Fatigue and body mass index in the Fragile X premutation carrier

Scott M. Summers\textsuperscript{a,b,*}, Jennifer Cogswell\textsuperscript{a,c}, John E. Goodrich\textsuperscript{d}, Yi Mu\textsuperscript{c}, Danh V. Nguyen\textsuperscript{f}, Steven D. Brass\textsuperscript{g} and Randi J. Hagerman\textsuperscript{a,c}

\textsuperscript{a}Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, University of California-Davis, Sacramento, CA, USA; \textsuperscript{b}Department of Psychiatry and Behavioral Sciences, University of California-Davis, Sacramento, CA, USA; \textsuperscript{c}Department of Pediatrics, University of California-Davis, Sacramento, CA, USA; \textsuperscript{d}School of Medicine, University of California-Davis, Sacramento, CA, USA; \textsuperscript{e}Department of Biostatistics, University of California-Davis, Sacramento, CA, USA; \textsuperscript{f}Institute for Clinical and Translational Science, University of California-Irvine, Irvine, CA, USA; \textsuperscript{g}Department of Neurology, University of California-Davis, Sacramento, CA, USA

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\textbf{Background:} Recent evidence has shown that mitochondrial dysfunction may be significant in carriers of the Fragile X premutation. \textbf{Purpose:} The present study examined fatigue severity and body mass index (BMI) (two possible outcomes related to mitochondrial dysfunction) in premutation carriers with and without the Fragile X-associated Tremor Ataxia Syndrome (FXTAS) as compared to controls. \textbf{Methods:} Surveys to gather data on height and weight and fatigue impact (Fatigue Severity Scale) were sent out to previous research trial participants with Fragile X premutation-related disorders. \textbf{Results:} On the Fatigue Severity Scale, carriers with and without FXTAS had mean scores of 4.5 (SD 1.9) and 3.8 (SD 1.6), respectively, that differed significantly ($p < 0.001$) from the control mean score of 2.9 (SD 1.4). The mean BMI of carriers with FXTAS was 29.6 kg/m\textsuperscript{2} (SD 5.3) which differed significantly ($p = 0.003$) from the mean BMI of carriers without FXTAS of 26.9 kg/m\textsuperscript{2} (SD 5.1) and controls 26.7 kg/m\textsuperscript{2} (SD 4.4). However, premutation carriers without FXTAS did not differ significantly in BMI from controls. \textbf{Conclusions:} The present study suggests potentially important clinical outcomes that may be related to the mitochondrial dysfunction seen in molecular studies previously done with premutation carriers.

\textbf{Keywords:} fatigue; Fragile X-associated Tremor Ataxia Syndrome; body mass index; trinucleotide repeat disorders; Fragile X premutation; FMR1

\section*{Introduction}

Fragile X Syndrome (FXS) has long been recognized as a heritable form of intellectual disability.\textsuperscript{[1]} However, it is a relatively rare condition affecting only about one in 4000 people.\textsuperscript{[2]} The premutation or carrier condition is considerably more common affecting between one in 130–250 women and one in 250–800 men.\textsuperscript{[3]} This carrier state was once believed to be benign beyond the risk of producing offspring with FXS. This is
no longer believed to be the case. Psychiatric disorders, such as mood and anxiety disorders, have been found to be prevalent in premutation carriers.[4] Recent evidence has also shown higher rates of migraine,[5] sleep apnea,[6] and hypertension.[7] In addition, a neurodegenerative condition known as Fragile X-associated Tremor-Ataxia Syndrome (FXTAS) has been identified in premutation carriers. This syndrome typically affects an individual in his/her early sixties and is characterized by symptoms of intention tremor, cognitive decline, cerebellar ataxia, and Parkinsonian features.[8]

The defective mechanism leading to the various pathologies of premutation carriers is less well understood than that of FXS. As opposed to the gene silencing seen in FXS, the levels of FMR1 mRNA in carriers are significantly increased compared to those with normal range CGG repeats. It has been hypothesized that the high level of mRNA itself is toxic.[9] This is supported by the presence of intranuclear inclusions containing the FMR1 mRNA in human carriers[10] and neurodegeneration secondary to elevated FMR1 mRNA in drosophila.[11]

New evidence is pointing to significant mitochondrial dysfunction in premutation carriers that may lead to neuronal death. Human premutation carrier fibroblasts have overall less mitochondrial proteins and functionally demonstrate less oxygen uptake. Notably, their mitochondrial dysfunction directly precedes oxidative/nitrative cellular damage.[12,13] This finding, along with decreased mitochondrial mobility, has been replicated in both the mouse model of the premutation[14] and in the drosophila model.[15] This premutation (with and without FXTAS) thus appears to be associated with mitochondrial dysfunction, a finding also seen in Parkinson’s Disease,[16] Alzheimer’s Disease,[17] and Charcot-Marie-Tooth Disease.[18]

There are at least two specific clinical outcomes that have historically been related to mitochondrial dysfunction. The first of these, fatigue, has been directly tied to mitochondrial dysfunction in a wide variety of illnesses including viral infection,[19] cancer,[20] and biliary cirrhosis.[21] Mitochondrial levels and dysfunction have also been related directly to chronic fatigue syndrome severity in multiple studies.[22–24] The second clinical outcome, obesity as measured by the body mass index (BMI; weight [kg]/height[cm]²) is also related to mitochondrial dysfunction. Twin studies involving discordant BMI have demonstrated lower levels of mitochondrial function involving the obese twin.[25] Mitochondrial function has been found to be lower in the sperm,[26] skeletal muscle,[27] and cardiac muscle[28] of obese individuals. Importantly, there is emerging evidence that the lipid-rich environment seen in obesity can itself lead to mitochondrial dysfunction in neuronal tissue.[29]

Given these many interactions in the literature, the present study examined the severity of fatigue and BMI in premutation carriers as compared to controls. As decreased mitochondrial function has been demonstrated in premutation carriers with and without FXTAS[12,13] and is hypothesized as a potential contributor to the disorder, it was deemed beneficial to separate out those two groups of premutation carriers to better understand the phenotype.

**Methods**

**Recruitment and collection**

This study was approved by the UC Davis Institutional Review Board. Adult control subjects as well as premutation carriers with and without FXTAS who had previously participated in studies at the UC Davis MIND Institute were contacted via a
personalized e-mail. Participants had previously been referred to the Institute for their initial study via clinicians and family members as well as area flyers. Subjects who were known to have CGG repeats in the gray zone (45–55 repeats) or to have CGG repeats in the range of the full mutation (>200) were excluded. Participants with mosaicism into either of these ranges were also excluded. The study e-mail included a link to an online survey as well as information about IRB approval, confidentiality and the general purpose of this study. Those subjects who either had not provided us with a contact e-mail address or did not respond to the e-mail solicitation were contacted by phone where an identical version of the survey was completed if the subject agreed. Of all those offered the opportunity to participate by phone or e-mail, 61% completed the survey including 62% of known premutation carriers with FXTAS, 70% of premutation carriers who did not meet criteria for FXTAS at their most recent visit, and 63% of control subjects. Some adult subjects participating in other studies at the UC Davis MIND Institute also completed the survey on local computers. In total, 86 control subjects, 51 premutation carriers without FXTAS, and 76 subjects with a diagnosis of FXTAS participated in the survey. One premutation carrier without FXTAS began the survey, but did not complete the Fatigue Severity Scale.

Survey design

The survey collected demographic information including premutation carrier status, history of FXTAS diagnosis, gender, and age. Subjects were asked to report their height and weight. All subjects completed the Fatigue Severity Scale (FSS).[30] This standardized scale utilizes nine statements about how strongly fatigue impacts daily functioning. The subjects were asked to rate their level of agreement with each item on a Likert scale with 1 representing strong disagreement and 7 representing strong agreement. The FSS score was the mean of the nine component ratings. Additionally, patients were asked if they had ever received diagnoses of sleep apnea or depression from a healthcare provider.

Statistical analysis

Descriptive comparisons of baseline categorical variables, including sex, history of depression, and sleep apnea, were analyzed with chi-square tests. Baseline participant age, a continuous variable, was compared between groups with ANOVA. The primary outcomes were the FSS scores and BMI values. To examine these outcomes among premutation carriers with or without FXTAS and control groups, we used general linear models (GLM) adjusted for age and sex. To jointly examine the effect of premutation status and history of depression plus history of sleep apnea, a GLM with these additional variables was fitted. Analyses were performed using SAS version 9.3.

Results

Characteristics of study cohort

Characteristics of the study cohort are summarized in Table 1. The mean ages for premutation carriers with and without FXTAS and control subjects were 67.3 (SD 9.1), 59.0 (SD 9.8), and 67.0 (SD 7.7), respectively. The study cohort differed in average age among groups ($p < 0.0001$; Table 1), except between controls and premutation carriers without FXTAS.
carriers with FXTAS. A significantly higher proportion of females was found in premutation carriers without FXTAS (74.0%, 37/50) in comparison to the other two groups: premutation carriers with FXTAS (43.4%, 33/76) and controls (45.4%, 39/86), \( p = 0.0012 \). In addition, a history of depression was more frequently reported in the premutation carrier groups compared to controls (\( p = 0.0018 \)). Sleep apnea reports were also higher in premutation carriers with FXTAS relative to premutation carriers without FXTAS and controls (\( p = 0.0013 \)).

**Fatigue symptoms and BMI**

Results comparing premutation carriers with and without FXTAS and control subjects are summarized in Tables 1 and 2. Premutation carriers with FXTAS showed significantly worse fatigue symptoms (\( p < 0.0001 \); Table 2) on the Fatigue Severity Scale (FSS; mean = 4.5; SD 1.9) compared to control subjects (mean = 2.9; SD 1.4), adjusted for age and sex (see Table 1). Premutation carriers without FXTAS had an intermediate mean score of 3.8 (SD 1.6) that differed significantly from both controls (\( p = 0.0187 \)) and carriers with FXTAS (\( p = 0.0046 \)), also adjusted for age and sex. A secondary model examined whether a self-reported history of depression and sleep apnea changed the estimate of differences in FSS scores amongst the groups. The results were similar (Table 2; model 1B) for premutation carriers with FXTAS, who still had a significantly higher FSS mean score compared to both control subjects and premutation carriers without FXTAS. However, the average increase in FSS score in the premutation carriers without FXTAS compared to control subjects (difference of 0.54 vs. 0.73 in FSS) was not statistically significant (\( p = 0.0691 \)) at the 0.05 level, which is

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### Table 1. (A) Characteristics of study cohort and (B) descriptive summary of outcome variables.

<table>
<thead>
<tr>
<th>(A) Variable</th>
<th>A = Pre w/FXTAS</th>
<th>B = Pre w/o FXTAS</th>
<th>C = Control</th>
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<tbody>
<tr>
<td>Age</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Count %</td>
<td>76</td>
<td>67.32</td>
<td>9.10</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43</td>
<td>56.58</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>33</td>
<td>43.42</td>
<td>37</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45</td>
<td>59.21</td>
<td>27</td>
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<tr>
<td>Yes</td>
<td>31</td>
<td>40.79</td>
<td>23</td>
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<tr>
<td>Sleep apnea</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>58</td>
<td>76.32</td>
<td>48</td>
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<td>Yes</td>
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<td>23.68</td>
<td>2</td>
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</table>

<table>
<thead>
<tr>
<th>(B) Variable</th>
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<th>Mean</th>
<th>SD</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>( p )-value*</th>
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<tr>
<td>Fatigue Severity Scale</td>
<td>76</td>
<td>4.52</td>
<td>1.85</td>
<td>50</td>
<td>3.76</td>
<td>1.64</td>
<td>86</td>
<td>2.89</td>
<td>1.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>76</td>
<td>29.63</td>
<td>5.28</td>
<td>50</td>
<td>26.92</td>
<td>5.05</td>
<td>86</td>
<td>26.69</td>
<td>4.43</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

*Comparison across all three groups.

SD, Standard Deviation.
largely explained by the history of depression ($p < 0.0001$). Overall, history of sleep apnea, age, and gender were not associated with FSS (Table 2).

When adjusted for age and sex, the average BMI differed significantly ($p = 0.0002$) between carriers with FXTAS (29.6 kg/m$^2$, SD 5.3) and controls (26.7 kg/m$^2$, SD 4.4). The mean BMI of carriers without FXTAS (26.9 kg/m$^2$, SD 5.1) also differed from those with FXTAS ($p = 0.0056$), but not from controls (Table 2). Age, history of depression, and sleep apnea were not significantly associated with differences in BMI.

**Discussion**

This preliminary study identified two potentially important new findings regarding premutation carriers. First, the impact of fatigue appears to be a significant problem. Those with FXTAS were considerably more affected by fatigue than those without. The FXTAS subjects had a mean score above 4, which demarcates clinically significant fatigue on the FSS.[30] Their mean score was similar to that found in other neurodegenerative diseases such as untreated Parkinson’s Disease or Amyotrophic Lateral...
Sclerosis, each with mean scores of 4.4 on the FSS.[31,32] Control scores on the FSS were largely in line with previous studies in healthy subjects.[33,34] The premutation carriers without FXTAS were significantly different from the other two groups on the FSS reflecting an intermediate level between FXTAS carriers and controls. Given the somewhat younger age of the premutation carriers, some of these individuals will likely develop FXTAS at a future date. New longitudinal studies may be able to determine if levels of fatigue are predictive of future neurologic symptoms.

The cause of fatigue, although hypothesized to be related to decreased mitochondrial function, is not clear from these results. Sleep apnea may play a role in fatigue given the higher prevalence of this disorder in premutation carriers with FXTAS [6] and the strong association of fatigue with sleep apnea.[35,36] However, the differences amongst the three groups were still significant even after adjusting for histories of sleep apnea. Similarly, depression has been correlated with fatigue and is more prevalent in premutation carriers.[4] Adjusting for depression does significantly reduce the difference in fatigue scores between controls and carriers without the permutation which may explain part of that difference. However, the difference in fatigue between subjects suffering from FXTAS and control subjects is not explained by differences in prevalence of self-report sleep apnea or depression. This leaves open the possibility of a progressive decline in mitochondrial function as being one source of fatigue.

The BMI findings presented here, in addition to potentially providing evidence of mitochondrial dysfunction, suggest a possible mechanism for the higher rates of sleep apnea seen in FXTAS patients. The direct correlation of BMI to the prevalence of sleep apnea is well established in the literature with a roughly six point increase in BMI correlating to a four-fold greater risk of developing the disease.[37] Here we see a roughly three point difference in mean BMI between control subjects and FXTAS carriers that could correspond with the roughly three-fold increase in sleep apnea prevalence seen in the literature.[6] Further, the lack of difference in mean BMI between premutation carriers without FXTAS and control patients mirrors the non-significant difference in prevalence of sleep apnea between these populations. Beyond sleep apnea, the finding of increased BMI raises a host of health concerns about premutation carriers later in life, perhaps for diabetes and coronary artery disease in particular. Mitochondrial dysfunction has already been implicated in both of these illnesses.[38,39]

This study provides preliminary evidence of clinical correlates of mitochondrial dysfunction seen in the Fragile X premutation. It was limited by several factors. Height and weight were self-reported which may contribute to inaccuracy, although there is no clear reason to believe premutation carriers would be any more or less accurate than control subjects. Similarly, depression and sleep apnea self-reporting were limiting factors in this study. Furthermore, mitochondrial function was not directly measured. Future research might examine the associations between mitochondrial function and fatigue, BMI, and a host of symptoms related to premutation carrier status. The direction of the causal relationships amongst depression, sleep apnea, fatigue, and body weight is not discernable from this study and is likely very complicated. A final concern is that current severity of depression and sleep apnea were not assessed, nor were other factors that could potentially contribute to fatigue or BMI such as anxiety, COPD, thyroid function, or anemia. Each of these is likely an area for future research.
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Notes on contributors

Dr Scott Summers is a fourth year resident in the Department of Behavioral Science and Psychiatry at the University of California at Davis with research interests in psychopharmacology and the Fragile-X Premutation.

Jennifer Cogswell is a staff research associate in the Department of Pediatrics University of California at Davis with research interests in the Fragile-X Premutation and movement disorders.

John Ethan Goodrich is a fourth year medical student at the University of California at Davis with broad research interests in areas concerning Fragile-X Syndrome.

Dr Yi “Lisa” Mu is a staff statistician in the Department of Biostatistics at the University of California at Davis with research interests in healthcare outcomes and statistical modeling.

Dr Danh Nguyen is a Professor in the Department of Medicine and Director of the Institute for Clinical & Translational Science at the University of California at Irvine with research interests in translational science and bioinformatics.

Dr Steven Brass is an Assistant Clinical Professor and Director of the Sleep Clinical Program in the Department of Neurology at the University of California at Davis with research interests in sleep apnea and the role of iron in neurological disease.

Dr Randi Hagerman is a Professor in the Department of Pediatrics, the endowed chair for Fragile-X Research and the Medical Director of the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute with very broad research interests in all aspects of Fragile-X Syndrome.

References


