

## A neuropsychological investigation of male premutation carriers of fragile X syndrome

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### Abstract

It is currently thought that fragile X syndrome (FraX; the most common inherited form of learning disability) results from having more than 200 cytosine–guanine–guanine (CGG) trinucleotide repeats, with consequent methylation of the fragile X mental retardation (*FMRI*) gene and loss of FMR1 protein (FMRP). It was also considered that premutation carriers (with 55–200 CGG repeats) are unaffected, although a tremor/ataxia syndrome has recently been described in older adult male carriers. We reported that premutation expansion of CGG trinucleotide repeats affects brain anatomy, which, together with other studies, indicates that the molecular model for FraX needs modification. However, there are few studies on the cognitive ability of adult male premutation carriers. Thus, we selected 20 male premutation carriers on the basis of their genetic phenotype, and compared them to 20 male controls matched on age, IQ and handedness. We investigated intellectual functioning, executive function, memory, attention, visual and spatial perception, and language and pragmatics. The premutation carriers had significant impairments on tests of executive function (Verbal Fluency, Trail Making Test and Tower of London) and memory (Names sub-test of the Doors and People, Verbal Paired Associates Immediate Recall and Visual Paired Associates Delayed Recall sub-tests of the WMS-R, and Category Fluency Test for natural kinds). We therefore suggest that CGG trinucleotide repeats in the premutation range affect specific neuronal circuits that are concordant with specific neuropsychological deficits; and that these deficits reflect an emerging neuropsychological phenotype of premutation FraX.

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### 1. Introduction

Fragile X syndrome (FraX) is the most common form of inherited learning disability, affecting approximately 1:4000–6000 males (Turner, Webb, Wake, & Robinson, 1996; Youings et al., 2000). FraX is associated with an expansion of cytosine–guanine–guanine (CGG) trinucleotide repeats in the 5' untranslated region of the fragile X mental

retardation 1 (*FMRI*) gene on the X chromosome. Expansion of the *FMRI* gene to more than 200 CGG repeats (full mutation) is generally accompanied by methylation of the *FMRI* gene and loss of *FMRI* protein (FMRP) production (Verkerk et al., 1991; Yu et al., 1991). The cognitive and behavioural phenotype of the full mutation of FraX has been described by many authors (reviewed in Turk, 1992; Bennetto & Pennington, 2002). Features include autistic-like symptoms; maladaptive behaviours such as unusual speech patterns and hand flapping; and neuropsychological deficits in attention, processing and remembering sequential information, short-term memory,

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visuo-spatial ability, visual-motor co-ordination, and pragmatic language.

Approximately 1:813 men are carriers of premutation expansions of the *FMRI* gene (with 55–200 CGG repeats) (Dombrowski et al., 2002). The prevalence for females is much higher; perhaps as high as 1:100 (reviewed in Hagerman & Hagerman, 2002). It was originally thought that premutation carriers of FraX had normal FMRP production, implying that they were clinically unaffected. However, recent molecular genetic investigations have demonstrated diminished production of FMRP (Kenneson, Zhang, Hagedorn, & Warren, 2001; Tassone, Hagerman, Taylor, & Mills, et al., 2000; Tassone, Hagerman, Taylor, & Gane, et al., 2000) and elevated levels of *FMRI* messenger RNA (mRNA) (Hagerman et al., 2001; Tassone, Hagerman, Taylor, & Gane, et al., 2000; Tassone, Hagerman, Chamberlain, & Hagerman, 2000) in men who are premutation carriers. These findings are supported by an increasing literature suggesting a clinical affect of premutation expansions of CGG repeats (reviewed in Hagerman & Hagerman, 2002). For example, female premutation carriers may have; (1) a mild form of the physical phenotype of FraX (Hull & Hagerman, 1993; Riddle et al., 1998); (2) elevated levels of follicle-stimulating hormone (Baat, Smits, & Tomas, 1999; Hundscheid, Braat, Kiemeny, Smits, & Thomas, 2001); (3) premature ovarian failure (Allingham-Hawkins et al., 1999; Conway, Hettitarachein, Murray, & Jacobs, 1995; Giovannucci Uzielli et al., 1999; Murray, Webb, Grimley, Conway, 1998; Partington, Moore, & Turner, 1996; Schwartz et al., 1994; Syrrou et al., 1999; Turner, Robinson, Wake, & Martin, 1994; Vianna-Morgante, Costa, Pares, & Verreschi, 1996; Vianna-Morgante, 1999); and (4) neuroanatomical abnormalities (Murphy et al., 1999). Behavioural abnormalities, such as social anxiety (Sobesky, Hull, & Hagerman, 1994; Franke, Barbe, Leboyer, Maier, 1996, 1998), psychosis (Fryns, 1986) and affective disorders (Franke et al., 1996, 1998; Reiss, Hagerman, Vinogradov, Abrams, & King; Thompson et al., 1994; Sobesky, Porter, Pennington, & Hagerman, 1995, 1996) have also been reported in females, with a recent study (Johnston et al., 2001) demonstrating that female carriers with >100 CGG trinucleotide repeats have more emotional problems than those with <100 CGG trinucleotide repeats. Neuropsychological studies of female carriers, on the other hand, have reported that their performance does not significantly differ from controls (Bennetto, Pennington, Porter, Taylor, & Hagerman, 2001; Franke et al., 1999; Mazzocco, Pennington, & Hagerman, 1993; Mazzocco & Holden, 1996; Myers, Mazzocco, Maddalena, & Reiss, 2001; Reiss, Freund, Adams, Boehm, & Kazazian, 1993; Simon et al., 2001).

However, studies of female premutation carriers are confounded by Lyonisation (i.e. random inactivation of one of the two X chromosomes) and consequent variation in activation ratios (i.e. the proportion of active X chromosomes that have an affected allele). The range of activation ratios is great; for example there is more variability in the degree

of *FMRI* mRNA elevation for females than males (Tassone, Hagerman, Taylor, & Mills, et al., 2000). Thus neuropsychological performance may be differentially affected at the individual subject level, resulting in random group effects. Investigations of male premutation carriers provide a clearer picture of the effect of premutation expansions on neuropsychological performance.

There have been relatively few studies of male premutation carriers, who, as grandfathers and uncles of individuals affected by the full syndrome, are less likely to be identified than female carriers. Studies suggest that male premutation carriers may have (1) the facial characteristics of FraX (Hagerman et al., 1996; Hull & Hagerman, 1993; Loesch, Hay, & Mulley, 1994); (2) an increase in behavioural abnormalities, such as alcohol use and dependence, and obsessive-compulsive behaviours (Dorn, Mazzocco, & Hagerman, 1994); (3) learning disability (Hagerman et al., 1996; Murray et al., 1996; Rousseau et al., 1994; Tassone, Hagerman, Taylor, & Mills, et al., 2000; Teague et al., 1998); (4) deficits in vocabulary and block design IQ subtests (Loesch et al., 1994), attention (Dorn et al., 1994), and executive function (Hagerman et al., 2001; Jacquemont et al., 2003). In contrast, a recent study found no significant differences in the cognitive ability of boys who were premutation carriers as compared to controls (Myers et al., 2001).

Neuroanatomical abnormalities associated with a tremor/ataxia syndrome in older male carriers (FXTAS) have also been described (Brunberg et al., 2003; Greco et al., 2002; Hagerman et al., 2001; Jacquemont et al., 2003) and we have found neuroanatomical abnormalities in carriers who are clinically unaffected (Moore et al., 2004).

Thus, there is evidence that premutation expansion of CGG repeats may affect brain function. However, prior studies are difficult to interpret because many were affected by ascertainment bias; they included people who were identified by their learning or physical disabilities (Hagerman et al., 1996; Murray et al., 1996; Rousseau et al., 1994; Tassone, Hagerman, Taylor, & Mills, et al., 2000; Teague et al., 1998) or neurological features (Brunberg et al., 2003; Greco et al., 2002; Hagerman et al., 2001; Jacquemont et al., 2003). Further, those studies not confounded by ascertainment bias have been relatively small, with groups of ten or fewer individuals (Loesch et al., 1994, 1984; Myers et al., 2001), and/or did not include control subjects of similar IQ (Loesch et al., 1994).

No comprehensive neuropsychological profile has yet to be reported for a large cohort of adult male premutation carriers in the absence of ascertainment through learning disabilities or clinical features. To address this issue, we recruited twenty carriers selected on the basis of their genetic phenotype only, via UK genetic services. Participants were given an intellectual assessment and all had IQs in the normal range (96–142). Performance of the carriers on an additional battery of tests was compared to male controls who did not differ significantly in age, IQ, or handedness. The neuropsychological features of the full mutation of FraX have

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