

## Annotation

# The fragile X continuum: new advances and perspectives

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## Abstract

Fragile X syndrome is the world's most common hereditary cause of intellectual disability in men and to a lesser extent in women. The disorder is caused by the silencing of a single gene on the X chromosome, the Fragile X Mental Retardation Gene-1. A substantial body of research across the disciplines of molecular genetics, child psychiatry and developmental neuroscience bears testament to a decade of exciting and innovative science that has advanced our knowledge about the fragile X 'signature' or influence across cognitive and social development. The core aims of this review are to first discuss fragile X syndrome and premutation involvement in the context of current advances that demonstrate the dynamic nature of the genotype on phenotypic outcomes. Second, to discuss the implications of these recent advances for the development of clinical and educational interventions and resource tools that target specific phenotypic 'signatures' within the fragile X continuum.

**Keywords** autism, fragile X syndrome, FXTAS, FMRP, intellectual disability, premutation

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## Introduction

Fragile X Syndrome (FXS) has been a well-recognised common genetic cause of developmental disabilities for over 25 years. Previously known as the Martin-Bell syndrome, FXS represents the world's most common form of inherited intellectual disability (ID) affecting one in 3600 men and one in 8000 women (Turner *et al.* 1996; de Vries *et al.* 1998; Kooy *et al.* 2000). The focus initially in women with FXS has been on those with significant cognitive deficits. However, the spectrum of involvement includes those with learning difficulties and/or emotional problems with an IQ in the broad range of normal. As most women with the full mutation fall in this category, the prevalence of affected women including this milder involvement will be greater than one in 8000. In recent years, the disorder has become one of the most widely researched of genetic conditions, in part owing to its single gene aetiology but most notably because FXS allows for clear relationships to be drawn among multiple levels of analysis (i.e. genetic, neurobiological, cognitive and behavioural) (Cornish *et al.* 2004a). An explosion of research discoveries, which began in the early 1990s and continues into the present day, testify to the dynamic nature of the FXS genotype and its phenotypic trajectories across the lifespan.

The uncovering of clinical and cognitive forms of involvement in premutation carriers further expands the continuum of involvement. Recent estimates indicate that the premutation is more common in the general population (one per 260 women and one per 800 men; Rousseau *et al.* 1995; Dombrowski *et al.* 2002) than FXS (one per 3600); thus, the frequency of the problems associated with the premutation are more common than the problems associated with the full mutation. Distinct premutation 'signatures' include premature ovarian failure (POF) in women and late onset tremor and ataxia in men and will be discussed below. The thrust of this review is two-folds: first, to discuss FXS and premutation involvement in the context of current advances and to situate these findings within a developmental context; and second, to discuss the implications of these recent advances for the development of clinical and educational interventions and resources that target specific phenotypic 'signatures' within the fragile X continuum.

### Molecular overview

Fragile X syndrome is caused by a full mutation cytosine guanine-guanine (CGG) repeat expansion (>200 repeats) in the 5'-untranslated region of the Fragile X Mental Retardation-1 (*FMR1*) gene. Individuals with premutation alleles (55–200 CGG repeats) (Maddalena *et al.* 2001) actually produce increased levels of *FMR1* mRNA (Tassone *et al.* 2000). These *FMR1* mRNA levels increase from 2 to 8 times normal levels with expanding CGG repeat size over the premutation range (Tassone *et al.* 2000a,b). Sometimes moderate deficits in *FMR1* protein (FMRP) levels occur in individuals with premutation alleles, particularly larger alleles both in peripheral blood leucocytes (Tassone *et al.* 2000a; Allen *et al.* 2004) and in lymphoblastoid cells (Kenneson *et al.* 2001). However, the majority of individuals with the premutation have FMRP levels within normal limits (Tassone *et al.* 2000a,b), as determined with the immunocytochemical methodology developed by Willemsen *et al.* (1997). This methodology scores a lymphocyte as either positive or negative for the presence of FMRP, detected by anti-FMRP antibody, and the level of FMRP is reported as the percentage of lymphocytes positive for FMRP. Using this methodology, the level of

FMRP correlates with cognitive involvement, physical features and degree of central nervous system (CNS) activation on *FMR1* studies in those affected by FXS (Tassone *et al.* 1999; Loesch *et al.* 2004; Menon *et al.* 2004). Even in premutation carriers, the level of CNS change correlates with the level of FMRP (Moore *et al.* 2004).

Fragile X Mental Retardation-1 protein is an RNA binding protein that transports messages to the synapse and participates in the regulation of translation of these messages into protein (Jin & Warren 2003; Willemsen *et al.* 2004). FMRP typically inhibits the translation of messages so that when FMRP is absent or deficient there is upregulation of the proteins from a number of genes including microtubule-associated protein-1B (MAP1B) that is important for synaptic plasticity and structure (Willemsen *et al.* 2004). The absence of FMRP also causes upregulation of the metabotropic glutamate receptor five pathway (mGluR5) leading to long-term depression in the hippocampus and the cerebellum (Huber *et al.* 2002; Bear *et al.* 2004; Koekkoek *et al.* 2005). The mGluR5 theory of fragile X treatment hypothesises that mGluR5 antagonists will significantly reverse both the neurological and cognitive aspects of FXS. This has been seen in the animal models of FXS including the knock out mouse and the *Drosophila* model when treated with an mGluR5 antagonist, MPEP or lithium (McBride *et al.* 2005, Yan *et al.* 2005).

The discovery of elevated *FMR1* mRNA levels in the premutation (Tassone *et al.* 2000b) opened the door to the study of clinical involvement in premutation carriers including POF and Fragile X-associated Tremor/Ataxia Syndrome (FXTAS). The elevated mRNA levels correlate with the CGG repeat expansion in the premutation range. This elevation leads to an RNA gain-of-function mechanism of involvement which is described below (Hagerman & Hagerman 2004).

### The Fragile X-associated Tremor/Ataxia Syndrome

When grandfathers of children with FXS were evaluated a consistent neurological disorder was discovered in a subgroup of these men that included both intention tremor and ataxia (Hagerman *et al.* 2001; Jacquemont *et al.* 2003). This phenotype is more common in aging male

premutation carriers than female carriers with an increasing prevalence with age (Jacquemont *et al.* 2004). The phenotype of FXTAS has been expanded to include autonomic dysfunction, such as hypertension and impotence (Jacquemont *et al.* 2003), psychiatric features including agitation, dys-inhibition and anxiety (Bacalman *et al.* 2006), neuropathy in the lower extremities (Berry-Kravis *et al.* 2007) and cognitive deficits including executive function and memory deficits and later cognitive decline (Grigsby *et al.* 2006a, b; Cornish *et al.* 2007a). We have described an RNA toxicity mechanism leading to FXTAS (Hagerman & Hagerman 2004) and formation of eosinophilic inclusions in both astrocytes and neurons throughout the brain (Greco *et al.* 2002; 2006). The addition of a premutation expansion leads to disease and inclusion formation in both mouse and *Drosophila* models of the premutation (Jin & Warren 2003; Willemsen *et al.* 2003). Moreover, Jin & Warren 2003 demonstrated that a 90-CGG repeat, as RNA, results in atrophy in the eye and the formation of inclusions in the *Drosophila* neurons. Willemsen *et al.* (2003) described the development of the eosinophilic inclusions in neurons (but not astrocytes) by 20 weeks of age in the premutation mouse model. Neurological problems, specifically motor problems, have now been observed in these premutation mice who are aging (Van Dam *et al.* 2005).

As the initial reports of FXTAS, there have been numerous studies from several countries assessing the prevalence of FXTAS in neurological disorders, including essential tremor, cerebellar ataxia, Parkinson's disease and multiple system atrophy (MSA) Macpherson *et al.* 2003; Deng *et al.* 2004; Tan *et al.* 2004, 2005; Garland *et al.* 2004; Milunsky & Maher 2004; Zuhlke *et al.* 2004; Biancalana *et al.* 2005; Brussino *et al.* 2005; Kamm *et al.* 2005; Seixas *et al.* 2005; Van Esch *et al.* 2005). We have summarised these studies in two reports, Hall *et al.* (2006) and Jacquemont *et al.* (2006). The diagnostic groups with the highest prevalence of premutation carriers are men over 50 with cerebellar ataxia (overall prevalence is 17/872, 2%, range 0–7%, Macpherson *et al.* 2003; Milunsky & Maher 2004; Biancalana *et al.* 2005; Brussino *et al.* 2005; Van Esch *et al.* 2005) and individuals with MSA cerebellar type with an overall prevalence of 4/280 (2%, range 0–3.95%, Biancalana *et al.* (2005) and Kamm *et al.*

(2005). Recently, we have begun to see children diagnosed with FXS through cascade testing because one of their grandparents was first diagnosed with FXTAS.

### Premature ovarian failure

A unique phenotype in premutation female carriers, not seen in women with the full mutation, and first recognised in 1991 (Cronister *et al.* 1991) is POF. Subsequent studies determined that approximately 20% of female carriers experience POF (Schwartz *et al.* 1994; Allingham-Hawkins *et al.* 1999; Murray *et al.* 2000; Sherman 2000a, b; Vianna-Morgante & Costa 2000). In a review of screening studies of women who present with POF, 9.5% (9/95; 95% CI: 4.4–17.2%) of those with familial POF have the premutation and of those with sporadic POF, 3.0% (8/267 CI: 1.3–17.2%) have the premutation (Conway *et al.* 1998; Murray *et al.* 1998; Uzielli *et al.* 1999; Marozzi *et al.* 2000; Mallolas *et al.* 2001; Bussani *et al.* 2004; Sherman *et al.* 2005).

Further endocrine studies demonstrate that although approximately 20% of carriers have POF, those carriers that are cycling normally also have endocrine dysfunction (Welt *et al.* 2004). Welt *et al.* (2004) studied 11 normally ovulating premutation carriers (ages 23–41 years) and demonstrated a significantly shortened cycle, elevated follicle stimulating hormone throughout the cycle (91% with elevations >2 SD above the mean), elevated inhibin B in the follicular phase, and elevated inhibin A and progesterone in the luteal phase, compared with controls.

A recent study by Sullivan *et al.* (2005) involving over 500 women representing a broad range of CGG repeats, from the normal range into the high end of the premutation range, demonstrated a significant, non-linear association between CGG repeat number and prevalence of POF. For those with a repeat <40, the prevalence of POF was 0.9%; for those with 41–58 repeats, the prevalence increased to 2.2%; for those with 59–79 repeats, the prevalence was 5.9%; for those with 80–99 repeats, the prevalence was 18.6%; and for those with ≥100 repeats, the prevalence decreased to 12.5%. The cause of this decrease after 100 repeats is not known and requires confirmation by other centres. POF is not seen in individuals with the full muta-

tion, suggesting it may be related to the toxic effects of the elevated *FMR1* mRNA which occurs almost exclusively in the premutation range (Allen *et al.* 2004; Hagerman & Hagerman 2004). *FMR1* is more highly expressed in ovarian follicles compared with other organs (Hinds *et al.* 1993), which would make it more vulnerable to *FMR1* mRNA toxicity.

### Linking the fragile X clinical and cognitive phenotypes

#### *Full mutation Fragile X Syndrome*

Intellectual disability and behavioural difficulties characterise many children with FXS. In boys, almost all present with IQ's within the mild-severe range of impairment with profiles emerging as young as 3 years of age (Skinner *et al.* 2005). In women, the phenotypic variation is such that some girls only show sub-clinical learning disabilities (Bennetto & Pennington 2002), while approximately 25% display more significant cognitive impairment (most with mild ID and rare individuals with moderate ID) similar in profile to boys with FXS. The X-inactivation status of the fragile X female is seen as the major contributor to the heterogeneity of ID and the broad range of cognitive deficits. However, a decade of research has confirmed that FXS is not defined by the degree of intellectual impairment but rather by a unique 'signature' of clinical and cognitive strengths and difficulties that differentiate FXS from other developmental disabilities (e.g. autism, Down syndrome, Williams syndrome). A key discovery has been to demonstrate the importance of looking beyond the general effects of developmental delay and so-called 'commonalities' in clinical and cognitive symptomatology to identify the distinct pathways and processes that represent the FXS phenotype.

Undoubtedly, behavioural problems often link with cognitive impairment and two disorders in particular that coexist in many individuals with FXS are Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD). Owing to the pervasiveness of these symptoms, a diagnosis of FXS may occur later in childhood or never at all if clinicians are unable to dissociate the FXS phenotype from a diagnosis of ASD or ADHD. To address this concern and provide much

needed information to clinicians and educators, the findings from a series of recent studies have begun to elucidate the FXS 'signature' associated with both ASD and ADHD.

#### *Autistic spectrum disorder*

Psychiatrically, conceptual confusion persists regarding the relationship between FXS as an *aetiological* entity and diagnosis, and commonly associated neuropsychiatric *clinically phenomenologically* diagnosed conditions such as autism. FXS accounts for 2–6% of cases of autism (Bailey *et al.* 1993; Reddy *et al.* 2005) and a substantial minority of children with FXS can be diagnosed as having autism, may be as many as a third (Turk & Graham 1997; Rogers *et al.* 2001; Hagerman 2006). There is emerging evidence that the rate of diagnosable autism increases with age in men with full mutations (Hatton *et al.* 2006) and that impairment in verbal skills best explains the comorbidity of autism and FXS (Loesch *et al.* 2007).

At the *cognitive level*, commonalities between FXS and ASD are clearly evident within the social domain and are most notable on skills that require successful social interaction and reciprocity (such as maintaining eye gaze and understanding the intentions of others) (for a review see Cornish *et al.* 2007b). However, closer inspection of the social cognitive profiles indicates that while some 'core' characteristics appear to unite FXS and ASD, these same characteristics also serve very different functions and are suggestive of disparate mechanisms underlying the phenotypic outcomes of these two conditions. *Eye gaze*, for example, is deficient in both FXS and ASD (Kerby & Dawson 1994; Klin *et al.* 2002; Senju *et al.* 2003; Garrett *et al.* 2004) but for different reasons. In ASD, atypical eye gaze is most acute in social interactions and appears to be motivated both by a lack of understanding of the social situation itself and by the absence of a desire to communicate. In contrast, eye gaze behaviour in FXS does not appear to be guided by a lack of social awareness or communication. The majority of individuals with FXS, although tending to avoid social interactions, will offer what is now classically termed the '*fragile X handshake*', whereby an initial wish to communicate socially, with a 'handshake', a socially acceptable remark or even brief initial eye contact, is coupled

with active and even persistent gaze avoidance. Subsequent interactions with familiar persons may be marked by the same active gaze avoidance despite the growing relationship. The gaze avoidance persists even when attempts are made to extinguish it; it may, in fact, increase in intensity. It has been suggested FXS is associated with a unique pattern of hyperarousal and social anxiety that can cause them to avert their eyes in a social situation (to avoid the sensory stimulation of eye contact), but may still wish to communicate socially (Wolff *et al.* 1989; Cornish *et al.* 2004b). Thus, individuals with FXS are more likely to exhibit autistic-like behaviours such as eye gaze aversion, which are more symptomatic of their hyperarousal and social anxiety rather than from an inherent lack of understanding of the social situation.

*Theory of mind* – the ability to understand the beliefs and intentions of others, is a well-documented deficit in ASD (e.g. Baron-Cohen *et al.* 1985; Baron-Cohen, 1999), and more recently in FXS (Garner *et al.* 1999; Cornish *et al.* 2005a; Grant *et al.* 2007). However, observation of the error patterns in performance of children with ASD and children with FXS reveal subtle but different end-states. For example, in a recent preliminary study by Grant *et al.* (2007), the authors compared 15 children with FXS alone, 15 children with FXS and autism and 15 comparison children with unknown aetiology on two standard first order belief tasks and two video-based non-verbal false belief reasoning tasks. At first glance, all three groups demonstrated significant theory of mind deficits commensurate with their ID; however, the underlying reasons for the deficits appear to be syndrome specific. In the case of FXS, the associated deficit suggests severe difficulties in general information processing that is impacting on working memory performance (most probably a deficiency in skills that require attentional, executive capacity) rather than the result of a core deficit in theory of mind.

#### *Attention deficit and hyperactivity disorder*

Children with attention deficit hyperactivity disorder (ADHD) are characterised by their poor attention to detail, difficulties in maintaining attention over a sustained period of time, and moment-to-

moment variability throughout task performance. Among the most distinctive and pervasive behavioural features of young boys with FXS are attentional and hyperactivity problems (e.g. Cornish *et al.* 2001; Hatton *et al.* 2002; Sullivan *et al.* 2006), the severity of which often leads to a clinical diagnosis of ADHD. At a finer-tuned level, however, the FXS profile appears to be characterised by unexpectedly extreme levels of inattentiveness, restlessness, fidgetiness, impulsive tendencies and distractibility even when their level of general development is taken into account. In one of the most comprehensive study's to date, Turk (1998) compared the ADHD profiles of 49 FXS boys (aged 4–16 years) with that of 45 boys with Down syndrome (aged 4–16 years), and 42 boys with ID of an unknown cause (aged 4–16 years). Although both groups of boys showed similar levels of motor activity, the boys with FXS show significantly more inattentiveness, restlessness, fidgetiness, distractibility and impulsive tendencies suggestive of Diagnostic Statistical Manual of Mental Disorders 4th edition (DSM-IV) ADHD predominantly inattentive type. Moreover, there is some evidence that these features do not necessarily improve with age (in contrast to most children with these traits), emphasising the need for early diagnosis and multi-disciplinary intervention. In girls with FXS, the research is not as extensive as that undertaken in affected boys but nonetheless points to a substantive minority of girls presenting with ADHD-inattentive type symptoms (Mazzocco *et al.* 1998). Together, these findings highlight a distinctive ADHD profile in the FXS full mutation that is not solely the artefact of ID.

At the *cognitive level*, FXS is characterised by a now well-documented attention 'signature' that includes a fundamental weakness in inhibitory control. By teasing apart the different cognitive subdomains that comprise attention (selective attention, sustained attention, divided attention and attentional control), Cornish and colleagues have demonstrated how performance of children with FXS can be differentiated from performance of children with Down syndrome even though at first glance both syndromes present with common symptoms of ADHD. From childhood onwards, the FXS 'signature' is one of a relative strength in sustained attention (the ability to maintain focus of concen-

tration over time) compared with moderate difficulty in selective attention (the ability to focus on one out of several competing attentional stimuli) but profound difficulty for skills that required attention switching and/or inhibitory control (Munir *et al.* 2000a; Cornish *et al.* 2001, 2007c; Wilding *et al.* 2002). The latter deficit represents a fundamental weakness in FXS that impacts across development and may explain the wide range and severity of deficits on skills that require attentional control across and within differing cognitive domains (e.g. speech, working memory) (Munir *et al.* 2000b; Belser & Sudhalter 2001). In contrast, for skills that do not require significant attentional control (e.g. vocabulary, long-term memory, face recognition), there is a profile of relative strengths. A recent study by Sullivan *et al.* (2007) assessed sustained attention and response inhibition in males with FXS using the Continuous Performance Test. Compared to the performance of mental age-matched typically developing children, males with FXS showed greater declines in response inhibition over task time but comparable rates of decline in sustained attention. What is especially interesting about the pattern of these findings is that when one looks specifically at the response inhibition performance both the FXS and comparison males began the task at a similar level but as the task progressed performance diverged such that by its completion males with FXS were experiencing significant problems with inhibitory control, performing at a much lower level than the mental age (MA)-matched comparison boys.

#### *Carriers of Fragile X Syndrome*

The premutation is not typically associated with severe intellectual impairment, as seen in the full mutation, and most individuals function within the normal population range of IQ. For this reason, it was generally assumed that carriers of FXS were 'phenotypic free', that is without any clinical or cognitive deficit that could be attributable to their FXS status. However, converging evidence now points a premutation 'signature' that is similar in profile, albeit milder in presentation, to that of the male full mutation.

In *carrier females*, the issue of clinical problems has been controversial for years because the stress

of raising a child with FXS can cause significant emotional problems that are difficult to separate from the effects of the premutation itself. Although a few studies have reported no emotional problems in female carriers compared with control women (Brainard *et al.* 1991; Reiss *et al.* 1993), others have found the premutation to be associated with increased shyness, social anxiety and depression in approximately 25% of carrier females (Sobesky *et al.* 1994, 1996). These problems were also seen by Franke *et al.* (1998), who compared premutation females, both with and without children with FXS, with control women who had children with autism. Social anxiety and social phobia were significantly higher in carriers compared with controls without the premutation. The rates of depression were similar in women with or without the premutation who had children with developmental disabilities. A more recent study by Johnston *et al.* (2001) gave greater insight into this issue by demonstrating a relationship between psychiatric problems and molecular variables. They studied 85 women with the premutation and found that those with greater than 100 CGG repeats had higher rates of depression and interpersonal sensitivity on the Symptom Checklist-90-Revised (SCL-90-R, Derogatis 1994) than women with CGG repeats of less than 100. They hypothesised that this difference was likely to be due to a lower level of FMRP in those with a higher CGG repeat level. However, a recent study demonstrated that elevation in *FMR1* mRNA has a strong correlation to psychological measures on the SCL-90-R in carriers (Hessl *et al.* 2005).

In *carrier males* (without FXTAS), a number of recent studies have identified an emerging phenotype that mirrors the FXS full mutation but without significant intellectual impairment. At the *clinical level*, the findings from a recent Australian study report ASD in one of seven premutation males (14%) (Clifford *et al.* 2007). Furthermore, in a family study, there were significant group differences in ASD and ADHD between premutation carrier boys presenting clinically (proband;  $n = 14$ ), non-proband carrier boys ( $n = 13$ ) identified through cascade testing of the family (siblings of the proband), and control siblings without the premutation ( $n = 16$ ) (Farzin *et al.* 2006). ASD diagnoses were considered using the Social Communication Questionnaire as the first screen.

For those with problems (score >15 or clinical concerns), the Autism Diagnostic Observation Schedule – General and/or the Autism Diagnostic Interview – Revised, was utilised followed by a clinical diagnosis with the Diagnostic Statistical Manual – Fourth Edition (DSM-IV, Autism Diagnostic criteria). Preliminary findings from a British study of adult male premutation carriers (Mills *et al.* 2002; Cornish *et al.* 2005b) suggest that men can experience a paradoxical combination of social disinhibition and overfriendliness and overcompliance with deficits in showing emotions and feelings, social perception and empathy problems. These same men were also found to experience difficulties reading emotions in others, and had difficulty in making friends. Hessel *et al.* (2007) recently demonstrated that young adult men with the premutation displayed deficits in both psychophysiological measures and functional Magnetic Resonance Imaging (fMRI) measures of amygdala activation to fearful faces compared with controls. Therefore, the connectivity or the processing of social information in the limbic system may be unusual in male premutation carriers.

At the *cognitive level*, deficits in inhibition and executive functioning (Loesch *et al.* 2003a,b; Moore *et al.* 2004; Cornish *et al.* 2007a; Grigsby *et al.* 2006b, 2007) are especially striking, not least because they occur in the absence of ID. Interestingly both Cornish *et al.* and Grigsby *et al.* have shown that executive function deficits in particular are the primary presenting neurocognitive deficits in individuals presenting with tremor and/or ataxia in FXTAS. A similar pattern of deficit has recently been found in the domain of working memory and specifically on tasks that require short-term manipulation and recall of complex information (Cornish, Kogan *et al.* submitted; Kogan *et al.* 2007). Together, these findings highlight the critical importance of identifying subtle yet important neurocognitive profiles in FXS carriers.

#### *Fragile X: aging and cognitive performance*

Recent studies have also highlighted the critical role that development plays in defining the fragile X phenotypes both in the full and premutation. By their very nature trajectories do not remain static over time and thus one cannot assume that the

adult end-state actually had its origins in the infant start-date. In a series of novel, empirically driven studies, Scerif and colleagues have compared infants, toddlers, children and adults with FXS to those with either Williams syndrome or Down syndrome across a range of selective attention measures (Cornish *et al.* 2007c; Scerif *et al.* 2004, 2005, 2007). New information on the FXS trajectory of attention came from considering how performance changed in line with chronological age and developmental level across groups. Overall, despite large delays and greater adult difficulties with attention, individuals with Down syndrome showed improvements by adulthood, whereas those with FXS did not, especially for measures tapping inhibitory control. These persistent difficulties with inhibitory control also held when compared to infants and toddlers with WS, whose full developmental trajectory of attentional processes remains to be investigated.

As for *FXS carriers*, a focus on changes over developmental time is uncovering exciting and novel information. For example, Cornish *et al.* (2007a) in their recent study of premutation males found a disproportionate aging effect on skills that required the ability to inhibit prepotent responses in contrast to other cognitive skills such as those needed for sustained attention, visual working memory, or visual spatial cognition. The inhibitory impairment differentiated premutation males from comparison men from age 30 onwards. With increasing age, the two groups follow different trajectories, with premutation males developing progressively more severe problems in inhibitory control. This deficit also has a strong co-occurrence in men displaying FXTAS-related symptomatology. Cornish *et al.* concluded that an inhibitory deficit and its impact across the lifespan are associated with the fragile X premutation status, and may be a precursor for development of a more severe form of cognitive impairment or dementia, which has been reported in patients with the diagnosis of FXTAS.

#### *Clinical and educational implications*

From a *clinical perspective*, the FXS phenotype demonstrates the benefits of extensive professional efforts to link the underlying dynamic cognitive

processes and unevenness with the presenting emotional, behavioural and other developmental features. The clinical consequences of these features and their potent interactions include sensory integration difficulties, language dysfluencies, social anxiety, general hyper-arousal, autistic and non-autistic social impairments, inattentiveness, impulsiveness, distractability and cognitive deficits. It follows that a common combination of clinical problems that present to services consists of ADHD, social and anticipatory anxiety states, disorganised thinking, self-fuelling excitement, social and communication problems and often severe sleep difficulties. Corresponding treatments ameliorate multiple components of the above-described exophenotype and endophenotype, including the alpha agonist clonidine for sleep, ADHD and anxiety (Ingrassia & Turk 2005), melatonin for settling and sleep induction problems (Turk 2003), stimulants for ADHD, selective serotonin reuptake inhibitors for anxiety, atypical antipsychotics for mood stabilisation (particularly aripiprazole; Berry-Kravis & Potanos 2004; Hagerman 2006) and cognitive behavioural psychotherapeutic programmes that take into account the individuals developmental difficulties as well as social and communicatory impairments (Turk 2005). Cognitive-behavioural approaches also appear to be useful for the common and frequently missed post-traumatic stress disorders which may well impact many individuals with FXS given their vulnerability to adverse life events and experiences, and their intrinsically high levels of obsessional and ruminative thinking, social anxiety and impressionability (Turk 2005). Other interventions highly relevant to the FXS profile of impairments include speech and language therapy, occupational therapy (in particular sensory integration approaches), special education and attention to social aspects.

In the *premutation*, stimulants work well for the ADHD that is often present in young boys and anxiety responds well to a selective serotonin reuptake inhibitor (Farzin *et al.* 2006). If mood instability is a significant problem then an atypical antipsychotic can be helpful such as aripiprazole. However, more established atypical antipsychotics, such as the benzixazole risperidone, and substituted benzamide amisulpiride can also stabilise mood and behaviour when presenting in cyclical, and even not

so cyclical, forms. These medications may also ameliorate some of the autistic social impairments as well as the attentional deficits, although caution is required regarding long-term prescribing, given the lack of longitudinal outcome data for individuals receiving these agents regularly and the significant problems with weight gain. Traditional anticonvulsants now known to have potent mood stabilising effects such as carbamazepine, sodium valproate and lamotrigine present alternatives. Selective serotonin reuptake inhibitors such as fluoxetine, and serotonin and norepinephrine reuptake inhibitors such as venlafaxine can be effective in tackling multiple problem areas including depressed mood, obsessive-compulsive tendencies, high levels of social and other forms of anxiety, ADHD and autistic aloofness. Treatment of adults with FXTAS include treatment for hypertension, treatment for thyroid or testosterone deficiency if present (Coffey *et al.* in press; Greco *et al.* 2007), treatment for psychiatric problems including anxiety and dysinhibition and anecdotal evidence suggests that venlafaxine is beneficial (Jacquemont *et al.* 2004; Hall *et al.* 2006). Pain related to neuropathy or fibromyalgia can be a significant problem for carriers who have FXTAS and gabapentin can be helpful for this pain.

Newer targeted psychopharmacological agents, such as fenobam, an mGluR5 antagonist, and ganaxolone, a GABA<sub>A</sub> receptor modulator that functions as an agonist, will both begin clinical trials this year and will hopefully be beneficial for behaviour and cognition in individuals with FXS. These medications are experimental and cannot be used clinically. Lithium, however, is available clinically and can be helpful for stabilising mood in FXS in addition to down regulating the mGluR5 system.

From an *educational perspective*, there is a critical need to expand specialist resource packages that can bridge the gap between this generation of new knowledge and the uptake and utilisation of these discoveries by educators and affected families. The National Fragile X Foundation at <http://www.fragilex.org> has begun a web-based resource by providing a large section of information regarding educational interventions for children and an adolescent programme of information regarding vocational training, sex education, guidance for counsellors and therapists and enhancement of

social skills. Additional information is available on this web site regarding FXTAS information and POF information. As a tool for *families*, access to this centralised resource programme will promote family involvement and partnership with schools and play an invaluable role in ensuring realistic academic expectations and goals are maintained across the academic trajectory; and, as a tool for *policy makers* to guide decisions about the development of education programmes and services. Often parents need to download this information on the web and provide it for teachers, therapists, counsellors and physicians.

#### Conclusions and future directions

Our aim in this review has been to draw together the plethora of findings from a decade of research on FXS and fragile X-related conditions. Together, these findings now clearly demonstrate the unique constellation of strengths and difficulties that impact across developmental time affecting both clinical and cognitive functioning. The last decade has seen tremendous advances in our understanding of this syndrome and its variability across many different levels most notably at the molecular, clinical and cognitive levels. Together, these advances highlight the importance of recognising the distinct phenotypic outcomes that characterise the fragile X premutation and full mutation. The findings warrant a multi-disciplinary approach to investigating the clinical, cognitive and developmental symptoms of FXS and to create an awareness that FXS does not always occur in isolation but that many children and adults also present with symptoms that resemble more common disorders such as ADHD and autism. Early diagnosis of FXS is crucial if educational and clinical interventions are to have maximum impact in enabling children with FXS to develop to their maximum potential. Early diagnosis will be facilitated by newborn screening for fragile X and the technology now exists for this to be a reality.

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