**Symposium Title:** Clinical impairments and key predictors of degeneration during aging in female premutation carriers of the Fragile X gene, *FMR1*

**Chair(s):** Matthew W. Mosconi[[1]](#footnote-1),[[2]](#footnote-2); Jessica Klusek[[3]](#footnote-3)

**Discussant:** Randi J. Hagerman[[4]](#footnote-4)

**Overview**: Premutation alleles of the Fragile X gene, *FMR1*, are associated with a range of psychiatric and physical health conditions that reduce quality of life for carriers and their families.Fragile X-associated tremor/ataxia syndrome (FXTAS), a neurodegenerative disease defined by action tremor, ataxia, and neurocognitive decline, represents the most severe condition of aging associated with *FMR1* premutation alleles. While FXTAS is far more penetrant among male relative to female premutation carriers, there is increased recognition that a subset of female premutation carriers develop FXTAS during aging and that their declines may be severe. Emerging evidence also suggests that clinical issues during aging and FXTAS presentation each may vary in sex-specific ways among premutation carriers. These findings highlight the urgent need to clarify aging-related changes in females and determine key predictors of FXTAS onset so that therapeutic strategies may be introduced early in disease course when they are most likely to be effective. During this panel, new results will be presented to define clinical phenotypes associated with aging in female premutation carriers and identify predictors of FXTAS degeneration in women. This symposium includes an interdisciplinary, multi-institute panel that will share new findings on sex-specific patterns of degeneration during aging among female *FMR1* premutation carriers.

**Paper 1 of 4**

**Title:** Sensorimotor, memory, and brain changes associated with aging in females with premutation alleles of the Fragile X gene, *FMR1*

**Authors**: Matthew W. Mosconi1,2, Robin Shafer1, Kathryn Unruh1, Abigail Driggers1,[[5]](#footnote-5), Sydney Gardner1, Sophia Peterson1, Cassandra Stevens1,2, Kristen McGatlin[[6]](#footnote-6), Andrea Lee[[7]](#footnote-7), Richard Dubinsky7, Randi J. Hagerman4, Flora Tassone[[8]](#footnote-8), Heather Bailey6

**Introduction:** Premutation alleles of the Fragile X gene, *FMR1*, are associated with a range of developmental, psychiatric, and medical issues. Fragile X-associated tremor/ataxia syndrome (FXTAS) represents the most severe medical condition associated with *FMR1* premutations. It is defined by action tremor, ataxic gait, and white matter degeneration of the cerebellum, but separate clinical and brain changes also may be present, including changes in executive and memory functions and white matter degeneration in cerebrum and corpus callosum. Diagnostic criteria for FXTAS were originally defined based on observations of male premutation carriers, but recent evidence suggests that FXTAS presentation may vary across sexes. The present study examined quantitative sensorimotor, memory, and brain features of aging in female premutation carriers with and without FXTAS.

**Methods:** We have studied 32 female premutation carriers ages 47-73 years and 21 age-matched female controls. All participants have completed genetic testing, clinical evaluations, T2-weighted MRIs, and quantitative tests of sensorimotor and memory functions. To assess sensorimotor abilities, participants completed a test of precision grip force while receiving visual feedback. During this test, participants pressed on opposing load cells with their thumb and forefinger while viewing a static “TARGET” bar and a “FORCE” bar that moved upwards with increased force. They were instructed to press on the load cells with their dominant hand so that the FORCE bar reached the level of the TARGET bar and then to maintain their force level as steady as possible for 15 sec. Reaction time, accuracy of initial force output, approximate entropy (ApEN; i.e., regularity) and standard deviation of the force time series were examined. To assess memory functions, verbal and visual paired associates tasks were administered.

**Results:** Preliminary analyses of 16 premutation carriers, including 7 diagnosed with FXTAS, and 11 controls have been completed. Analyses of the full sample (N=53) will be presented at the Conference. During precision grip testing, female premutation carriers showed increased sustained force regularity (p=0.001, one-tailed; Cohen’s d=1.33) and variability relative to controls (p<0.001, one-tailed; Cohen’s d=1.40). Their reaction times and accuracy of initial force output were not different from controls (p’s>0.41; d’s<0.31). During memory testing, premutation carriers showed reduced verbal (p=0.049, one-tailed; Cohen’s d=0.74) and visual episodic memory abilities, though differences in visual memory were not significant (p=0.09, one-tailed; Cohen’s d=0.43). FXTAS females showed elevated force regularity and variability during precision gripping relative to controls and asymptomatic carriers (entropy: p=0.009; variability: p=0.005) but no differences in episodic memory abilities. Among females with FXTAS, 1/7 showed cerebellar white matter degeneration while 7/7 showed white matter degeneration within the corpus callosum.

**Conclusions:** Our findings that female premutation carriers, and especially females with FXTAS, show increased regularity and variability of sustained grip force suggest reduced ability to reactively adjust motor output in response to sensory feedback error information. We also found that female premutation carriers demonstrate reduced episodic memory abilities relative to population controls, though these differences are not as robust as sensorimotor differences, and they appear to impact both asymptomatic female premutation carriers and those with FXTAS. Our results also indicate that females with FXTAS rarely show cerebellar degeneration but frequently (if not universally) show white matter lesions of the corpus callosum. These findings suggest that brain changes associated with FXTAS in females are distinct from those seen in males, and that major radiological criteria for FXTAS in females may need to be reconsidered.

**Paper 2 of 4**

**Title:** Cognitive impairment in women with the *FMR1* premutation

**Authors**: Jessica Klusek3, Laura Friedman3, Thomas Christensen3, Elizabeth Berry-Kravis[[9]](#footnote-9), Anya Benitez[[10]](#footnote-10), Federico Rodriguez-Porcel[[11]](#footnote-11), Christine Cooper11, Jane Joseph10

**Background**: Women who carry a premutation allele on the *FMR1*geneare at risk for developing Fragile X Tremor Ataxia Syndrome (FXTAS), a neurodegenerative disease involving movement and cognitive problems, including dementia. Women with the *FMR1* premutation who do not have FXTAS may also be vulnerable to age-related health problems, such as decline in certain aspects of cognition12,13. Moreover, converging evidence suggests interaction between *FMR1* and disease pathways implicated in Alzheimer’s disease (AD), such aspostmortem data showing high rates of AD neuropathology in women with the *FMR1* premutation14 and well-established molecular-genetic evidence supporting a role of *FMR1* in the synthesis of amyloid precursor proteine.g., 15. Despite this growing body of evidence, few studies have directly characterized risk for cognitive impairment in women with the *FMR1* premutation.

**Methods:** Participants were 91 women with the *FMR1* premutation and 91 control women (*M* age = 48 years, range 28-69). Control women were mothers of neurotypical children and did not have a known family history of fragile X. The groups did not differ on age (*p*=.799), education (*p*=.859), race (*p=*.176), ethnicity (*p*=.305), or nonverbal IQ (*p*=.437). Women with the *FMR1* premutation did not have clinical diagnoses of FXTAS and most had a child with fragile X syndrome (71%). The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was administered as part of a larger telehealth battery. The women submitted buccal swabs for *FMR1* genotyping (Asuragen).

**Results:** Women with the *FMR1* premutation were 3x more likely than controls to score below the MoCA cut-off for cognitive impairment (total score <26), even after controlling for age, education, and race; χ2*=*10.62, *p* =.001, OR=2.95 (95% CI [1.46, 6.00]). A general linear model testing group differences in the mean total MoCA score, controlling for age, education, and race, indicated lower total scores in the *FMR1* premutation group (*p* < .001, *η*2p = .08). Analysis of the MoCA cognitive domain index scores showed lower performance in the *FMR1* premutation group on the Memory Index Score (*p* < .011, *η*2p = .03) but no group differences on the Executive Function (*p=*.597), Visuospatial (*p=*.851), or Language (*p=*.180) index scores. General linear models tested CGG repeat length as a predictor of the MoCA total and Memory Index scores within the *FMR1* premutation group, controlling for age, education, race, and testing the interaction between CGG repeat length and education (college degree/no college degree). CGG repeat length was not a significant predictor of the MoCA total score but did predict performance on the Memory Index Score in interaction with education level (*p* = .022, *η*2p = .05). Among women with higher CGG repeats, non-completion of a college degree was associated with poorer memory performance, whereas college degree attainment was not associated with memory scores among women with lower CGG repeats. Finally, sensitivity analyses were conducted to test differences in premorbid function as a potential confounder; inference across all models remained unchanged when adding IQ as a covariate.

**Conclusions:** Cognitive impairment is more common in women with the *FMR1* premutation, with our data showing that women with the *FMR1* premutation without FXTAS were 3x more likely than controls to score within the impaired range on a well-established cognitive screener. Differences were predominately related to memory deficits, with scores on the executive, language, and visuospatial subdomains failing to differentiate the groups. Women with higher CGG repeat lengths were particularly vulnerable to memory problems, with evidence that college degree attainment mitigates this effect presumably by offering neuroprotection via increased cognitive reserve.

**Paper 3 of 4**

**Title:** Identifying Associated Comorbid Health Conditions Among Women with Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) Symptoms

**Authors**: Emily G. Allen[[12]](#footnote-12), Lisa Shubeck12, Krista Charen12, Nicole D. Tortora[[13]](#footnote-13), Anne Glicksman13, Tiffany McGuire13, Shira Russell-Giller[[14]](#footnote-14),[[15]](#footnote-15), Amanda Kenepp14,15, Shantal Taveras14,15, Sonia Seehra14,15, Rachel Goldman14,15, Veronica J. Hinton14,15, Tatyana Adayev13, Jessica Ezzell Hunter[[16]](#footnote-16), Stephanie L. Sherman12

**Introduction:** The fragile X premutation occurs when there are 55-200 CGG repeats in the 5’ UTR of the *FMR1* gene. An estimated 1 in 148 women carry a premutation allele, with ~6-15% of these individuals at risk for fragile X-associated tremor/ataxia syndrome (FXTAS) and 20-30% at risk for fragile X-associated primary ovarian insufficiency. Our previous study of self-reported health histories on 355 premutation women identified a distinct cluster of eleven women with FXTAS symptoms. Intriguingly, in this group of women, the average age at menopause was more representative of the general population (47.2 ± 5.6 years) and there were not any women defined as having FXPOI in this group (menopause before age 40). As many women with a *FMR1* premutation have concerns about developing FXTAS, identifying associations with other, earlier onset characteristics could provide information for identifying women with a premutation at risk for FXTAS.

**Methods:** We have collected self-report reproductive and health histories from 545 women with a premutation. Logistic regression models were used to determine associations with FXTAS symptoms, including tremor, ataxia, and neuropathy. Predictor variables tested included age at interview, race/ethnicity, repeat size, education, income, body mass index (BMI), smoking, FXPOI status (age at menopause or binary variable for FXPOI), and other comorbid conditions (e.g., depression, anxiety, migraine headaches, tension headaches, and thyroid conditions).

**Results:** A total of 51 women (9.4%) reported having a tremor. Significant predictor variables for tremor included age at interview (p<0.0001), depression (p<0.0001), and migraine headaches (p=0.0099). Ataxia was reported by 65 women (11.9%), and the significant predictor variables for ataxia were age at interview (p<0.0001), depression (p<0.0001), repeat size (p=0.0072), and thyroid conditions (p=0.0146). Neuropathy was reported by 93 women (17.1%), and significant predictor variables included repeat size (<0.0001), tension headaches (p<0.0001), age at interview (p=0.0015) and anxiety (p=0.0017). In a model with women who reported two or more symptoms (51; 9.4%), significant predictor variables included age at interview (p<0.0001), depression (p=0.0020), repeat number (p=0.0011), tension headaches (p=0.0172), and education (p=0.0284). FXPOI status was not a significant predictor for any of the models, indicating that there is not an association with women with FXPOI being at increased risk for developing FXTAS.

**Conclusions:** These results indicate an association between FXTAS symptoms and several comorbid health conditions in addition to age and repeat size. Mental health conditions (e.g., depression and anxiety), headaches, and thyroid conditions were associated with FXTAS symptoms. Further characterization, including age of onset and severity of symptoms, for each of these conditions could provide insight into identifying which women with a *FMR1* premutation are at risk for FXTAS.

**Paper 4 of 4**

**Title:** Influences of working memory on quality of life among females with the *FMR1* premutation

**Author**: Nell Maltman[[17]](#footnote-17)

**Introduction:** Females with the *FMR1* premutation are at risk for fragile X-associated tremor/ataxia syndrome (FXTAS), which is characterized in part by executive dysfunction1–3. Prior work from Hessl and colleagues4 suggests that declines in working memory – a component of executive functioning – are associated with the onset and progression of FXTAS among males with the premutation. However, less is known about such changes among females and how changes in working memory may impact quality of life, including mental health and well-being. There is some evidence to suggest that in the early stages of FXTAS, executive functioning and mental health symptoms are linked in males, but not females5. Understanding these relationships will be essential to clinicians in order to provide adequate supports for executive functioning, mental health, and social wellness among females at risk for FXTAS. The present study evaluated the impact of working memory on quality of life among females with the *FMR1* premutation.

**Methods:** Participants included 31 females with the *FMR1* premutation between the ages of 30-65 without a diagnosis of FXTAS. Participants completed a two-hour virtual visit with an examiner. Working memory was measured using the Behavior Rating Inventory of Executive Functioning- Adult version6 (working memory t-score) and a direct assessment Digit Span task. Quality of life was measured by self-report assessments of social satisfaction (NeuroQoL7), sleep quality (NeuroQoL7), anxiety (State Trait Anxiety Inventory; STAI8), and depression (Center for Epidemiologic Studies Depression Scale; CES-D9). Statistical analyses included multiple linear regressions, controlling for age and education. Additionally, given prior work that suggests females with FXTAS symptoms have elevated anxiety and depression5,10, we conducted follow-up group comparisons of working memory and quality of life according to the presence or absence of any tremor symptoms based on the Tremor Disability Questionnaire11.

**Results:** Within the sample, 29% (*n*=9) had clinically significant working memory difficulties. Above and beyond the effects of age and education, working memory significantly predicted lower social satisfaction (*b* = -.28, *p*=.002), poorer sleep quality (*b* = .32, *p*<.001), and more symptoms of anxiety (*b*=.46, *p*<.001) and depression (*b* = .42, *p*<.001). Our follow-up analyses indicated that females with any symptoms of tremor (*n*=13) had poorer working memory (digit span; *t*(29)=1.75, *p*=.029, Cohen’s *d* =2.33), lower social satisfaction (*t*(29)= -1.75, *p*=.044, Cohen’s *d* =6.87), poorer sleep (*t*(29)=-1.97, *p*=.029, Cohen’s *d* = 6.64), and more symptoms of depression (*t*(29)= -1.75, Cohen’s *d* = 9.97, *p*=.046), with large effects. A marginal but non-significant trend was observed with anxiety (*p*=.089).

**Discussion:** Together, these findings highlight an emerging profile among females with the *FMR1* premutation that point to working memory as a significant contributor to overall well-being. These results have important implications for holistic approaches to clinical support for this population. For instance, it may be that interventions targeting working memory difficulties among females with the *FMR1* premutation could provide broader improvements to overall well-being. More research is needed with individuals with known FXTAS symptoms to confirm these findings.

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