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Prevalence and Risk of Migraine Headaches in Adult Fragile X Premutation Carriers

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Abstract

FMR1 premutation carriers are common in the general population (1/130-260 females and 1/250 – 810 males) and can be affected by fragile X-associated tremor ataxia syndrome (FXTAS), fragile X-associated primary ovarian insufficiency (FXPOI), anxiety, depression, hypertension, sleep apnea, fibromyalgia, and hypothyroidism. Here we report the results of a pilot study to assess the prevalence and risk of migraine in *FMR1* premutation carriers. 315 carriers (203 females; 112 males) and 154 controls (83 females; 71 males) were seen sequentially as part of a family study. A standardized medical history, physical examination and confirmation of diagnosis of migraine headaches were performed by a physician. The prevalence of migraine was 54.2% in female carriers (mean age/SD: 49.60/13.73) and 26.79% in male carriers (mean age/SD: 59.94/ 14.27). This prevalence was higher compared to female (25.3%; mean age/SD: 47.60/15.21; $p = 0.0001$) and male controls (15.5%; mean age/SD: 53.88/13.31; $p = 0.0406$) who underwent the same protocol and were confirmed to be negative for the *FMR1* mutation by DNA testing. We

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Conflicts of Interests

Randi Hagerman receives funding for clinical trials regarding treatment for fragile X syndrome, FXTAS or autism from Seaside Therapeutics, Roche, Novartis, Forest and Curemark. She has also consulted with Novartis regarding treatment of fragile X syndrome. CDR Akins is a Navy Physician; however, the views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense or the United States Government. No other authors declare any conflicts of interest.

Authors' Contributions

Jacky Au helped write the manuscript and gather patient data. Roger Akins contributed to the evaluation of patients for this study and helped write the manuscript. Laura Berkowitz-Sutherland helped gather patient data. Hui-Tung Tang helped perform the molecular analyses. Yucui Chen helped write the manuscript. Antoniya Boyd gathered and organized clinical information. Flora Tassone performed the molecular analyses and helped write the manuscript. Danh Nguyen performed the data analysis, interpreted results and helped write the manuscript. Randi Hagerman contributed to funding, study organization, writing the manuscript, and the recruitment and evaluation of patients for this study. All authors approved and read the final manuscript.

hypothesize that the increased prevalence of migraine headaches in *FMR1* premutation carriers is likely related to the mitochondrial abnormalities that have recently been reported. Screening for migraine should be considered when evaluating *FMR1* premutation carriers in the future.

Keywords

Fragile X premutation; Fragile X Tremor Ataxia Syndrome; Headaches; Migraine Disorders

Introduction

FMR1 premutation carriers have between 55 and 200 CGG repeats in the *FMR1* gene. Approximately 1 per 130 females and 1 per 250 to 810 males are *FMR1* premutation carriers (1-3). Although the full mutation of fragile X syndrome has greater than 200 CGG repeats with methylation of the gene and a lack of transcription and translation leading to a deficit of *FMR1* protein (FMRP), the *FMR1* premutation is associated with elevation of the *FMR1* mRNA, around 2 to 8 times that of normal levels. The elevated *FMR1* mRNA in carriers can lead to toxicity and sequestering of proteins including DROSHA and DGCR8 that causes dysregulation of miRNAs (4-5). Subsequent problems such as immune mediated disorders, emotional problems and/ or neurological diseases can develop in aging carriers (6-7). Approximately 40% of male carriers and 8% to 16% of female carriers develop the fragile X-associated tremor ataxia syndrome (FXTAS) (8-9). The core features of FXTAS are intention tremor and ataxia which begin on average in the early 60s (10). Additional features in carriers with FXTAS include autonomic problems, such as hypertension (11), orthostatic hypotension, impotence, and late onset urine and bowel incontinence (12), as well as neuropathy (13) and cognitive decline beginning with memory and executive function deficits (14-15). Psychiatric problems are also common in carriers both with and without FXTAS, including depression, anxiety, and irritability (7, 16-17).

Our understanding of medical problems in *FMR1* premutation carriers has broadened beyond features of FXTAS. Approximately 20% of females with the *FMR1* premutation experience fragile X-associated primary ovarian insufficiency (FXPOI) before age 40 (18). Emotional difficulties, including anxiety and/or depression can be seen in 30% to 50% of carriers (16-17, 19-20) typically at earlier ages than the onset of FXTAS. A recent study of adult females with the *FMR1* premutation demonstrated a significant increase in fibromyalgia and hypothyroidism compared to controls (6, 9), a finding which has been confirmed by others (21). We have also clinically observed the frequent occurrence of migraine headaches in adults with the *FMR1* premutation.

Migraine is a neurologic disorder characterized by episodic headaches and it is most common in those aged 30 to 39, where prevalence in women and men reaches 27.3% and 9.7%, respectively (22). It is thought to have a polygenic and multifactorial etiology and models of complex pathophysiology involving both vascular and neuronal mechanisms have been proposed. It has also been associated with mitochondrial dysfunction, and is in fact a common symptom in various mitochondrial disorders (23-26). Additionally, migraineurs,

even without a diagnosed mitochondrial disorder, exhibit impairments in mitochondrial oxidative phosphorylation (27-30).

Recently abnormalities of mitochondrial function have been reported in *FMR1* premutation carriers both with and without FXTAS(31). Mitochondrial dysfunction in carriers includes uncoupling between electron transport and synthesis of ATP in addition to decreased levels of mitochondrial proteins including the ATPase β -subunit (ATPB) from complex V, cytochrome c oxidase subunit IV from Complex IV (CCOIV) and MnSOD as part of the mitochondrial antioxidant defense (31). The levels of mitochondrial proteins correlate inversely with CGG repeat numbers in the *FMR1* premutation range (31). These protein changes increase oxidative stress, increase oxidative modification of mitochondrial proteins and activate the unfolded protein response (UPR) and phosphorylation of the alpha subunit of the heterotrimeric eukaryotic translational initiation factor 2 (eIF2 α), resulting in a decrease in protein translation (31-32). In the mouse model of the *FMR1* premutation, neuronal cell cultures have demonstrated early cell death by 21 days in culture (33). Thus, we hypothesize that many of the clinical features of *FMR1* premutation carriers including FXTAS and perhaps migraine headaches are related to mitochondrial dysfunction which is part of the RNA toxicity problem that worsens with age.

Additionally, a mild deficit of FMRP has been found in some *FMR1* premutation carriers in peripheral blood (34-35) and in the *FMR1* premutation mouse in the CNS (36). Lowering of FMRP leads to enhanced activity of the metabotropic glutamate receptor 5 (mGluR5) pathway (37) and lowered activity of the GABA_A receptor (38). Dysregulation of both GABA and glutamatergic pathways has been associated with the presence of migraines (39).

Therefore, the following study was undertaken to assess the prevalence and risk of migraine headaches in *FMR1* premutation carriers compared to controls.

Materials and Methods

Subjects

315 carriers of the *FMR1* premutation (203 female; 112 male) were compared to 154 controls (83 female; 71 male) and assessed for presence or absence of migraine. See Table 1 for subject data. All subjects were seen sequentially as part of a family study of probands diagnosed with fragile X syndrome (FXS) or part of an adult study of individuals with FXTAS and their relatives. No subject was referred to our clinic for headache or related problems. All subjects were seen at the UC Davis Medical Center MIND Institute, Fragile X Treatment and Research Center between March of 2006 and March of 2012. All subjects signed an informed consent. Subjects were diagnosed with FXTAS if their neurological examination included tremor and ataxia and their MRI included features of FXTAS as described by Jacquemont et al. and met criteria for definite or probable FXTAS (40). A standardized medical history and physical examination were performed by a physician (RA or RH). The medical history addressed specific questions about headaches and study physicians asked if the headaches had been diagnosed as migraine by a physician. If they had been diagnosed as migraine by a physician and if the headache characteristics were

consistent with migraine on our evaluation then they were scored as positive for migraine headaches.

Of the 315 *FMR1* premutation carriers, 298 (95%) underwent confirmatory *FMR1* DNA testing at our facility; 17 (5%) did not undergo confirmatory *FMR1* DNA testing but were determined to be obligate carriers. *FMR1* molecular measures included CGG repeat number, activation ratio (AR), and *FMR1* mRNA levels using Southern Blot and PCR analysis as previously described (41-42)(Table 2A). All controls in our sample were confirmed to have less than 40 CGG repeats by DNA testing.

Statistical Analysis

Prevalence/proportion of migraine was estimated by gender. Univariate p-values comparing prevalence between *FMR1* premutation carriers and controls and *FMR1* premutation carriers with and without FXTAS were based on Fisher's exact test. Descriptive comparisons of participant age by group and gender were based on t-tests. To obtain adjusted relative risk of migraine in *FMR1* premutation compared to controls in our primary analysis, a generalized linear model (GLM) adjusted for age and sex was fitted using a binomial distribution with log link. Secondary analyses examined further the relative risk of migraine for *FMR1* premutation carriers with and without FXTAS and the effects of molecular variables. The adjusted relative risk estimates were similarly obtained for *FMR1* premutation carriers with and without FXTAS. To assess the effects of molecular variables (CGG and *FMR1* mRNA), the GLM models included CGG repeat size and *FMR1* mRNA levels; this secondary analysis was based on available data on 275 carriers (Table 2B).

Results

The mean ages for male and female carriers in our sample were 59.94 (SD 14.13) and 49.60 (SD 13.73), respectively. Mean ages of male and female controls were 53.88 (SD 13.32) and 47.60 (SD 15.21) respectively (Table 1A). Raw prevalence by gender is provided in Table 1B. The prevalence of migraine in female carriers was 54.2% (110/203), which was significantly higher than that of female controls, which was 25.3% (21/83; $p = 0.0001$). Similarly, migraine was also significantly more prevalent in male carriers (26.79%; 30/112) compared to male controls (15.49%; 11/71; $p = 0.0406$). The last column of Table 1B summarizes the relative risk [RR] (combined RR 2.06; 95% confidence interval [CI]: 1.49 – 2.86; $p < 0.001$) of migraine in *FMR1* premutation carriers relative to controls, adjusted for age and sex. Also provided are age-adjusted relative risks, stratified by gender, showing that both male and female *FMR1* premutation carriers have higher risk of migraine.

Table 1C summarizes the relative risk of *FMR1* premutation carriers with FXTAS relative to *FMR1* premutation carriers without FXTAS, adjusted for age and sex. The age-adjusted RR for males is 1.75 (95% CI: 0.79 – 3.88; $p=0.1675$) and for females is 1.34 (95% CI: 0.94 – 1.91; $p=0.1118$). Thus, although both male and female *FMR1* premutation carriers with FXTAS have higher risk of migraine, the trend is not formally statistically significant. However, a combined analysis collapsed over gender indicates overall increased risk (RR 1.40; 95% CI: 1.01 – 1.96; $p = 0.046$).

We also examined whether CGG repeat size and *FMR1* mRNA expression level are associated with migraine risk based on available molecular data on N = 275 carriers. Although the observed *FMR1* mRNA expression level was lower in *FMR1* premutation carriers with migraine (mean 2.32, SD 0.63) compared to carriers without migraine (mean 2.53, SD 0.77), both CGG repeat size and *FMR1* mRNA expression were not significantly associated with migraine risk ($p = 0.096$ and $p = 0.594$, respectively) after adjusting for age and sex. Similarly, the difference in the CGG repeat expansion among those with migraine (mean 87, SD 18) and without migraine (90, SD 19) was not significant. Activation ratio (which indicates the percentage of cells with the normal allele on the active X) among female carriers with and without migraines was also similar (mean/SD: 0.51/0.19; 0.53/0.19). See Table 2 for details.

Discussion

This initial study found migraine prevalence and adjusted relative risk (RR=2.06) to be significantly increased in *FMR1* premutation carrier adults, compared to controls (Table 1B). This finding occurs in males and females, with and without FXTAS, adjusted for age (Table 1C). However, the CGG repeat number within the *FMR1* premutation range and the *FMR1* mRNA levels do not correlate with the risk of migraine headaches, so it is likely that additional genetic or environmental effects are additive to the *FMR1* premutation to influence the risk of migraines. FXTAS status, however, does seem to increase risk for presence of migraine, and those with FXTAS have an age-adjusted relative risk of 1.40 overall ($p = 0.046$) compared to those with the *FMR1* premutation without FXTAS. Our data (Table 1C) suggest that this trend holds true for both males (RR = 1.75) and females (RR = 1.34) with FXTAS, though migraine prevalence in neither group individually had enough statistical power to reach a level of significance over carriers without FXTAS, as the combined group did.

Although the precise relationship between FXTAS and migraine is still equivocal, a correlation would not be surprising. The two already share a number of other co-morbidities such as fibromyalgia (6, 43), mitochondrial dysfunction (31, 44), and even neurodegeneration (45-47), particularly with respect to white matter lesions and cerebellar involvement (45, 48)(49). In light of these co-morbidities, our preliminary data presented here warrant further investigation into the specific prevalence of migraine headaches within the FXTAS subgroup, and into any possible shared pathophysiology between the two. The relative effect size (risk of migraine) associated with FXTAS in our study is smaller than the effect size of *FMR1* premutation carriers relative to controls, so future investigations would require a larger sample to more fully elucidate this association of FXTAS to migraine risk.

Individuals with migraine are also at increased risk for mild cognitive impairment, anxiety, and depression (43), all of which are common in *FMR1* premutation carriers (7, 17, 50). Early identification and treatment of migraines may improve the prevalence of these co-morbidities. Since effective treatments are available, including triptans which have been found to acutely restore migraine-related cognitive function and decrease clinical disability (51), screening for migraine should be considered in the routine evaluation of *FMR1* premutation carriers.

The physiological state preceding a migraine, particularly the cortical hyperexcitability followed by spreading depression and reduced regional cerebral blood flow, also sets the stage for an epileptic episode (52-53) Epilepsy is seen in approximately 10% of carriers, (54-55), particularly young boys and it is associated with the development of social deficits including autism in these children. This study did not evaluate children with the *FMR1* premutation and we recommend further investigation regarding the association of migraines and epilepsy in *FMR1* premutation children and their consequences.

Our preliminary data demonstrate the need for future studies of the pathogenesis of migraine headaches in *FMR1* premutation carriers. This pathogenesis may be related to the increased prevalence of depression, anxiety, fibromyalgia, hypertension, sleep apnea and other neurological problems in *FMR1* premutation carriers (9, 11, 19, 56-57). In addition some carriers may also demonstrate a dysregulation of GABA and glutamate pathways particularly if their FMRP levels are somewhat low (58). We hypothesize that RNA toxicity leading to sequestration and protein dysregulation and the subsequent influence on mitochondrial function leads to the increased prevalence of migraines in *FMR1* premutation carriers. Numerous reports in the literature point to a connection between mitochondrial dysfunction and migraine (23-25, 44, 59). There is a defect in brain and muscle energy metabolism in migraineurs (60-65), specifically in mitochondrial oxidative phosphorylation both during and between attacks (27-30). Furthermore, there is a decrease in mitochondrial enzymatic activity, such as that of monoamine-oxidase, succinate-dehydrogenase, NADH-cytochrome-c-reductase, and succinate-cytochrome-c-reductase (29, 60, 62, 66-67), as well as a reduced yield of energy from each molecule of ATP during ATP hydrolysis (68). Altogether, this results in a lowered energy reserve in the brain, rendering it less able to cope with increased energy demands (27). This abnormal mitochondrial oxidative metabolism can increase the permeability of cell membranes and promote neuronal hyperexcitability (61, 69). Neuronal hyperexcitability has actually been demonstrated in *FMR1* premutation neurons (70) and it is hypothesized that this hyperexcitability, amidst the backdrop of a hypoenergetic brain reduces the threshold for migraine attacks (61, 69, 71).

Limitations of this pilot study include the lack of data regarding the frequency and type of migraine experienced by patients, which may end up correlating with such molecular factors as CGG repeat size or *FMR1* mRNA levels, even though overall risk of migraine did not. Thus, the analysis was necessarily limited to comparisons of overall migraine prevalence and lacks specificity of migraine types. We also did not study the cognitive or neurological sequelae of migraines and further studies of this are warranted along with the benefits of early treatment. Furthermore, we acknowledge the existence of possible confounds such as stressful parenting of fragile X children, medication use, and concomitant health conditions that may impact migraine risk and prevalence. Unfortunately, it was not within the purview of this observational study to control for all of these variables, although future studies should consider these factors. With regards to the stress of raising children with FXS, none of the male carriers in our study had children with FXS, and many of the female carriers were older and already had their children out of the house. Furthermore, though we did not collect data regarding age of migraine onset, in the general population it typically tends to start in the teenage or early adult years (72), usually before childbirth. Therefore, we conjecture that the effects of stressful parenting is only relevant to a minority of our subjects. However, to

more fully elucidate the contributing effect of stressful environments, future studies need to ascertain information on migraine onset and severity over time to compare *FMR1* premutation carriers with and without children with FXS.

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Table 1

Migraine Prevalence and Relative Risk.

(A)	Premutation		Control		P-value
	Male (n=112)	Female (n=203)	Male (n=71)	Female (n=83)	
Age (mean $\pm$ SD) yrs	59.94 $\pm$ 14.13	49.60 $\pm$ 13.73	53.88 $\pm$ 13.31	47.60 $\pm$ 15.21	Female: p = 0.278 Male: p = 0.004
(B)	Premutation		Control		P-value (RR, 95% CI)*
History of Migraine % (count/n)	26.8% (30/112)	54.2% (110/203)	15.5% (11/71)	25.3% (21/83)	Combined: p < 0.001 (2.06, 1.49 – 2.86) Male: p = 0.0406 (1.92, 1.03 – 3.57) Female: p = 0.0001 (2.15, 1.46 – 3.18)
(C)	Premutation with FXTAS		Premutation without FXTAS		
	Male (n=75)	Female (n=40)	Male (n=37)	Female (n=163)	
History of Migraine % (count/n)	26.7% (20/75)	60.0% (24/40)	27.0% (10/37)	52.8% (86/163)	Combined: p = 0.046 (1.40, 1.01 – 1.96) Male: p = 0.1675 (1.75, 0.79 – 3.88) Female: p = 0.1118 (1.34, 0.94 – 1.91)

* 95% confidence interval (CI) and p-values for relative risk (RR) of premutation relative to control and premutation with FXTAS relative to premutation without FXTAS, both adjusted for age and gender.

Table 2

Premutation Molecular Characteristics (A) and Association with Migraine Risk (B).

(A)	Premutations with history of Migraine		Premutations without history of Migraine		P-value
	Mean (N)	SD	Mean (N)	SD	
CGG size	87 (130)	18	90 (168)	19	0.216
<i>FMR1</i> mRNA	2.32 (124)	0.63	2.53 (152)	0.77	0.013
Activation Ratio	0.51 (97)	0.19	0.53 (81)	0.19	0.625
(B)	Association with Migraine Risk				
	Relative Risk	95% Confidence interval	P-value *		
CGG size	0.993	0.984 – 1.001	0.096		
<i>FMR1</i> mRNA	0.939	0.746-1.183	0.594		

* Multivariate model adjusting for age and sex based on available data on 275 *FMR1* premutation carriers (123/152 with/without migraine).