



## Exploring inhibitory deficits in female premutation carriers of fragile X syndrome: Through eye movements



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### ABSTRACT

There is evidence which demonstrates that a subset of males with a premutation CGG repeat expansion (between 55 and 200 repeats) of the fragile X mental retardation 1 gene exhibit subtle deficits of executive function that progressively deteriorate with increasing age and CGG repeat length. However, it remains unclear whether similar deficits, which may indicate the onset of more severe degeneration, are evident in female PM-carriers. In the present study we explore whether female PM-carriers exhibit deficits of executive function which parallel those of male PM-carriers. Fourteen female fragile X premutation carriers without fragile X-associated tremor/ataxia syndrome and fourteen age, sex, and IQ matched controls underwent ocular motor and neuropsychological tests of select executive processes, specifically of response inhibition and working memory. Group comparisons revealed poorer inhibitory control for female premutation carriers on ocular motor tasks, in addition to demonstrating some difficulties in behaviour self-regulation, when compared to controls. A negative correlation between CGG repeat length and antisaccade error rates for premutation carriers was also found. Our preliminary findings indicate that impaired inhibitory control may represent a phenotype characteristic which may be a sensitive risk biomarker within this female fragile X premutation population.

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### 1. Introduction

Fragile X syndrome (FXS), the leading cause of inherited intellectual disability worldwide (Cornish, Turk, & Hagerman, 2008), is caused by a large CGG repeat expansion (>200 CGG repeats) on the 5' untranslated region of the fragile X mental retardation 1 (FMR1) gene. While those with a CGG repeat expansion of up to 45 are considered free from any deleterious effects, those with expansions from 55 to 200 CGG repeats, otherwise known as premutation (PM) expansions, are now known to be vulnerable to both neurodevelopmental and neurodegenerative changes (Jacquemont, Hagerman, Hagerman, & Leehey, 2007). Approximately 45% of male and 8–17% of female PM-carriers over the age of 50 develop fragile X tremor/ataxia syndrome (FXTAS) (Rodriguez-Revenaga et al., 2009). For female PM-carriers there is also an enhanced

risk for fragile X primary ovarian insufficiency (FXPOI), which can include premature menopause in approximately 20% of PM-carriers compared to 1% in the general population (Rodriguez-Revenaga et al., 2009; Sherman, 2000). However, FXTAS and FXPOI alone do not account for the full spectrum of involvement in the PM, which includes a range of specific executive processing impairments (Cornish, Li, et al., 2008; Cornish et al., 2008, 2009; Cornish, Hocking, Moss, & Kogan, 2011; Hocking, Kogan, & Cornish, 2012; Hunter, Abramowitz, Epstein, Tinker, & Sherman, 2012; Kogan & Cornish, 2010). Given the most recently documented prevalence rates of PM in males (1:430) and females (1:209) in a North American sample (Tassone et al., 2012), and the possibility that subtle cognitive changes may reflect either neurodevelopmental effects and/or the very earliest signs of neurodegeneration, further investigation of the neurocognitive profiles of PM-carriers is warranted.

Executive dysfunction, a feature of FXTAS, has been demonstrated in male PM-carriers in the absence of clinical features. Specifically, studies have found that the subcomponents of response

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inhibition (Cornish, Li et al., 2008; Cornish et al., 2008, 2011), and working memory (Cornish et al., 2009; Kogan & Cornish, 2010) are impaired, regardless of FXTAS status, and that there is a relationship between decline in these subcomponents of executive function and increasing age and CGG-repeat length (Cornish, Li, et al., 2008; Cornish et al., 2008, 2009, 2011; Hocking et al., 2012).

For female PM-carriers, the relationship between executive function and CGG repeat size is more complex due to X-inactivation, the phenotypic expression of only one set of X-linked genes. Increased rates of anxiety and depression symptoms, inattention, impulsivity, and problems with self-concept have been self-reported by female PM-carriers, and there is evidence for low-level visuospatial processing deficits (Hunter, Abramowitz, et al., 2012; Hunter, Leslie, et al., 2012; Kéri & Benedek, 2009; Kéri & Benedek, 2010). Attentional, visuospatial, and neuromotor impairments have also been reported, and appear to affect to a greater extent those with CGG-repeat lengths greater than 100 (Goodrich-Hunsaker et al., 2011; Hunsaker, Goodrich-Hunsaker, Willemsen, & Berman, 2010; Hunsaker et al., 2011). However, these studies are yet to specifically and empirically target executive processing subcomponents of inhibition and working memory in female PM-carriers, which may resemble a subtle form of impairment reported in male PM-carriers (Cornish et al., 2008, 2009, 2011; Cornish, Li, et al., 2008; Kogan & Cornish, 2010).

Emerging evidence suggests that PM-carriers exhibit neuroanatomical differences that may underlie these observed deficits. In male PM-carriers without FXTAS, alterations in white matter connectivity were found bilaterally in the cerebellar peduncles, specifically in the middle cerebellar peduncle compared to controls, and in the left fornix when compared to PM-carriers with FXTAS (Hashimoto, Srivastava, Tassone, Hagerman, & Rivera, 2011). Moreover, regions-of-interest analysis has revealed grey matter volumetric reductions within the cerebellum, particularly within lobule I/II of the vermis, which is implicated in the control of eye movements and balance, as well as in lobule III of the left hemisphere for PM-carriers compared to controls (Hashimoto, Javan, Tassone, Hagerman, & Rivera, 2011). In female PM-carriers without FXTAS, reduced cortical inhibition in GABA and cortico-cerebellar motor networks has been identified using transcranial magnetic stimulation (Conde et al., 2013). Beyond the cerebellum, a combined group of male and female PM-carriers has been found to have reduced cortical activation in inferior prefrontal areas (right ventral inferior frontal cortex and left dorsal inferior frontal cortex/premotor cortex), regardless of FXTAS status, during a verbal working memory task (Hashimoto, Backer, Tassone, Hagerman, & Rivera, 2011). Collectively, these findings demonstrate structural and functional differences primarily in the prefrontal and cerebellar regions of the brain; which have known links to the control of executive processes (Kozioł, Budding, & Chidekel, 2012). While imaging is a compelling and sophisticated method of examining deficits at a neuroanatomical level, reinforcing these studies through a clear understanding of the behavioural phenotype is critical for potential identification of early clinical markers suggestive of cognitive decline.

One of the most sensitive behavioural methods for investigating neural (dys)function is assessment of ocular motility. Ocular motor paradigms have been used extensively in a range of neurodevelopmental and neurodegenerative conditions to examine not only control of lower level motor control processes, but of higher order cognitive control processes, in particular response inhibition and working memory (Fielding, Georgiou-Karistianis, Millist, & White, 2006; Fielding et al., 2010; Lasker, Mazzocco, & Zee, 2007). The networks and nodes implicated in generating saccadic eye movement are well defined, spanning almost the entire brain: distributed throughout the neocortex (particularly prefrontal areas), subcortical and cerebellar regions (Leigh & Zee, 2006). In addition, a close

relationship between input and motor output facilitates precise measurement and provides an exquisitely sensitive behavioural measure of sensorimotor processing. To date, only a single study has examined ocular motility within the context of the FXS spectrum. This study found that adolescent females with FXS (CGG > 200) had greater difficulty generating accurate and timely saccades on gap/overlap and memory-guided tasks, the latter result suggestive of compromised working memory capabilities (Lasker et al., 2007).

The present study sought to examine the utility of saccadic paradigms to detect subtle cognitive changes in female PM-carriers. It specifically investigated executive dysfunction, focusing on response inhibition and working memory impairments that have previously been reported in male PM-carriers. We also examined the relationships between ocular motor task errors and performance on neuropsychological tasks. Mindful of the emerging evidence of prefrontal and cerebellar deficits in female PM-carriers, we anticipate specific inhibitory and working memory deficits similar to those previously identified in male PM-carriers.

## 2. Method

### 2.1. Participants

Fourteen female PM-carriers (55–200 CGG repeats) were recruited through local and national fragile X syndrome support groups, via a population-based fragile X carrier screening pilot study (Metcalfe et al., 2008) and a large carrier screening study currently underway in Victoria and Western Australia (unpublished). Fourteen controls were recruited through the current population-based fragile X carrier screening study, local networks and via online advertisements. A thorough neurological history was taken for all controls. Female PM-carriers and controls were found to be well-matched on age [ $t(20.95) = -.60, p = .56$ ] and IQ [ $t(26) = 1.39, p = .18$ ], as determined using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) (see Table 1).

Female PM-carriers were screened for features related to FXTAS (tremor, ataxia or parkinsonism) with the FXTAS Rating Scale (Leehey, 2009), with all PM-carriers found to be asymptomatic for FXTAS related features. All PM-carriers were confirmed with genetic analysis (see below for protocol) and had CGG repeat sequences within the PM range. No participant demonstrated visual impairment, or a history of serious head injury or neurological dysfunction. This study was approved by Monash University and Southern Health Human Research Ethics Committees. In accordance with this, all participants provided signed informed consent and the study procedures were consistent with the declaration of Helsinki.

DNA was extracted from 2 ml whole blood from PM-carrier participants using the Promega Maxwell<sup>®</sup> 16 instrument and associated Maxwell<sup>®</sup> 16 Blood DNA Purification Kit (Promega Cat No.: AS1010). PCR was performed using the Asuragen<sup>®</sup> AmpliDeX<sup>™</sup> FMR1 PCR Kit, as this assay has been shown to detect a full range of fragile X expanded alleles (Chen et al., 2010). PCR products were assessed via capillary electrophoresis on an Applied Biosystem 3130 Genetic Analyzer, with electropherogram analysis conducted

**Table 1**

Age, IQ and CGG repeat length for controls and asymptomatic PM-carriers.

	Controls (n = 14)		PM-carriers (n = 14)	
	Mean ± SD	Range	Mean ± SD	Range
Age	39.64 ± 11.94	23–56	41.93 ± 7.00	25–52
Full-scale IQ (WASI)	117.93 ± 9.44	99–133	112.93 ± 8.89	101–127
CGG length			79.36 ± 11.28	61–102

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