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Risk Factors for Cognitive Impairment in Fragile X-Associated Tremor/Ataxia Syndrome

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Abstract

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disease with motor, psychiatric, and cognitive manifestations that occurs in carriers of the fragile X mental retardation 1 (*FMR1*) gene premutations. This was a retrospective chart review of 196 individuals (127 men, 69 women) with FXTAS. Forty-six (23%) participants were cognitively impaired, of whom 19 (10%) had dementia. Risk factors for dementia were examined (CGG repeat size; alcohol, benzodiazepine, and opioid use; diabetes; hyperlipidemia; hypertension; hypothyroidism; obesity; sleep apnea; surgeries with general anesthesia; depression; and family history of dementia). Thirteen individuals with FXTAS and dementia were compared with thirteen cognitively intact individuals matched on age, gender, and FXTAS stage. CGG repeat size was significantly higher (mean 98.5, SD = 22.2) in the dementia group, compared to the cognitively intact group (mean = 81.6, SD = 11.5; p=0.0256). These results show that CGG repeat size is a risk factor for FXTAS dementia.

Keywords

cognitive impairment; dementia; FXTAS

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Background

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder with motor, psychiatric, and cognitive manifestations that occurs in carriers of the premutation (with 55 to 200 CGG repeats) of the fragile X mental retardation 1 (*FMR1*) gene.[1,2] FXTAS affects approximately 40% of male carriers in their 60's and 8–16% of female carriers.[3,4] Clinically, FXTAS is believed to represent a continuum of symptoms, with psychiatric manifestations typically preceding neurological deficits which, in turn, may be followed by cognitive impairment later in the course of the illness.[5–9] Underlying neurobiological correlates are not yet clear, although progressive mRNA toxicity, production of polyglycine-*FMR1* protein, and altered connectivity in white matter tracts that serve cognitive, emotional, and motor functions have been found and postulated to be related or causal to FXTAS.[2,5,10–12] The longitudinal trajectory of FXTAS and the approximate timeline of clinical progression have yet to be elucidated. Previous studies have shown that up to 42% of men with FXTAS may develop dementia.[6,7] However, at this time it is not known which premutation carriers will develop cognitive impairment, who will convert to dementia, and what risk factors, if any, predispose individuals to this severe FXTAS manifestation.

The median ages of onset of major depressive disorder (MDD), panic disorder, and specific phobia have been shown to be significantly higher in premutation carriers compared to the general population, supporting the hypothesis that different pathophysiological mechanisms are at play.[5] Tremor occurs around 55–60 years of age, followed by ataxia after a variable time period, identified by some researchers as 1–2 years and others as 5–7 years.[1,5,13] Clinically significant cognitive deficits can occur 1–13 years after the onset of motor symptoms in those with FXTAS, although subtle deficits have been demonstrated in both male and female carriers without FXTAS.[6,14–19] The predominant cognitive deficit is executive dysfunction, which has been well characterized in carriers with and without FXTAS and shown to be correlated with age and CGG repeat size.[17,18,20] Rarely, FXTAS can also present with a rapidly progressive dementia or gradual cognitive decline preceding the onset of notable motor symptoms.[6,21,22]

In this study, we set out to examine the potential impact of several risk factors on cognitive impairment in FXTAS. We selected risk factors known to be associated with other dementias such as Alzheimer's disease (AD) or vascular dementia and/or factors we believed might be associated with FXTAS dementia: CGG repeat size; alcohol, benzodiazepine, and opioid medication use; diabetes mellitus; hyperlipidemia; hypertension; hypothyroidism; sleep apnea; surgeries with general anesthesia; lifetime history of depression, and family history of dementia. We controlled for age, FXTAS stage, and gender, which have already been shown to significantly differ in cognitively impaired, compared to cognitively intact carriers with FXTAS.

Age

Advanced age is the main risk factor for several dementias. The prevalence of AD doubles approximately every five years after age 60.[23] Similar associations, albeit in small samples, have been described among individuals with FXTAS, with older carriers being more prone

to cognitive deficits, including dementia.[6,7,17] In the 68 individuals with FXTAS we described previously, cognitively impaired participants were significantly older (mean age, 69 years; range, 55 to 89) than those who were cognitively intact (mean age, 62.8 years; range, 42 to 81; p=0.009).[6] Participants showed progressive decline in executive function (verbal fluency, working memory), attention, memory, language (confrontational naming), visuospatial skills, and personality changes.[6] In another study, two of eleven (18%) carriers between ages 50–60 and 21/39 (53%) over age 60 had cognitive deficits, as evaluated by a neuropsychological test battery including measures of general cognition, executive function, and memory.[1] Significant reductions in general intelligence scores and marginally significant deficits in logical memory have also been shown in male carriers with FXTAS over age 50, compared to their noncarrier male siblings.[24]

CGG repeat size

CGG repeat size has been shown to inversely correlate with the onset age of tremor and ataxia and age of death in FXTAS patients.[25,26] In a population-based study, the penetrance of marked cognitive impairment in male premutation carriers with over 70 CGG repeats was six times higher than in controls (33.3% vs. 5.1%), which was not true for those with CGG repeat sizes of 45–70.[27] Cornish and colleagues showed that male carriers aged 18–69 years with less than 100 CGG repeats were relatively risk-free from cognitive aging effects, whereas those with CGG repeat sizes over 100 had reduced performance on executive function tests involving inhibition and working memory.[17] In the cohort of 68 individuals with FXTAS we previously reported, the mean CGG repeat size in the 21 men with dementia was 97 (standard deviation, SD 20).[6] Jenkins and colleagues described five men with FXTAS and dementia whose mean CGG repeat size was 104 (SD 24).[28]

FXTAS stage

FXTAS stages parallel the length of illness and correlate with the severity of clinical involvement. Six FXTAS stages have been described based on progression of motor deficits. They are as follows: 1, subtle or questionable tremor and/or balance problems; 2, minor tremor and/or balance problems, with minimal interference in activities of daily living (ADLs); 3, moderate tremor and/or balance problems with significant interference in ADLs; 4, severe tremor and/or balance problems, having to rely on a cane or walker; 5, daily use of a wheelchair; and 6, patients are bedridden.[29] By 16 years into the course of illness, half of the patients have significant difficulty with their ADLs; median survival is 21 years from the onset of first signs of FXTAS.[13,30] In the cohort described by Gane and colleagues, all seven men with FXTAS dementia were in more advanced stages (3–5).[7]

Gender

Female gender is a risk factor for AD.[23] Women with the premutation have less severe clinical involvement and were initially believed to not develop FXTAS dementia, due to the protective effects of the second X chromosome.[3,6] Only several women with FXTAS and dementia have been reported to date.[31–35] Since there is a pronounced gender disparity with regard to cognitive impairment in FXTAS, we chose to control for gender in this study.

Lifetime depression

Depression can be a prodrome as well as a risk factor for dementia. Individuals with late-life depression and associated cognitive changes (which typically subside after remission of depression) often develop dementia a few years after the onset of depression.[36,37] A lifetime history of depression increases the risk of AD, regardless of family history of dementia.[38] Also, patients with mild cognitive impairment and depression have a higher risk of progression onto dementia, especially vascular dementia.[39] Patients with FXTAS have a 65% lifetime prevalence of mood disorders, including MDD, which is significantly higher than that of the age-matched general population.[9] Therefore, it is important to assess the potential impact of lifetime depression on cognitive status in FXTAS.

Other medical illness

Female premutation carriers may have primary ovarian insufficiency, thyroid problems, peripheral neuropathy, hypertension, fibromyalgia, autoimmune diseases, and migraines, while male carriers often have type II diabetes, hypertension, sleep apnea, migraines, and cardiovascular disease.[3,4,40–42] These medical problems typically occur before the onset of FXTAS.[2] Hypothyroidism is a well-known, usually reversible, etiology of cognitive impairment. The cerebrovascular risk factors (diabetes mellitus, hyperlipidemia, and hypertension) heighten the risk of vascular dementia and have also been linked to AD, along with midlife obesity, smoking, depression, low educational attainment or cognitive inactivity, and physical inactivity.[43,44] Approximately a third (31.4%) of premutation carriers with FXTAS have sleep apnea.[41] Sleep apnea contributes to the development of metabolic syndrome and cognitive disorders.[45,46] The mechanisms through which obstructive sleep apnea affects cognition are not yet clear; cerebrovascular insult and cortisol dysregulation have been implicated.[46,47]

Substance use

Alcohol and other CNS depressants, such as benzodiazepine or opioid medications, may contribute to cognitive impairment. In a chart review of 184 premutation carriers with and without FXTAS, 24% were found to have substance abuse or dependence, based on DSM-IV TR criteria (most often alcohol, and more frequently in men).[48] Also using DSM-IV-TR criteria, Kogan et al. showed significantly higher rates of alcohol abuse in male carriers and age-matched family controls, compared to non-family controls.[49] Due to this high prevalence of substance use among carriers, we examined alcohol, benzodiazepine, and opioid medication use in our sample and their potential contribution to FXTAS dementia.

Surgeries with general anesthesia

There is anecdotal evidence that surgeries involving general anesthesia may exacerbate premutation-associated changes. Several carriers over 60 years of age reported onset of tremor or ataxia within weeks of surgery with general anesthesia.[2] The pathophysiological mechanism is not well understood; it could involve hypoxia or direct effects of one of the agents used during general anesthesia.[2]

Methods

Study design and participants

The study protocol was approved by the Institutional Review Board at the University of California (UC) Davis Medical Center. All participants gave informed consent. Participants were *FMR1* premutation carriers with FXTAS enrolled in a large research study at the UC Davis Medical Investigation of Neurodevelopmental Disorders (MIND) Institute between 2002 and 2014. This was a retrospective chart review of 196 premutation carriers (127 men, 69 women) with FXTAS, stages 2–6. Data collected included demographic (age, gender, education level), molecular (CGG repeat size), and clinical variables: FXTAS stage, mini-mental state examination (MMSE), alcohol, benzodiazepine, and opioid medication use, body mass index, diabetes mellitus, hyperlipidemia, hypertension, hypothyroidism, sleep apnea, surgeries with general anesthesia in adulthood, lifetime depression, and family history of dementia.

All participants received a detailed medical and neurological examination, medical history, neuropsychological test battery, and psychiatric assessment. Collateral information was obtained from caregivers. The participants' current and past medication lists were reviewed, noting opioid and psychotropic medications. Individuals with history of cerebrovascular accidents, traumatic brain injury, and/or neurosurgical interventions were not excluded. FXTAS diagnosis and stages were established based on published criteria.[2,29,40] Comorbidity with diabetes, hyperlipidemia, hypertension, and hypothyroidism was ascertained from the medical history form (self-report or caregiver report) and by double-checking the medication list for medications used to treat these conditions. The body mass index (BMI) was calculated for each participant, based on their height (cm) and weight (kg), then classified into normal range (BMI<24.9), overweight (BMI 25–29.9), and obese (BMI>30). Sleep apnea and surgeries with general anesthesia during adulthood were ascertained from the physical examination and medical history forms.

Psychiatric assessments were performed by experienced clinicians and consisted of open-ended interviews until August 2007. Starting in September 2007, the Structured Clinical Interview for DSM-IV-TR (SCID)-I was used, customized to capture the most common psychiatric conditions in *FMR1* premutation carriers (mood, anxiety, substance use, somatoform, and adjustment disorders, plus the screening questions for psychotic symptoms).[50] The SCID provides information on lifetime and current psychiatric diagnoses. For purposes of this study, lifetime diagnoses were collected and analyzed. Due to low numbers in each category, MDD, dysthymia, and depressive disorder not otherwise specified (NOS) were grouped together as "depression" for analytic purposes.

The diagnoses of cognitive disorder NOS and dementia were established in two ways: through retrospective chart review, for early participants (2002–2005); and through psychiatric interviews, for later participants (2006–2014). Cognitive disorder NOS was diagnosed according to DSM-IV-TR criteria, based on the presence of cognitive deficits that did not meet criteria for delirium or dementia.[51] Dementia was diagnosed using the National Alzheimer's Coordinating Center (NACC) criteria: deficits in two or more cognitive domains (including executive function, complex attention, memory, language, visuospatial

skills, and personality), progression of deficits, and functional decline.[52] Memory impairment was not a necessary criterion, although it was often present, and functional decline had to be deemed secondary to the cognitive, rather than motor, deficits.[6] As part of the larger research study, many participants returned for annual follow-up visits. If data from more than one visit were available, the most recent visit was taken into consideration, given the potential progression of cognitive deficits. MMSE scores from the same visit were used, in order to accurately reflect the participants' cognitive status at the time. Family history of dementia was ascertained through SCIDs or clinical interviews, as available.

Statistical analysis

Descriptive statistics were summarized as mean ± SD or frequency (%). Normality of the data distribution for each continuous variable was checked using the Shapiro-Wilk test prior to inferential analysis. Participants with a history of traumatic brain injury (TBI, n=2), cerebrovascular accidents (CVA, n=1), and deep brain stimulation (DBS) surgery (n=3) were excluded from the statistical inter-group comparisons. One participant with dementia was also excluded from the comparison analysis, due to an outlier MMSE score of 3. A subset of 29 cognitively impaired participants was then compared with 29 cognitively intact individuals with FXTAS, matched on age (± 5 years), gender, and FXTAS stage. Matches were found for only 29 of the cognitively impaired participants because there were fewer cognitively intact individuals in advanced FXTAS stages. The two groups of FXTAS patients (cognitively impaired and intact) were compared with regard to demographic, molecular, and clinical parameters using t-tests for continuous measures or Wilcoxon tests for those that were not normally distributed and chi-square (Fisher's exact) tests for categorical measures as appropriate. The two groups (cognitively impaired and cognitively intact) were then stratified by FXTAS stages: early (2–3) and late (4–5), and further compared in separate analyses. No cognitively intact individuals were found in stage 6 who could match the cognitively impaired participants by age or gender; thus, no stage 6 participants were included in this analysis.

The next analyses focused on 13 participants with FXTAS and dementia, compared with 13 cognitively intact individuals, matched by age (± 5 years), gender, and FXTAS stage. Again, these numbers are lower than the number of participants with dementia (n=19) in the overall group, because there were fewer cognitively intact individuals among older participants and thus no suitable matches could be found. The two subgroups were compared with regard to the demographic, molecular, and clinical variables, as described above. Q-values (i.e., false positive rate adjusted p-values) were calculated to account for multiple testing.[53] A two-sided p-value <0.05 was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc.).

Results

After excluding those with a history of CVA, TBI, and DBS surgery, 46 (23%) of the 196 participants with FXTAS were cognitively impaired, of whom 19 (10%) had dementia. Table 1 summarizes the demographic, molecular, and clinical characteristics of the study participants, first presenting the entire group of cognitively impaired individuals (n=46),

then a subgroup of 29 cognitively impaired participants for whom matches were available, and then a group of 29 cognitively intact individuals matched in age (± 5 years), gender, and FXTAS stage with the previous subgroup. At the time of the chart review, among the cognitively impaired participants, seven had died, two had been placed in long-term care, and one had entered hospice four years prior and was lost to follow-up, whereas two cognitively intact participants had died.

When comparing the two subgroups of cognitively impaired and cognitively intact individuals with FXTAS, no significant differences were found, except for MMSE scores. As expected, the mean MMSE score in the cognitively impaired group was lower (27, SD 3.4) than the mean MMSE score of cognitively intact participants (29.2, SD 0.7; p=0.0006) (see Table 1). This difference remained consistent when stratified by FXTAS stages: early (2–3) and late (4–5). The mean MMSE scores for the cognitively impaired participants (27.3, SD 3.9 in early stages; 26.7, SD 3.1 in late stages) were consistently lower than the mean MMSE scores of cognitively intact matches (29.3, SD 0.7 in early stages; 29.1, SD 0.7, p=0.0021 in late stages).

Table 2 summarizes the demographic, molecular, and clinical characteristics of the participants with FXTAS and dementia, first for the entire group (n=19), then a subgroup of 13 individuals with dementia, and then a group of 13 cognitively intact individuals matched in age (± 5 years), gender, and FXTAS stage with the previous subgroup. Three (16%) of the 19 participants with dementia also had anxiety disorders, including generalized anxiety disorder, panic disorder, posttraumatic stress disorder, social phobia, and specific phobia; five (26%) had depressive disorders, including major depressive disorder, dysthymia, and depressive disorder not otherwise specified; and four (21%) had alcohol abuse or dependence. Many carriers had multiple comorbid psychiatric diagnoses.

When comparing the 13 individuals with FXTAS dementia with the 13 cognitively intact matches, again no significant differences were found, with the exception of MMSE scores and CGG repeat size. As expected, the mean MMSE score in the dementia group was significantly lower (24.7, SD 4.1) than the mean MMSE score among cognitively intact participants (29, SD 0.8; p=0.0003). Mean CGG repeat size was significantly higher in those with dementia (98.5, SD 22.2), compared to cognitively intact participants (81.6, SD 11.5; p=0.0256) (see Table 2).

Discussion

To our knowledge, this is the largest cohort to date of cognitively impaired individuals with FXTAS (n=46), including the largest group of carriers with FXTAS and dementia (n=19). This is also the first study to explore risk factors for cognitive impairment (and more specifically, dementia) in FXTAS. An extensive body of literature characterizes the cognitive impairment in premutation carriers, however there are few studies focusing on FXTAS dementia and only one comparison study with another neurodegenerative disease, AD.[6,29,35] FXTAS dementia was first described in 2006 as a frontal-subcortical dementia by Bacalman and colleagues.[29] Subsequent neuropsychological, psychiatric, and cognitive event-related potential studies showed that the pattern of cognitive deficits in FXTAS is different from that

of AD.[6,19,54] Over the last decade, FXTAS dementia has emerged as a distinct cortical-subcortical dementia, characterized by psychomotor slowing and deficits in multiple cognitive domains, including executive function, memory (retrieval and recall), attention, language, visuospatial skills, and social cognition (described as personality changes in earlier studies).[6,29,35,55] Eosinophilic ubiquitin-positive intranuclear inclusions have been demonstrated in both neurons and astrocytes in cortical (especially frontal cortex and hippocampi) and subcortical areas (including the cerebral and cerebellar white matter and deep cerebellar nuclei).[6,26,35] Tassone et al. reported on eight female premutation carriers, three of whom had FXTAS and dementia.[35] On neuropathological examination, all of the women had the ubiquitin-positive intranuclear inclusions specific for FXTAS. Three of the eight women also had cortical neurofibrillary tangles and amyloid plaques consistent with comorbid AD, and a fourth had cortical Lewy bodies.[35] The authors concluded that FXTAS can co-occur with other neurodegenerative processes, in some cases hastening clinical progression. In the present study, the diagnosis of FXTAS dementia was established clinically.[5] All participants with dementia met descriptive criteria for FXTAS dementia (see Table 3).[6,35,55] Only 10% of the larger cohort met clinical diagnostic criteria for dementia, a lower percentage than that found in previous studies (31% overall, 42% for men).[6] The present study examined all cognitively impaired participants from a large cohort of carriers with FXTAS studied for over a decade, thus 10% is likely the most accurate estimate of dementia prevalence among individuals with FXTAS to date. The rate of dementia among women with FXTAS was low in our study, consistent with previous findings (4 out of 69 women in the overall cohort, 6%), whereas 12% of men with FXTAS had dementia (15 out of 127 men in the overall cohort). Of note, if DSM-5 diagnostic criteria for major neurocognitive disorders were used, more participants would have met criteria, since DSM-5 only requires deficits in one or more cognitive domains, whereas NACC criteria call for impairment in two or more domains.[52,56]

The present study examined cognitive risk factors in a group of 46 carriers of both genders with FXTAS, including 19 participants with dementia and 27 with cognitive disorder NOS. Older age, male gender, and FXTAS stages 3–5 have previously been shown to be associated with FXTAS dementia.[6,7] Higher education level is known to be protective against cognitive loss.[57] Our cognitively impaired participants and cognitively intact matches had a similar educational attainment (15 years, on average), typical for premutation carriers.[6,7,58] The present study was a comprehensive analysis of multiple variables and revealed only one factor significantly associated with the development of FXTAS dementia, namely CGG repeat size. CGG repeat size had been previously associated with other FXTAS clinical features, such as age of onset of tremor and executive dysfunction.[17,25] However, this is the first study implicating this genetic marker as a risk factor for FXTAS dementia. This is consistent with previous studies showing mean CGG repeat sizes of 97 and 104, respectively, in carriers with dementia.[6,28] Other researchers uncovered an age-CGG repeat size interaction, wherein male carriers with over 100 CGG repeats were more susceptible to aging effects on measures of executive function.[17] Similar associations have been revealed in other neurodegenerative diseases. For instance, higher CAG repeat size predicts an earlier onset of Huntington’s disease.[59]

Recent research suggests there may be at least two FXTAS motor phenotypes.[1] The more common phenotype has tremor as the predominant manifestation, with ataxia being salient in the second phenotype.[1,60] Juncos and colleagues showed that the duration of ataxia was significantly longer in cognitively impaired participants, when compared to cognitively intact individuals with FXTAS; on the other hand, duration of tremor was not associated with cognitive impairment.[1] This is consistent with a recent prospective study of patients with Parkinson's disease (PD), showing that gait dysfunction, along with cardiovascular autonomic dysfunction, REM sleep behavior disorder, and color discrimination ability strongly predicted the development of PD dementia (PDD).[61] Other risk factors for PDD include age over 75 years, length of illness (longer than 10 years from diagnosis), rigid-akinetic phenotype (of which gait dysfunction is a component), low education level, and postural instability.[62] Duration of ataxia was not noted nor differentiated from tremor duration in the present study. Additional studies should seek to replicate the association between the FXTAS ataxia-predominant phenotype and cognitive impairment.

In our group of 19 participants with FXTAS dementia, three were noted to convert from cognitive disorder NOS to dementia over time, although these data were not systematically collected. Factors that predict conversion of mild cognitive impairment to AD include genetic markers (apolipoprotein E ε4), neuropsychiatric symptoms (particularly depression), and small hippocampal volume, among others.[63–65] In a study of 44 *FMR1* premutation carriers, presence of at least one apoE ε4 allele increased the risk for developing FXTAS.[66] Future prospective studies will be helpful in uncovering risk factors for conversion to dementia in FXTAS. The present study had a retrospective design and thus, it could not provide the data necessary to make any inferences in this regard. Additional neuropsychiatric symptoms in FXTAS dementia have been described: disinhibition, impulsivity, mood lability, irritability, apathy, and agitation.[29] Future studies should also explore the prevalence of these symptoms and any correlation with cognitive impairment.

A history of depression has been linked to risk of dementia, although the correlation still warrants elucidation. The duration of untreated depression correlates with hippocampal volume loss, which in turn accelerates cognitive decline.[65,66,67] In the present study, most depressed participants either took or had taken antidepressant medications. The onset and duration of depressive symptoms were explored however it was not consistently noted whether these were adequately treated. The lifetime prevalence of depressive disorders in our sample was over 50% in both the cognitively impaired and cognitively intact groups. This is not surprising, given that previous research had found a similar (44%) combined lifetime prevalence for MDD and dysthymia in premutation carriers with and without FXTAS, also by using the SCID.[9,58] These results confirm that depressive disorders are common in premutation carriers, although no differences were observed between cognitively impaired and intact participants with FXTAS in the present study.

Given the high prevalence of cardiovascular disease in *FMR1* carriers, particularly men, we explored the association of cerebrovascular risk factors (diabetes, hyperlipidemia, hypertension, and obesity) with cognitive impairment and dementia in FXTAS. We found that approximately half of the participants had hyperlipidemia (48%) and even more had high blood pressure (65%), although only 22% had diabetes. Similarly, about half (51%) of

the participants were obese. However, there were no significant differences on any of these variables when comparing the cognitively impaired and intact groups. Cerebrovascular risk factors should be addressed in any patient population in order to reduce the risk of co-occurring vascular dementia and AD.

Alcohol and other CNS depressants are known risk factors for cognitive impairment, and rates of substance use have been found to be high in premutation carriers with and without FXTAS.[48,49] In the present study, no differences were found when comparing alcohol use among cognitively impaired and cognitively intact participants. It is possible that numbers were too low for a meaningful comparison. The percentage of benzodiazepine users (13%) is consistent with previous treatment studies in FXTAS.[68,69] This could be because clinical practice guidelines strongly suggest avoiding benzodiazepines in patients with FXTAS, especially those with dementia, due to deleterious cognitive effects and high risk of falls.[48,70]

Other variables examined with regard to potential risk of cognitive impairment in FXTAS were surgeries with general anesthesia and family history of dementia. Data were incomplete in these areas. Exact dates of surgeries were available for some participants but not for all; in some cases, general anesthesia history was not specifically listed and had to be inferred based on the anatomical location of the surgery. One cognitively impaired participant in this study had had a severe allergic reaction (coma) to succinylcholine, confirming prior reports that premutation neurons are more sensitive to toxins, including general anesthesia.[2] Future studies should elucidate this aspect, as well as the contribution of family history to FXTAS dementia. Family history of dementia is a known risk factor in other dementias and an anecdotal association has been described in female *FMR1* premutation carriers.[33,38]

In the present study, both comparison analyses (cognitively impaired vs. intact, and dementia vs. cognitively intact, respectively) revealed significant differences in mean MMSE scores. As in our previous studies, the MMSE was not emphasized, because it mostly measures cortical functions, whereas FXTAS dementia combines cortical and subcortical features.[6,18,29,69] While MMSE scores may be lower in a subgroup of participants with FXTAS and prominent recall deficits, this may not be true of others. Future research can utilize other instruments, better suited for detecting executive dysfunction and subcortical cognitive deficits.

In conclusion, CGG repeat size is a risk factor for developing FXTAS dementia. Further studies with larger samples and longitudinal designs are warranted to confirm this result and explore other risk and protective factors.

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Table 1

Demographic, molecular, and clinical characteristics of study participants.

	All cognitively impaired (n=46)		Cognitively impaired with matches(n=29)		Cognitively intact matches (n=29)		Comparison		
Variable	**N (%)**	**Mean (SD)**	**N (%)**	**Mean (SD)**	**N (%)**	**Mean (SD)**	**p-value (stages 2–5)**	**p-value (stages 2–3)**	**p-value (stages 4–5)**
Age (years)	46	68.4 (7.8)	29	66.8 (8.3)	29	67.2 (7.3)	0.8271	0.6686	0.9234
Education (years)	46	15.8 (2.9)	29	15.4 (2.9)	29	15.3 (3.3)	0.9326	0.3764	0.4665
CGG repeats	46	94.7 (18.6)	29	94.5 (19.6)	29	87.6 (15.7)	0.1451	0.7816	0.0623
MMSE	42	26.7 (3.2)	28	27 (3.4)	29	29.2 (0.7)	0.0006 * (q=0.0078)	0.0850	0.0021 * (q=0.0280)
Gender									
Female	9 (20)		7 (24)		7 (24)				
Male	37 (80)		22 (76)		22 (76)				
FXTAS stage									
2	3 (7)		3 (10)						
3	11 (24)		11 (38)						
4	22 (48)		12 (41)						
5	8 (17)		3 (10)						
6	2 (4)		0 (0)						
Cognitive disorder									
Cognitive dis. NOS	27 (59)		16 (55)				–	–	–
Dementia	19 (41)		13 (45)				–	–	–
BMI									
All	41	30.3 (4.7)	26	30 (3.7)	25	29.4 (4.8)	0.8760	0.3201	0.2581
Normal (<24.9)	4 (10)		2 (8)		4 (16)		0.7352	0.3710	0.6951
Overweight (25–29.9)	16 (39)		12 (46)		11 (44)				
Obese (>30)	21 (51)		12 (46)		10 (40)				
	N[a]	**Yes**[b] **n (%)**	**N**[a]	**Yes**[b] **n (%)**	**N**[a]	**Yes**[b] **n (%)**			
Alcohol	41	6 (15)	27	4 (15)	29	4 (14)	1	0.6483	1
Benzodiazepines	46	6 (13)	29	5 (17)	29	4 (14)	1	0.3845	0.4828
Opioids	43	4 (9)	28	2 (7)	29	2 (7)	1	n/a	1

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	All cognitively impaired (n=46)		Cognitively impaired with matches(n=29)		Cognitively intact matches (n=29)		Comparison		
Variable	**N (%)**	**Mean (SD)**	**N (%)**	**Mean (SD)**	**N (%)**	**Mean (SD)**	**p-value (stages 2–5)**	**p-value (stages 2–3)**	**p-value (stages 4–5)**
Diabetes	46	10 (22)	29	6 (21)	29	1 (3)	0.1020	0.5956	0.2241
Hyperlipidemia	46	22 (48)	29	15 (52)	29	10 (34)	0.2889	1	0.0656
Hypertension	46	30 (65)	29	18 (62)	29	18 (62)	1	0.7036	0.6999
Hypothyroidism	46	10 (22)	29	7 (24)	29	5 (17)	0.7470	0.6483	1
Sleep apnea	46	16 (35)	29	9 (31)	28	9 (32)	1	1	0.7152
Surgeries	42	35 (83)	28	24 (86)	28	24 (86)	1	1	1
Depression[c]	35	21 (60)	24	14 (58)	28	14 (50)	0.5879	0.2671	1
FH of dementia	24	3 (13)	15	3 (20)	21	7 (33)	0.4682	0.6186	0.6329

[*] Statistically significant difference at $p < 0.05$; q is the false positive rate (FDR) adjusted value of p-value accounting for multiple testing.

[a] N = the number of participants in each category for whom data were available

[b] Yes = the number of participants who used alcohol, benzodiazepines, or opioid medications or who had diabetes, hyperlipidemia, hypertension, hypothyroidism, sleep apnea, surgeries with general anesthesia, depressive disorders, or family history of dementia

[c] Based on DSM-IV-TR criteria: includes major depressive disorder, dysthymia, and depressive disorder not otherwise specified; several participants had both dysthymia and major depressive disorder.

BMI = body mass index; FH = family history; FXTAS = fragile X-associated tremor/ataxia syndrome; MMSE = Mini Mental State Examination; NOS = not otherwise specified; SD = standard deviation.

Table 2

Demographic, molecular, and clinical characteristics of participants with dementia.

	All dementia (n=19)		Dementia with matches (n=13)		Cognitively intact matches (n=13)		
Variable	**N (%)**	**Mean (SD)**	**N (%)**	**Mean (SD)**	**N (%)**	**Mean (SD)**	**p-value**
Age (years)	19	71.7 (8)	13	70.7 (7.7)	13	70 (6.6)	0.8081
Education (years)	19	15.4 (3)	13	15.2 (3.1)	13	14.9 (4.3)	0.8366
CGG repeats	19	94.1 (21.3)	13	98.5 (22.2)	13	81.6 (11.5)	0.0256* (q=0.1886)
MMSE	15	24.5 (4)	12	24.7 (4.1)	13	29 (0.8)	0.0003* (q=0.0044)
Gender							
Female	4 (21)		2 (15)		2 (15)		
Male	15 (79)		11 (85)		11 (85)		
FXTAS stage							
2	1 (5)		1 (8)		1 (8)		
3	3 (16)		3 (23)		3 (23)		
4	8 (42)		6 (46)		6 (46)		
5	5 (26)		3 (23)		3 (23)		
6	2 (11)		0 (0)		0 (0)		
BMI							
All	16	29 (5)	11	28.4 (3.6)	13	29.2 (3.7)	0.6139
Normal (<24.9)	2 (13)		1 (9)		1 (8)		0.6792
Overweight (25–29.9)	9 (56)		8 (73)		7 (54)		
Obese (>30)	5 (31)		2 (18)		5 (38)		
	N[a]	**Yes**[b] **n (%)**	**N**[a]	**Yes**[b] **n (%)**	**N**[a]	**Yes**[b] **n (%)**	
Alcohol	15	4 (13)	11	2 (18)	13	3 (23)	1
Benzodiazepines	19	1 (5)	13	1 (8)	13	2 (15)	1
Opioids	17	2 (21)	12	1 (8)	13	0 (0)	0.4800
Diabetes	19	4 (21)	13	4 (31)	13	0 (0)	0.0957
Hyperlipidemia	19	9 (47)	13	8 (62)	13	6 (46)	0.6951
Hypertension	19	13 (68)	13	8 (62)	13	9 (69)	1

	All dementia (n=19)		Dementia with matches (n=13)		Cognitively intact matches (n=13)		
Variable	**N (%)**	**Mean (SD)**	**N (%)**	**Mean (SD)**	**N (%)**	**Mean (SD)**	**p-value**
Hypothyroidism	19	3 (16)	13	2 (15)	13	2 (15)	1
Sleep apnea	19	8 (42)	13	6 (46)	13	4 (31)	0.6882
Surgeries	16	14 (88)	12	11 (92)	13	12 (92)	1
Depression[c]	12	5 (42)	9	3 (33)	13	7 (54)	0.4149
FH of dementia	10	1 (10)	7	1 (14)	10	4.(40)	0.3382

[*] Statistically significant difference at p <0.05; q is the false positive rate (FDR) adjusted value of p-value accounting for multiple testing.

[a] N = the number of participants in each category for whom data were available

[b] Yes = the number of participants who used alcohol, benzodiazepines, or opioid medications or who had diabetes, hyperlipidemia, hypertension, hypothyroidism, sleep apnea, surgeries with general anesthesia, depressive disorders, or family history of dementia

[c] Based on DSM-IV-TR criteria: includes major depressive disorder, dysthymia, and depressive disorder not otherwise specified; several participants had both dysthymia and major depressive disorder.

BMI = body mass index; FH = family history; FXTAS = fragile X-associated tremor/ataxia syndrome; MMSE = Mini Mental State Examination; SD = standard deviation.

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Table 3

Clinical features of FXTAS dementia.[6,28,55]

Clinical features	
Prevalence[a]	10–31%
Cognitive domains affected	
Executive function	Common, may be severe (inability to follow sequence of steps, difficulty shifting sets, impaired planning skills)
Memory	Common (retrieval and recall)
Attention	Relatively common
Personality/social cognition	Relatively common (disinhibition, apathy, loss of social decorum, loss of empathy)
Language	Rare (word-finding difficulties)
Visuospatial skills	Rare
Motor symptoms	Intention tremor, gait ataxia, parkinsonism
Neuropsychiatric symptoms	
Anxiety[b]	15–16%
Depression[c]	20–26%

[a] 12% in the present study; 31% in previous study[6]

[b] 15% in previous study by symptom review,[6] 16% in the present study by Structured Clinical Interview for DSM-IV-TR (SCID)

[c] 20% in previous study by symptom review,[6] 26% in the present study by SCID