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Towards an Understanding of Neuropsychiatric Manifestations in Fragile X Premutation Carriers

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Abstract

Fragile X-associated disorders (FXD) are a group of disorders caused by expansion of non-coding CGG repeat elements in the fragile X (*FMR1*) gene. One of these disorders, fragile X syndrome (FXS), is the most common heritable cause of intellectual disability, and is caused by large CGG repeat expansions (>200) resulting in silencing of the *FMR1* gene. An increasingly recognized number of neuropsychiatric FXD have recently been identified that are caused by 'premutation' range expansions (55-200). These disorders are characterized by a spectrum of neuropsychiatric manifestations ranging from an increased risk of neurodevelopmental, mood and anxiety disorders to neurodegenerative phenotypes such as the fragile X-associated tremor ataxia syndrome (FXTAS). Here, we review advances in the clinical understanding of neuropsychiatric disorders in premutation carriers across the lifespan and offer guidance for the detection of such disorders by practicing psychiatrists and neurologists.

Keywords

FMR1; Fragile X Syndrome; Fragile X Premutation; Fragile X-associated Tremor Ataxia Syndrome; FXTAS; Depression; Anxiety; Autism; ASD; ADHD

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Introduction

Recent advances in clinical neurosciences have led to an increased recognition of illnesses that blur the historical distinctions between “neurologic” and “psychiatric”. The fragile X-associated disorders (FXD) represent just such a group of neuropsychiatric illnesses, which include both fragile X syndrome (FXS) and fragile X premutation (FXPM) disorders. FXS is the most common cause of heritable intellectual disability and is also often associated with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), learning difficulties, and anxiety [1]. It is caused by an expansion of the CGG trinucleotide to >200 copies in the 5′ untranslated region of the fragile X mental retardation 1 (*FMR1*) gene on the X chromosome (Xq27.3) [2]. Initially, it was believed that FXS was the only FXD and that anyone with the premutation (55-200 CGG repeats) was clinically unaffected. That is now known not to be the case. Individuals with the premutation, or “carriers” as we will refer to them from now on, are susceptible to several FXD throughout the lifespan. Individuals with 45-54 CGG repeats in *FMR1* have a “gray zone” allele, usually have mild elevations of *FMR1* mRNA and may be susceptible to FXPM disorders, although to a lesser degree [3–6].

This review will focus primarily on carriers and the neuropsychiatric consequences of premutation status. We will discuss the various neurodevelopmental phenotypes that commonly present in carriers, such as ASD, ADHD, and seizures. We also discuss the burden of mood and anxiety disorders that affect many adult and some female child carriers. These are sometimes accompanied by cognitive decline that may precede FXTAS and an associated cortical-subcortical dementia, the details of which continue to be fully elucidated. We highlight some of the clinical neuroimaging findings in these disorders to emphasize both the clinical and endophenotypic overlap with other neuropsychiatric disorders. Suggestions for appropriate genetic testing are provided, taking into consideration both psychiatric and neurological symptoms, with a strong emphasis on family history. Lastly, we provide treatment suggestions for psychiatric symptoms based on reported clinical experience and offer our thoughts on the most fruitful areas of future research to improve our understanding and treatment of FXPM disorders.

Neurodevelopmental Disorders in Carriers

Initial studies comparing psychiatric phenotypes of carriers with related non-carriers suggested that there were few if any differences [7]. However, with expanded study, it became clear that some carriers were clinically affected, presenting with intellectual disability, learning difficulty or ASD [8–11]. There has since been significant investigation into the frequency of ASD in the carrier population. Many studies use a design that compares the phenotype of probands, carriers that are identified by presenting to clinicians for medical purposes, to related non-probands, carriers that are identified secondary to genetic testing of family members of a proband. In an early case series, Aziz et al described 10 proband boys with high rates of social impairment, hyperactivity, delayed receptive and expressive vocabulary, and impaired social use of language [12]. The rate of ASD in carrier probands has since been found to be significantly higher than both non-probands and related non-carriers [10,11]. Farzin et al compared 14 male probands, 13 non-probands, and 16 related controls [10]. They found that 79% of probands met the criteria for an ASD; 29% for

autistic disorder and 50% for pervasive developmental disorder-not otherwise specified. In contrast, only 8% of non-probands met criteria for ASD. In a study of 50 boys (25 probands, 25 non-probands) with the premutation, Chonchaiya et al observed similar trends in the relative frequency of ASD [11]. Compared with non-carriers, ASD was significantly more frequent in both probands and non-probands [11]. In studies of young adult male carriers social deficits consistent with ASD have also been observed [13]. Compared with unrelated non-carriers, carriers had poorer social cognition, with the most notable impairment on interpersonal skills that require accurate social perception, such as recognizing complex emotions from photographs of eyes [13].

Additional epidemiological data comes from a national survey that asked parents to report neuropsychiatric symptoms such as attention problems, hyperactivity, aggressiveness, self-injury, autism, seizures, anxiety or depression, along with the mutational status of all of their children [14]. They identified 211 female and 65 male carriers and compared them to sex-matched controls. In male carriers, 33% were reported to have developmental delays (DD), 41% attention problems, 19.3% aggressiveness, 19.3% autism, 11.3% seizures, and 33.3% anxiety [14]. All conditions were significantly more common in carriers than in controls. In contrast, only 8.6% of females were reported to have DD, 1.1% autism, 18.5% attention problems, 35.6% anxiety and 34.2% depression, suggesting that mood disorders may be the most predominant psychiatric disorder in female children with the premutation [14]. The main limitation to this study was that all data was ascertained from parent report, and was not verified for accuracy. Additionally, there was a low response rate from low socioeconomic status and ethnic minority groups. Therefore, these results may not be broadly generalizable to all carriers. However, Clifford et al observed similar trends in autism frequency in a study of 7 male and 43 female carriers who ranged in age from 5 to 80 years, with 14.3% of males and 7% of females meeting criteria for ASD [15]. Together, the data from these studies suggest that the relative frequency of ASD in carriers is approximately 10-20% in males and 1-7% in females. While frequency estimates of ASD in carriers varies somewhat between studies, likely due to small sample sizes and variable study design, there is a consistent trend of elevated ASD rates in male carriers, and possibly female carriers, compared to the general population.

As seen in the national survey, there is some evidence that carriers, especially those with ASD, may also be at elevated risk for additional neurodevelopmental disorders, such as ADHD and seizure disorders [14]. In an early cohort study, daughters of carrier fathers, blinded to their father’s carrier status, reported more frequent behaviors related to adult ADHD [16]. This was followed by several case studies reporting ADHD behaviors in child carriers, such as difficulty focusing and sitting still in class [8,12,17] and a case-control study observing increased rates of ADHD in probands compared to non-probands and non-carriers [10]. Additional systematic studies have found a higher prevalence of adult ADHD in carriers compared to non-carriers [18]. The risk of developing a seizure disorder is similarly elevated in in carriers. Chonchaiya et al observed a significantly higher number of probands with a history of seizures (28%) than non-probands (0%) or non-carrier control brothers (0%), consistent with prior reports [11,14]. Probands with ASD were much more likely to have a seizure disorder, suggesting a potential etiologic overlap with idiopathic ASD, where seizures are also common [19].

Neuropsychiatric Phenotypes in Adult Carriers without FXTAS

Adult carriers without FXTAS do not exhibit significant deficits in general intelligence compared with the normal population [20]. However, aging carriers can experience significant executive function deficits and disinhibition [21–23]. Clinical reports have suggested that specific cognitive deficits may coincide with or precede the motor dysfunction of FXTAS in some cases [24,25]. While Hunter et al did not initially find evidence of executive dysfunction in carriers younger than 50 [26], several other studies have identified deficits in declarative and working memory, selective attention, and response inhibition in similar groups without FXTAS [20,22,27,28]. Thus far, a limitation of such studies is that they do not track patients longitudinally in order to determine whether cognitive deficits predict development of FXTAS or represent a separate phenotype.

Initial investigations of the prevalence of neuropsychiatric disorders in carriers focused on mothers of children with FXS and found subtle differences or no differences at all compared to non-carriers [7,29]. However, subsequent studies have found elevated rates of mood and anxiety disorders in carriers. For example, in carrier mothers of children with FXS, Franke et al reported a 55.7% lifetime incidence of mood disorders, of which 19.7% was major depression, and a 41% lifetime incidence of anxiety disorders [30]. Within the anxiety disorder classification, carriers may be at increased risk of developing social phobia, with recent estimates of lifetime prevalence of 34.2% in a population of both men and women carriers, compared to 12.6% in the general population, as measured in the National Comorbidity Survey Replication (NCS-R) [31]. There is evidence that the elevated risk in this population may be secondary to a synergy between social stressors and the genetic risk itself. Franke et al observed a frequency of social phobias of 18.0% in female carriers who have children with FXS, compared to 5.9% in intra-familial female carriers without a child with FXS [30]. Both of these represent statistically significant elevations over the rate of non-carrier females with an autistic child of 0% that was used as the control. This study is limited by small sample size, as the 5.9% is a result of a single individual with social phobia and the prevalence of social phobia within the general population is >0% (NCS-R data, for example). However, it does suggest that the combination of the premutation with social stressors, such as raising a child with FXS, may put women at significantly elevated risk of developing social phobia. Increased risk of other mood and anxiety disorders in carriers has also been observed. Roberts et al. conducted a study comparing 93 carrier females with 2,159 gender and age-matched controls from the NCS-R data set [32]. Using structured clinical interviews, they found elevated lifetime risk of major depression (43.0% vs. 31.9%), panic disorder without agoraphobia (8.6% vs 2.3%) and current agoraphobia without panic disorder (3.2% vs. 0.7%), but, interestingly, not social phobia. Several studies using similar methodology have similarly observed rates of depression, anxiety disorders or both at about 40% in carriers [34]. Taken as a whole, FXPM carriers appear to have a greater propensity to develop mood and anxiety disorders than the general population. Importantly, carriers have an average older age of onset for major depression, panic disorder and specific phobias compared to the general population [34].

There is very limited evidence on the frequency of personality or psychotic disorders in carriers. There has been reported elevations in schizoid and obsessive compulsive spectrum

personality features along with deficits in social cognition in carriers [13,35]. While individual cases of psychotic disorders have been noted in the literature [36,37] and schizotypal features have been reported [30,38], the rate of distinct psychotic disorders is not thought to be elevated compared to the general population [30,39].

A number of studies have identified structural or functional deficits on MRI in adult carriers, which may underlie a vulnerability to developing neuropsychiatric phenotypes. Several studies have found reduced volume or neuronal density of the hippocampalamygdala complex in subgroups of carriers and reduced amygdala activation has been correlated with global psychological symptom severity [40]. Hessl et al have reported that such blunted amygdala response is associated with deficits in social cognitive processing in adult carrier males [40,41]. Reduced hippocampal volume has been associated with anxiety symptoms in female carriers and reduced hippocampal activation during memory recall has been associated with higher psychiatric morbidity in male carriers [42,43]. Moreover, two recent studies have demonstrated reduced hippocampal and frontal cortex activation during memory tasks and reduced connectivity between these structures [44,45]. Finally, diffusion tensor imaging studies have demonstrated white matter deficits in carriers asymptomatic for FXTAS [45,46]. That such deficits exist in adults asymptomatic for FXTAS, particularly in limbic and frontal cortical areas, suggests a unique underlying neurobiological basis for increased susceptibility to neuropsychiatric phenotypes including ADHD, executive function deficits, disinhibition and impulsivity in carriers.

While disturbances in brain structure and function may predispose to the development of neuropsychiatric illness, several other factors are likely relevant. Some carriers may be more sensitive to psychosocial life stressors and case reports have suggested greater vulnerability when exposed to neurotoxic chemicals [47,48]. Higher rates of alcohol abuse have been documented in both male and female carriers, putting them at further risk for neuropsychiatric comorbidities [49,50]. The fragile X premutation may also predispose individuals to non-CNS medical conditions, which may contribute to the development of neuropsychiatric disorders [50,51]. For example, before age 40, about 20% of female carriers develop fragile X premature ovarian insufficiency (FXPOI), which is characterized by decreased ovarian function and can lead to infertility and early menopause [52]. The associated estrogen deficits and potential feelings of reproductive inadequacy put them at increased risk for mood disorders [53,54]. Likewise, carriers with and without FXTAS have substantial rates of thyroid dysfunction, a known risk factor for mood and anxiety disorders [51]. Carriers may also have an increased susceptibility to conditions such as migraine headaches, fibromyalgia, restless legs syndrome and sleep apnea [55–58]. On a stress-diathesis model of the development of neuropsychiatric disorders, all of these factors may combine with underlying brain abnormalities to produce an elevated risk for neuropsychiatric phenotypes in carriers.

Neuropsychiatric Phenotypes in FXTAS

FXTAS is an often-debilitating movement disorder that occurs in some carriers and increases in prevalence with age. While rare before age 50, it affects 17% of male carriers in their 50s and 75% in their 80s [59] and up to 16% of female carriers [51,59–62]. Rarely,

gray zone carriers may also develop FXTAS as well [3].FXTAS is characterized by progressive symptoms of tremor, ataxia and parkinsonism. Cognitive decline may occur in about 50% of men with FXTAS, at times progressing to dementia [25,34,63–65]. Female carriers become cognitively impaired less often, although there have been reports of women with FXTAS and dementia [66–69]. The predominant cognitive deficit is executive dysfunction, with only mild to moderate decrements in memory, as assessed by the Folstein Mini Mental State Examination (MMSE) [22]. Structured dimensional observations by caregivers using the NeuroPsychiatric Inventory (NPI) noted marked agitation, disinhibition, irritability, apathy and depression, which were often out of proportion to the mild decrements measured on the MMSE [70]. Interestingly, language and visuospatial skills, which are impaired early in Alzheimer's disease, remain relatively intact in FXTAS [22].

This pattern of deficits indicates that FXTAS dementia is a mixed cortical-subcortical dementias, similarly to corticobasal degeneration and dementia with Lewy bodies, which also have parkinsonism as a prominent feature [65,71]. Due to the overlap of clinical signs and symptoms and the limited body of knowledge available to date, FXTAS dementia is difficult to distinguish from other dementias with movement disorders [71]. FXTAS may be mistaken for Parkinson's disease (PD) or spinocerebellar ataxia (SCA) in some cases, although studies have identified the *FMR1* premutation in less than 1% of men clinically diagnosed with multiple system atrophy, PD or SCA [72–74].

A variety of affective and behavioral symptoms can also be seen in FXTAS [35]. Mood and anxiety disorders are common in FXTAS and occur at rates higher than in both age-adjusted controls and carriers without FXTAS [31]. There is a 52% lifetime prevalence of anxiety disorders in patients with FXTAS, including increased rates of panic disorder, specific phobias, and PTSD, as well as a trend toward greater social anxiety compared to the general population prevalence [31]. Similarly, there is a 65% lifetime prevalence of mood disorders in FXTAS, with major depressive disorder occurring twice as often as in age-adjusted norms [31]. Importantly, MDD has a considerably later onset in FXTAS (median age 50) than is seen in the general population (median age 32) and typically precedes the onset of tremor and ataxia [34]. A similar pattern appears to hold for anxiety disorders [34]. Suicidal thoughts occur in at least 5% of patients [39], which is particularly concerning given the frequent co-occurrence of impaired impulse control [31] and substance use disorders [39], which may further increase suicide risk. Suicide attempts in patients with FXTAS have also been reported [39]. The behavioral disturbances seen in FXTAS are likely related to brain changes in areas known to affect behavior. For example, gray matter atrophy has been observed in the dorsomedial prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex, amygdala and insula [40,44,75–77], areas implicated in behavioral disturbances in other dementia syndromes [78].

Clinical Indications for Genetic Testing in Carriers

Clinical pedigree analysis is important in placing premutation disorders in a proper context. The American Academy of Pediatrics currently recommends *FMR1* DNA testing for all children with developmental delay [79] and recommends testing as part of the etiologic workup of children with ASD [80] with or without developmental delay. It follows that

adults with undiagnosed developmental delay or ASD should be tested for *FMR1* mutations. Any evidence of FXS, or even intellectual disability or ASD, in a patient's family pedigree should also lead to greater clinical suspicion for a premutation disorder and trigger consideration of *FMR1* DNA testing. Given the increased incidence of mood or anxiety disorders in carriers [31], adults with mood or anxiety disorders who have a family history of FXS, developmental delay, or ASD should also be screened [38].

Testing for the premutation should be offered to women suffering from POI, as the carrier status has been identified in ~1-8% of women with POI and up to ~13% of women with a family history of POI [81–83]. In the psychiatrist's office, women with both a mood or anxiety disorder and a history of POI or infertility should have *FMR1* DNA testing. Critically, the development of one of these premutation disorders such as FXPOI does not necessarily predispose a carrier to FXTAS [51]. FXTAS also clusters in families so that if a patient has relatives with FXTAS, this will increase the premutation carrier patient's risk for FXTAS with age, presumably because of background genetic factors associated with FXTAS such as APO E4 alleles [84].

Recently, two Spanish studies examined the incidence of the premutation in women with fibromyalgia. One study identified a non-significant trend towards increased frequency of the premutation, with 1/88 women with fibromyalgia testing positive for the premutation compared to 1/250 women without fibromyalgia, which is consistent with published frequency data for the average population (~1/250-1/400) [57]. Another study observed a frequency that was similar to the estimated general population frequency (3/700 or 0.4%) [85]. Further research into the incidence and differing clinical presentations of women with the premutation and fibromyalgia is indicated before recommending screening in this population, unless there are other symptoms such as tremor or a family history of FXD.

It has previously been recommended that adults with mood or anxiety disorders who have a family history of dementia, especially dementia with a movement disorder, should be tested for the premutation [25]. Carrier screening may be considered in adults presenting with cognitive impairment with or without a movement disorder [86], although screening of patients within the parkinsonism clinical spectrum without additional relevant history has not been found to be productive [72,73]. Finally, clinicians may encounter a patient being evaluated for cognitive impairment with or without movement disorders with an MRI finding of middle cerebellar peduncle T2 hyperintensity or "MCP sign." Given the high specificity of this finding, *FMR1* DNA testing is indicated [87,88]. Patients with dementia on clinical examination who have a concurrent movement disorder, in particular tremor and/or ataxia, should also be considered for *FMR1* DNA testing [5]. A summary of recommendations can be seen in Table 1.

Treatment of Premutation Disorders

Currently, there are no personalized treatments available for ASD, DD, ADHD, or epilepsy specifically associated with FXPM. There are ongoing experimental targeted treatments in FXS that will hopefully inform the development of more precise treatments of neurodevelopmental disorders associated with FXPM in the future [1]. For mood and

anxiety disorders, selective serotonin and selective norepinephrine reuptake inhibitors are often used effectively [5,89]. Psychotherapy, particularly, cognitive-behavioral and problem solving therapy are also indicated, focusing on guilt, anxiety and depressive feelings related to carrier status [39]. Albeit rare, agitation or psychosis may develop at later stages of the FXTAS dementia; atypical antipsychotics are preferred over typical agents to minimize exacerbation of parkinsonism [38]. There are specific pharmacological treatments that can improve tremor, such as propranolol and primidone, that are discussed in detail elsewhere [89–91]. Deep brain stimulation has also been shown to be effective for tremor and sometimes ataxia [92]. While anecdotal reports have indicated cognitive benefits with cholinesterase inhibitors or memantine [24,93], a recent controlled trial of memantine did not show efficacy on measures of tremor severity or selected executive function tests [94]. Support of the spouse or partner of the patient with FXTAS is essential, as depression is common in these caretakers as FXTAS progresses [95].

Conclusion

Fragile X premutation conditions, as described in this review, may present prominently with neurological and psychiatric manifestations across the lifespan. Thus, the spectrum of premutation disorders can be conceptualized as ranging from early disturbance in neurodevelopment to later neurodegenerative phenotypes. Premutation cases may therefore present in a variety of clinical contexts, often resulting in referral to either neurologists or psychiatrists. Children with the premutation are most likely to present with ASD or ADHD in boys and anxiety in girls. Those with ASD generally lack the dysmorphic features and intellectual disability seen in FXS. Adult carriers may present with psychiatric manifestations on the depression and anxiety spectra, often with an onset later in life than is typical in the general population. Finally, these same adult carriers are at increased risk of developing a progressive dementia with tremor, ataxia, and parkinsonism often accompanied by depression and anxiety.

It is critical to understand that FXPM conditions are mechanistically and phenomenologically distinct from FXS. While the latter results from a loss of *FMR1* mRNA and protein, FXPM results in elevated *FMR1* mRNA and normal or slightly reduced protein levels. Multiple lines of evidence suggest that pathology in FXPM conditions results from toxic gain of function effects of the elevated mRNA, though a relative reduction of functional FMRP may contribute in some cases. In the broader context of neuropsychiatric illness, FXPM conditions are representative of an evolving class of disorders with both neurologic and psychiatric features. Because the genetic lesion underlying FXPM disorders has been identified, these conditions may act as an illustrative model of neuropsychiatric disease with a strong genetic basis. Currently, standard treatments are recommended for associated mood, anxiety, cognitive and movement disorders. However, increasing recognition of FXPM cases by practicing physicians will facilitate enrollment of research subjects and enable the next generation of advances in our understanding of this class of neuropsychiatric disorders.

Future Perspective

Disorders on the FXPM spectrum offer a unique opportunity to link a defined genetic lesion to structural alterations in the brain that underlie neurological and psychiatric symptoms. Several open questions regarding the etiology of FXPM conditions remain to be answered. While structural and functional alterations in the brains of FXPM carriers likely contribute to the risk of neuropsychiatric phenotypes, it remains unclear to what extent the underlying process is neurodevelopmental versus degenerative in nature. Larger and more complex longitudinal studies of FXPM carriers would be helpful to elucidate which clinical manifestations are eventually associated with the development of a degenerative process. Ultimately, neuropsychiatric manifestations in FXPM carriers likely result from a complex interplay of developmental, neurodegenerative and environmental factors. Additionally, it remains unclear why some carriers develop FXD while others display no symptoms whatsoever.

As our understanding of the molecular and cellular mechanisms involved in FXPM pathology advances, it is likely that new therapeutic avenues will emerge. While a toxic mRNA gain of function mechanism is thought to explain neurodegeneration in FXTAS, some FXPM carriers also have reduced FMRP potentially leading to milder phenotypes on the fragile X spectrum[5,96]. Evidence exists correlating both increased mRNA expression and reduced FMRP with clinical phenotypes in FXPM carriers [35,41]. However, such studies must be interpreted cautiously given that their use of proxy measurements from blood may not accurately reflect levels in the affected brain regions. Work in animal models of FXPM disorders will be critical to understand the molecular genetic processes that lead to neuropsychiatric phenotypes. As we turn to the future, scientific advances in each of the domains described above will likely lead to an increasingly nuanced understanding of the etiology of FXPM spectrum disorders. Such discoveries add to our evolving understanding of the relationship between genetic risk and complex neuropsychiatric phenomenology. Our hope for the future is that such advances will provide the context for earlier detection and increasingly targeted disease modifying therapies for patients with these conditions.

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Executive Summary

Neurodevelopmental Disorders in Carriers

- ASD is more common in carrier boys, and maybe in carrier girls, than related non-carriers or the general population
- Carrier girls are at high risk for developing anxiety disorders
- There is mounting evidence that ADHD and seizure disorders may be more common in carriers, especially in those with ASD

Neuropsychiatric Phenotypes in Adult Carriers without FXTAS

- Adult carriers are at increased risk to develop mood and anxiety disorders even before developing symptoms of FXTAS.
- Mood and anxiety disorders in adult carriers are likely to develop later in life than in the general population

Neuropsychiatric Phenotypes in FXTAS

- FXTAS is a disorder primarily characterized by tremor, ataxia, and parkinsonism, that is often accompanied by cognitive decline, sometime progressing to a full dementia syndrome
- FXTAS can be confused with other disorders that have both movement and cognitive symptoms, so screening for other FXD in the family history can be particularly helpful in making the correct diagnosis

Clinical Indications for Genetic Testing in Carriers

- Genetic testing should be considered for any individual with a family history of FXD and clinical phenotype associated with FXPM, such as ASD, POI, late-life mood or anxiety disorders, or new-onset tremor/ataxia.

Treatment of Premutation Disorders

- Treatment of both neurodevelopmental and mood and anxiety disorders in carriers is currently symptomatic; no targeted medications are yet available
- Good responses to SSRIs and SNRIs for depression and anxiety in carriers have been observed
- Cognitive-behavioral and problem solving therapy have been reported to be effective in reducing guilt, anxiety and depressive feelings related to carrier status

Table 1

Clinical Indications to Obtain Genetic Testing for Fragile X-associated Disorders

	Obtain Testing	**Consider Testing**
Children	• Developmental Delay (DD) • Autism Spectrum Disorder (ASD) • Family history of FXS *and* mood/anxiety disorder	
Women	• Premature Ovarian Insufficiency (POI) • Family history of POI *and* mood/anxiety disorder	• Family history of POI • Fibromyalgia *and* any other clinical indicator
All Adults	• Developmental Delay (DD) • Autism Spectrum Disorder (ASD) • "MCP sign" on MRI • Family history of FXS, DD, or ASD *and* mood/anxiety disorder	• Dementia *and* mood/anxiety disorder • Family history of dementia *and* mood/anxiety disorder