes in some gray zone carriers occur similar to that seen in the premutation. As the repeat size increases from 39, the upper range considered normal, there is an increase in the level of *FMR1* mRNA and a decrease in *FMR1* protein (Loesch et al. 2007; Kenneson et al. 2001). Classic FXTAS has also been reported in persons with an unmethylated full mutation or a mosaic full (Loesch et al. 2012; Pretto et al. 2013; Santa Maria et al. 2014). These cases had elevated *FMR1*-mRNA even though they had a full mutation so RNA toxicity can develop in these cases. These individuals would meet diagnostic criteria except that they were not premutation carriers. Given these findings, the diagnostic criteria for FXTAS has been amended to allow for the diagnosis in individuals carrying gray zone or full mutation with a lack of methylation or mosaic alleles (Hagerman and Hagerman 2015; Hall et al. 2014).

Guidelines for Testing

Before *FMR1* gene testing, genetic counseling for the patient and concerned family members is essential (McConkie-Rosell et al. 2007) (see Chap. 14). Some elderly symptomatic persons are reluctant to undergo genetic testing since disease modifying therapy is not yet available. However, treatment is available for symptoms and accurate diagnosis is important for the patient. Diagnosis is also very important for the family, as immediate family members may be at risk of having progeny with fragile X syndrome or a premutation associated disorder.

Guidelines for deciding whom to test have been proposed and are presented in Table 1.2. In general, a reasonable way to keep the diagnosis of FXTAS in mind when seeing patients with any of the many clinical signs consistent with FXTAS is to include questions about *FMR1*-related disease when obtaining family history. One should ask about fragile X syndrome (developmental delay, learning disability, autism), POI, psychiatric symptoms, chronic muscle pain, and FXTAS. Thus, the history of a grandchild with a form of developmental delay should immediately alert the clinician to consider FXTAS.

The presented guidelines (Table 1.2) are for diagnosis of symptomatic persons, but persons without symptoms who are at risk for the carrier status should also

Table 1.2 Testing guidelines for FXTAS

Cerebellar ataxia of unknown cause, onset ≥50 years old
Action tremor of unknown cause, onset ≥50 years old, if also has cerebellar ataxia, parkinsonism, or dementia
Dementia of unknown cause, onset ≥50 years old, if also has cerebellar ataxia, parkinsonism, or action tremor
Multiple system atrophy, cerebellar subtype
Some FXTAS signs
MRI hyperintensities within MCP or splenium of the corpus callosum
Patient history or family history of premature ovarian insufficiency
Family history of an *FMR1* disorder

MCP sign, increased T2 signal intensity in the middle cerebellar peduncles

consider *FMR1* testing. A positive result would enable them and their family to understand important health risks. The presence of MRI hyperintensities within MCP, family history of *FMR1* mutation that confers at-risk premutation carrier status, and patient history of POI, even without signs of FXTAS, are appropriate criteria for *asymptomatic* testing.

For a number of reasons, FXTAS at present is probably underdiagnosed. First, since the initial report was only published in 2001, many physicians are not yet familiar with the disorder. Further, the types of doctors seeing these patients are not the ones that are currently most aware of it. A retrospective chart review study showed that 70 % of persons diagnosed with FXTAS were being managed by general neurologists, 26 % by primary care physicians, and only 4 % by movement disorders neurologists (Hall et al. 2005). Movement disorders neurologists, the physicians that are most aware of FXTAS at present, generally treat persons with ataxia and tremor. But persons with FXTAS are not being referred to movement disorders neurologists because their presentation is often a combination of signs, e.g., tremor, ataxia, and dementia, which are common in the elderly. The latter is another reason that the diagnosis is missed—the nonspecific presentation with signs common in the elderly. Individually, these signs could be due to a variety of causes in the elderly and thus, even when they present in combination, their etiology is often not pursued. Finally, the disorder is hard to recognize in some cases because the heterogeneous nature of the disorder facilitates misdiagnosis, especially in the earlier stages.

Summary and Future Perspectives

FXTAS is the most common single gene cause of tremor and ataxia, but at present the diagnosis is often missed. To improve the frequency of diagnosis, neurologists and primary care physicians need to be educated about the disorder and a family history of *FMR1*-related signs, especially any form of developmental delay, should be obtained in suspect patients. Physicians need to be aware of the heterogeneity of

the clinical presentation and that the patient may simply present with a combination of signs that are common in the elderly. While the MCP sign on MR imaging is helpful in recognizing the disorder, the sign is present in only ~60% of affected persons. Thus, a negative finding does not rule out FXTAS. Guidelines for which clinic patients are most appropriate for gene testing have been presented (Table 1.2). Accurate diagnosis is essential, not only for the patient but also for the family, so they can be informed of important genetic and health risks. Before *FMR1* gene testing, patients and families need genetic counseling.

Most of the research on FXTAS has been done in men. Studies to date find that women are less commonly affected and that they have similar but less severe motor signs. Interestingly, the frequency of muscle pain/fibromyalgia and thyroid disease is higher in women with FXTAS than controls, and this has not been found in affected men. Prospective studies in carrier women are needed to define their full phenotype.

Further research is needed in other areas also. Genetic, epigenetic, and environmental factors that predispose carriers to develop FXTAS need identification. A prospective study of disease progression and modifying factors would provide valuable information needed for life planning. Prospective data and validated reliable quantitative tools are needed for measurement of disease in cross-sectional, longitudinal, and therapeutic trials. To date only one randomized, controlled trial to study modification of progression of FXTAS has been conducted (Seritan et al. 2014). Work in this area is an important direction for future studies.

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