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FRAXE
Underdiagnosed, undertreated, under-researched and misunderstood

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FraX-E: underdiagnosed, undertreated, under-researched and misunderstood?

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Abstract
This article focuses on the consequences of having FraX-E, the rare but well recognised variant of fragile X syndrome. The authors provide some background on the condition and report on recent research and evidence. Three case reports are outlined and the specific behavioural aspects of the syndrome are considered. The authors argue that it is important that the behavioural phenotype for FraX-E is clearly identified and defined in order to give those with the condition relevant psychological and educational support in the future.

Key words
mental health needs; learning disabilities; intellectual disabilities; FraX-E; fragile X syndrome

Introduction
Fragile X syndrome is the most common identifiable cause of inherited learning disability. Its name derives from the appearance of the X chromosome, caused by excess trineucleotide repeats of the bases CGG. This produces hypermethylation which prevents expression of a protein thought to be necessary for neurodevelopment. It is the absence of this protein (FMR-1) that is responsible for the clinical phenotype (Hagerman & Hagerman, 2002). Clinicians are usually referring to FraX-A (subtype A of fragile X syndrome) when describing fragile X syndrome. This is by far the most common subtype. Other examples include FraX-F (Hirst *et al*, 1993) and FraX-E (Knight *et al*, 1993). There has been much research into FraX-A and its clinical significance. FraX-F is less well understood and is believed to almost certainly be a benign condition. FraX-E however has been studied largely at the genetic level and very little is known about its developmental, emotional and behavioural aspects.

FraX-E is thought to be extremely rare. The precise prevalence figures are, to an extent, guesswork because of its allegedly mild and probably frequently overlooked nature. Twelve studies have looked at the prevalence of FraX-E in populations with learning disabilities. Eight of these studies found no individuals with the condition, but four affected individuals were found out of 6326 people studied (Wang *et al*, 1993; Allingham-Hawkins & Ray, 1995; Holden *et al*, 1996; Knight *et al*, 1996; Murray *et al*, 1996; Tranebjaerg *et al*, 1996; Barnicoat *et al*, 1997; Mazzocco *et al*, 1997a; 1997b; Mila *et al*, 1997; Elbaz *et al*, 1998; Patsalis *et al*, 1999; Youings *et al*, 2000; Pandey, Phadke & Mittal, 2002).

Taking all the above studies into account, the prevalence of FraX-E *within the learning disabled population* appears to be four per 6326 persons studied or about one in 1600. The UK population is about 50 million. It is estimated that around 2% of the UK population have learning disabilities (about one million). It is therefore possible that up to about 600 people in the UK may be affected with FraX-E based on the above rather crude statistics. Due to lack of general population screening, it is impossible to make definite statements regarding the prevalence of FraX-E. However it has been quoted as occurring in approximately one in every 75,000 males in a leading study (Brown, 2002).

FraX-E is a semi-dominant X-linked genetic condition involving DNA expansion pathology or gene deletion. The FraX-E locus was first discovered by Sutherland and Baker in 1992. It is located at position Xq28 on the X chromosome's long arm, just beyond the FraX-A gene. Like FraX-A, it is hypermethylation of an adjacent CpG island that is responsible for the lack of expression of a protein. The trinucleotide repeat responsible for causing FraX-E (CCG) is present in the general population, the normal range being 6–30 repeats. An intermediate expansion of 31–60 repeats represents 'carrier status' and is reportedly asymptomatic. However, a pre-mutation of between 61 and 200 is unstable and can expand transgenerationally. The full mutation is present when there are over 200 repeats, and causes clinical expression due to inactivation of the FMR2 protein in males and some females. It should be noted that the number of repeat copies characterising the pre and full mutations do vary slightly between studies (Sutherland & Baker, 1992; Pintado & Moron, 2001; Santos *et al*, 2001).

FMR1 is the abbreviation for the gene which is switched off in FraX-A. FMR1 is believed to have roles in the transport of material between nucleus and cell cytoplasm, and the binding of messenger RNA to ribosomes. It is thought that the protein formed from this gene has functions similar to the FMR2 protein which is deficient in FraX-E. Thus it would be reasonable to expect some overlap of symptomatology (Davidovic *et al*, 2006). However, the precise function of the FMR2 protein is still uncertain owing to the rarity of individuals confirmed as having FraX-E, and the reportedly highly variable clinical phenotype.

FraX-E is difficult to distinguish from FraX-A using conventional cytogenetic techniques. This is because of the relative proximity of the two genes, leading to easy confusion between them when chromosomes are scrutinised using ordinary light microscopy. Nonetheless, this is how most cases of FraX-E have been ascertained. In practice, given its supposed rarity, it is often thought unnecessary to test for FraX-E. The best test is the molecular genetic DNA based analysis, done initially using a Southern blot with a double digest of HindIII and NotI, along with the probe OxE20. This is then followed by polymerase chain reaction techniques to determine triplet repeat number.

The physical phenotype for FraX-E is not clearly defined. Commonly reported features have been noted which are similar to those witnessed in individuals with FraX-A. These include a long, narrow face; high-arched palate and laxity of joints, although findings are inconsistent. In general, however, individuals with FraX-E are characterised by the normality of their physical appearances (Hamel *et al*, 1994; Russo *et al*, 1998; Barnicoat *et al*, 1997; Abrams *et al*, 1997).

It is widely reported that FraX-E can be a cause of learning disability. However, due to the rarity of ascertained full mutations and premutations there is as yet no clear description of a clinical phenotype, whether physical or psychological. Four studies have looked at the

behavioural aspects of FraX-E using psychometric and behavioural assessments. The most detailed to date (Abrams *et al*, 1997) was on two unrelated boys both expressing FraX-E. They were assessed cognitively, behaviourally and neuroanatomically. Both individuals met DSM-III criteria for ADHD and had some features of high-functioning autistic spectrum disorder. Only one of them managed to fulfil enough criteria for a diagnosis of autism. Cognitively both the boys were below average IQ (88 and 78). Individual one showed poor abstract visual reasoning and language skills, and poor motor co-ordination. Individual two had problems with short-term memory and language skills. However, he was above average in visuo-spatial memory skills. Three other studies (Barnicoat *et al*, 1997; Russo *et al*, 1998; Turk, 1995) have found consistencies with the behavioural traits identified by Abrams *et al* (1997), but there is a lack of specific information within each of the diagnostic categories.

We have identified 16 studies in the literature describing behavioural aspects in a total of 39 individuals with FraX-E (Hamel *et al*, 1994; Knight *et al*, 1994; Mulley *et al*, 1995; Barnicoat *et al*, 1997; Carbonell *et al*, 1996; Knight *et al*, 1996; Meadows *et al*, 1996; Murray *et al*, 1996; Murgia *et al*, 1996; Abrams *et al*, 1997; Mazzocco *et al*, 1997a; 1997b; Mila *et al*, 1997; Crawford *et al*, 1998; Russo *et al*, 1998; Gecz, 2000; Nigro *et al*, 2000). Common recurring features included:

- mild to moderate learning disability (IQ 35-70), although findings have been reported outside this range.
- delayed speech and language development, notably dyslalia and stuttering
- overactivity, attention and concentration difficulties, sometimes fulfilling DSM-IV criteria for ADHD
- autistic features, including poor eye contact, echolalia, rocking, obsessive traits and ritualistic behaviour
- motor in-coordination
- psychiatric problems
- epilepsy.

Knight and colleagues (1996) suggested that similarities between the FraX-A and FraX-E phenotypes could be due to mutation at the FraX-E locus causing reduced FMR-1 expression and thus leading to a milder version of fragile X syndrome. However, neither this nor other theories explain the different physical and psychological manifestations of FraX-E. More research is needed. It has also been proposed that familial environment may have an important role in the developing phenotype of a FraX-E affected individual (as it would be expected to in anybody with or without a genetic anomaly); the provision of stimulating play from an early age as well as a loving and caring environment helping to modulate the severity and hence final outcome of the condition. Most studies concerning FraX-E are in concordance with the idea of the need for further standardised cognitive and psychometric testing. This will be important in the recognition of further individuals with FraX-E and will help improve diagnostic criteria, providing affected individuals and their families with relief from uncertainty, help and information about the disorder and how to obtain the best possible outcome for individuals and their families.

Table 1: Clinical features of FraX-E identified in some studies

Case (reference)	Cognition	ADHD features	Autistic features	Dysmorphic features	Medical	Medical history
1 (Abrams 1997)	IQ88 Poor abstract visual reasoning, poor language	ADHD (DSM-III)	Body-rocking, repetitive language, preservative thoughts	-	Poor co-ordination	Normal
2 (Abrams 1997)	IQ 78 Poor language, good visuospatial memory	ADHD (DSM-III)	Autistic spectrum disorder	Facial hypoplasia	Poor co-ordination and organisation	Mother IQ 91
3 (Barnicoat 1997)	IQ 54 Illiterate	Poor concentration hyperactive	Resistant to change, obsessive/ compulsive, rituals and stereotypy	-	-	Mother and grandmother express FraX-E, illiterate, (two brothers following)
4 (Barnicoat 1977)	IQ50	Inattentive, impulsive, aggressive, restless	Repetive speech, ritualistic	-	-	-
5 (Barnicoat 1977)	IQ54	Concentration difficulties and restlessness	-	-	-	-
6 (Barnicoat 1997)	IQ 65	Aggressive, restless, hyperactive, fidgety	Gaze aversion, decreased interactive and symbolic play, repetitive speech, pronoun reversal, stereotyped movements, repetitive and routine	-	-	-
7 (Barnicoat 1997)	IQ 88	Hyperactive, aggressive, fidgety, impulsive, inattentive	Obsessive/ compulsive, echolalia, repetitive speech	Simple pinnae, failure to thrive, hearing problems and ear reconstruction	-	Brother has IgG deficiency and poor language development
8 (Russo 1998)	IQ46 Poor language	Severe attention impairment	Echolalia, stereotypy	Mid-face hypoplasia	-	Two male cousins with mild intellectual disability, four related female carriers
9 (Russo 1998)	IQ 45	Severe attention impairment	-	Mid-face hypoplasia, long face, macrocephaly	-	-
10 (Turk 2000)	Language Delay	-	Autism (ICD10)	-	-	-
11 (Turk, Callias & Taylor 2000)	Language delay	-	Pervasive developmental disorder (ICD10)			

Methods

The aim of this small, detailed, exploratory, pilot, clinical series was to investigate the possibility of there being a consistent presentation of certain developmental and psychological traits suggestive of a behavioural phenotype in FraX-E, of diagnostic, prognostic and therapeutic clinical significance.

A literature review was undertaken followed by detailed evaluation of individuals diagnosed genetically as having FraX-E using the following assessment instruments:

- Childhood Behaviour Checklist (Achenbach, 1991)
- Diagnostic Instrument for Social & Communication Disorders (autistic features) (Leekam *et al*, 2002)
- Parental Account of Childhood Symptoms (ADHD features)
- Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1999)
- intelligence tests
- physical examination.

Results

Three boys, aged 15, 19 and 23, and their mothers consented to participating in the study. All three participants had DNA confirmation of FraX-E. For confidentiality, their names have been coded as A, B and C.

Case report A

A was born on 7 March 1991 and is now 15 years old. He attends secondary school which he enjoys, although he struggles in some areas academically. He receives help in some classes from a specialist teacher. Pregnancy was uneventful. A was born at 32 weeks, but was healthy weighing 5lb 6oz. The first time A's mother noticed something unusual was at about six years as his language and motor skills didn't develop appropriately when he started school.

A had some delayed motor milestones, notably sitting up and walking. He was clumsy during development but this has decreased over time. There are problems with executive functioning and A doesn't plan his movements well. Physical examination revealed a fine hand intention tremor. A's gross motor skill development is very good.

A and his mother report that although difficulties have been long-standing and severe in areas, there has been little burden on the family as a whole and A was troubled only a little as his family have accepted his disabilities well and have appropriate expectations.

A's self-care has always been good and he has no problems with toilet training, feeding or dressing. He does however have some slight problems with intricate activities like doing up buttons and tying shoelaces as he has poor fine motor co-ordination. He is capable of helping with chores around the house if he wants to, but is easily distracted.

A's speech development was slow and his language skills are delayed. His understanding of receptive language, assessed using the British Picture Vocabulary Scale (BPVS), was at an age equivalent of eight years, seven months. Expressive language tested using the Expressive One-Word Picture Vocabulary Test (EOWPVT) showed an age equivalent of eight years five months, implying that levels of attainment are below average. The two results are similar suggesting consistent developmental rates in different language domains.

A's mother reports that, as a young child, he didn't have a good understanding of the concept of future events. However this has improved with time. A has a good sense of humour and appears to understand complex sentences and instructions. Expressively A's language is well developed although he has trouble forming complicated sentences and can sometimes reverse pronouns. Non-verbal communication appears fine, although he does have trouble understanding declarative, instrumental and emotional gestures. However he shows few atypical behaviours in this area except that occasionally he may use different voices; particularly directed at his mother, if he is in an 'odd mood'.

Social skills are one of A's strengths. He has friends his own age, interacts with adults well and has never shown any atypical behaviour in this area. A has been bullied in the past but this has ceased. According to his mother A's social and leisure activities are about average for a 15-year-old boy. His interests include football and computer games. A is good at taking turns, reacts well to losing (usually) and has no problems with being a member of a team.

A has never had any problems with the quality and development of imaginative skills and role play activities. He has never shown any atypical behaviour in this area such as problems with the imitation of social or domestic actions.

A's visuomanual and visuospatial skills are quite unbalanced. Although he has trouble using scissors he is able to draw pictures of intricate detail. His ability in drawing is above that of both his intellectual and age peers. However the contents of his drawings are somewhat lacking in imagination.

A has been diagnosed with dyslexia and reportedly has a reading age of 10 years. During development he was reportedly slow to start reading and writing. Currently A shows little interest in reading so he is encouraged to read magazines about things he enjoys, such as football, in order to produce some motivation. Writing is hard for A; he is incredibly slow to produce a written sentence and it is evident on examining his work and observing him write that he has some serious difficulties with spelling.

A's cognitive skills are good and he has understanding in line with his ability in the areas of numeracy, knowledge of money, days, months and years. However he still has trouble telling the time on an analogue clock (but not a digital one) as the quarter hours confuse him. A has a poor memory for routes and events and is often quite forgetful.

A has never had any problems with repetitive stereotyped activities such as body-rocking or hand-flapping, resistance to change or responses to proximal stimuli. His overall pattern of activities is varied and non-repetitive.

A has problems concentrating – especially on work which he finds difficult. He is easily distracted and finds it a problem to return to a task once stopped. His mother perceives this as being a substantial disability, both in school and at home. A is quite impulsive; he admits to regularly acting without thinking and may often interrupt conversations. A has always been an independent child and is capable of taking care of himself on his own for a day. He does have some problems in avoiding danger such as when crossing the road because of impulsiveness.
Evaluation using the Diagnostic Instrument for Social and Communication Disorders (DISCO) confirmed that A showed few features of autistic spectrum disorder. The results of the Strengths and Difficulties Questionnaire (SDQ), self-completion and parent versions, and the Parental Account of Childhood Symptoms (PACS), confirm many longstanding features

of restlessness, inattentiveness, impulsiveness, distractibility and fidgetiness which are consistent with a diagnostic label of DSM-IV attention deficit-hyperactivity disorder, predominantly inattentive type.

Case report B

B was born on 29 October 1986 and is now 19 years old. Following an uneventful pregnancy B was born at 40 weeks by caesarean section. During delivery the umbilical cord detached and needed to be clamped. There was significant haemorrhage so B was kept in the special care baby unit for monitoring. He was small-for-dates and had slight microcephaly but no other physical problems.

Soon after birth it was discovered that B was allergic to dairy and wheat products which lead to diarrhoea, vomiting and abdominal pain. He latched poorly onto his mother's breast which led to further feeding problems. B suffered with early developmental delay, which was first noticed by his parents when his speech and gross motor development did not progress as expected.

It was found in the neonatal period that B had hearing problems. Grommets were inserted bilaterally but he has still needed a hearing aid for a good proportion of his life. He has also been hypersensitive to high-pitched noises since a young age which has affected his ability to communicate. Pre-speech development was delayed. His sight however is reportedly fine.

B's gross motor milestones were delayed. B still has co-ordination problems and has marked clumsiness and still frequently falls off his bike. His fine motor co-ordination is poor and he has problems with hand–eye co-ordination and visuospatial tasks such as jigsaws.

Although B was late to be dry by day (six years) and night (13 years), he shows few atypical behaviours with self-care and eating. Most of his problems in this area can be attributed to a lack of fine or gross motor co-ordination, such as problems with buttons, laces and clothes in general. However B is 'very sensory' and he refused to eat foods with certain textures in his early years. He also disliked the feeling of being washed when younger. He lacks awareness of the suitability of clothing – one example being wearing shorts and a t-shirt during a cold winter.

In terms of helping around the house, B still lacks some skills but this is mostly believed to be because of his lack of co-ordination. However B does cook for his family once a week although it is usually the same dish and he is uncomfortable with unfamiliar tasks.

If asked to take a simple message, B was reportedly often forgetful and distracted and learned to do this rather later than expected. B is currently quite independent, can go out unsupervised and can be left alone without any problems, although he has difficulties in recognising and avoiding dangers.

B's language skills show developmental discrepancies. A much higher ability in receptive language was found, as tested using the British Picture Vocabulary Scale (BPVS) (Dunn *et al*, 1997), which showed a current level of 16.0 years (confidence interval 15 years 5 months–17 years). Expressive language, which was measured using the Expressive One Word Picture Vocabulary Test (EOWPVT) (Brownell, 2000), showed an expressive language level of 13 years 4 months (confidence interval 12 years 11 months–13 years 9 months). This marked difference is confirmed by his mother's account. B seemed to have particular difficulties in

early life where he reportedly developed language slowly with stuttering speech. However comprehension was reportedly better and although there were some concerns about hearing in early years this didn't affect him too badly. B showed echolalia earlier on but this has mostly gradually disappeared although he still reportedly repeats what he has heard on the television and is often heard talking to himself. The quality of B's speech is satisfactory, but there is some evidence of long-windedness and deviation of context on occasion. B's non-verbal communication is good. He appears to have good understanding of facial expression and gestures. He uses the correct non-verbal signals in social reciprocation such as winking cheekily or smiling.

One of B's stronger areas is social interaction. He appears to have no problems interacting with adults or peers and has a good quality of social relationships with others. Although he has been bullied several times in his life, he is learning to cope with this in a mature way.

B is proficient at social play and leisure activities, participating well in groups and taking turns, although when younger he had a bad reaction to losing. B's imagination appears to have been slow to develop and he still doesn't seem to engage in role playing games and activities or pretend play while alone.

B has a diagnosis of dyslexia and claims that a recent evaluation showed that he has a reading level of approximately 10 years (at a chronological age of 19 years). He reportedly has a significantly lower level of writing skill and requires a lot of help with this. A formal IQ estimate hasn't yet been carried out on B, but he has a good language level, can do simple mathematics and has good knowledge of currency and dates, although he was reportedly slow to develop these skills.

B showed a few stereotyped behaviours during development including hand-flapping, self-spinning, odd shrieks and facial grimacing, which his mother described as 'cheesy grinning'. However he no longer exhibits these behaviours. When he was younger B would respond to several proximal stimuli including playing with saliva, self-emesis, scratching surfaces, spinning and adverse reactions to both gentle and firm touch. Now however few of these tendencies remain but he still scratches at surfaces, especially on table ridges, and reacts to touch excessively. During his early years it was noticed that B had an unusual fascination with mouthing objects such as snails and stones. Although he no longer does this, B is still fascinated with stones which he collects from beaches and arranges in lines. He seems to have an interest in parts of objects, especially in small sections of video which he rewinds over and over again. He likes routines and likes to keep things the same in his immediate surroundings.

Although he is not clingy, he used a transitional toy as a child which was hard for him to give up. B's pattern of activities is varied. He has problems with his attention span, has a poor memory and is easily distracted and often fidgety.

B had an excessive fear of the dark as a young child although this has faded now. He does feel emotionally down sometimes and is quite an anxious person. This can be brought on by a novel situation that puzzles him. There are few disruptive problems. He does get angry at his parents occasionally, but is never physically aggressive. He is however demanding of attention, can sometimes interrupt conversations and sometimes show manipulative behaviour towards other people, especially his mother.

Comprehensive evaluation using the DISCO confirms that while B may have had some social and language problems of a qualitative nature in the past, he does not currently qualify for a diagnosis of autistic spectrum disorder. However, results from the SDQ, parent and self-completion versions, confirm B shows features of long-standing inattentiveness, restlessness, fidgetiness, impulsiveness and distractibility consistent with a DSM-IV diagnostic label of attention deficit-hyperactivity disorder, predominantly inattentive type.

Case report C

C, B's older brother, was born on 16 August 1982 and is now 23 years old. He has a full-time job as a bus driver. He enjoys his employment and has had no issues at work. He also has a good home and social life.

C was born at term by a normal delivery and was of a good weight. He had several medical problems early in life. He was admitted into hospital for a week with meningitis. He has hearing difficulties; at two-and-a-half years he had a grommet inserted in to his left ear and had successful reconstructive surgery at age four in St Guys Hospital, London for an underdeveloped external ear. Hearing has been a major problem for C and he still has difficulty hearing on his left hand side. C was easily startled by loud noises, and he found loud sounds uncomfortable to deal with. These factors led to slow speech development, which caused him trouble during schooling. At the age of six, C used less than 30 phrases to communicate. He often refused to use speech and got desired objects by gesturing or pointing. There were some signs of atypical patterns of speech as he showed evidence of echolalia and repetition of words and phrases. However, C's current level of speech is good and he can be understood well by strangers.

C had some communication problems as a child and did not respond to social cues well. He actively avoided eye contact, 'looked through people' and often showed no reaction to the appearance of a new person. He also had some problems relating to people.

His mother first noticed C's problems at four years of age when he fell behind in maths and English at school. C reportedly had problems with concentration and didn't manage to finish tasks. He was impulsive, he interrupted people's conversations and often acted without thinking, which led to him being accident-prone and frequently injuring himself.

C was argumentative, disobedient, jealous and demanding of attention, regularly having temper tantrums. He found it difficult to understand the concept of waiting for future events and was an impatient child. He was not nervous or anxious but did have an excessive fear of dogs that has reportedly faded with increasing age. He was somewhat afraid of going to school because of being bullied, but he learned to manage and cope with this as he got older.

When he was younger, C purportedly did not use toys appropriately, often manipulating objects by twirling or banging them. He showed some evidence of stereotyped behaviour in the forms of hand-flapping and tiptoe walking.

Cognitive assessment using the British Ability Scales (Elliot, Murray & Pearson, 1996) showed that he had difficulties with recall of digits and visual recognition, which rated significantly lower than the other subtest scores. Overall C's IQ was estimated at 88 (Confidence interval 85–93).

Neurological examination showed slight clumsiness in fine motor tasks. He made many mistakes and showed hesitation on the Finger Opposition Test. Gross motor co-ordination was normal. No tremor was identified.

C did not fulfil diagnostic criteria for an autistic spectrum disorder. However, he did show high levels of inattentiveness, fidgetiness and activity consistent with a DSM-IV diagnosis of attention deficit hyperactivity disorder, combined type as a lifelong diagnosis, with a current diagnosis of attention deficit hyperactivity disorder, inattentive type.

Discussion

Cognition

All three participants had IQs within the normal to mild learning disability range, although their abilities were not level across all skill areas. However, no evidence of a consistent pattern of intellectual strengths and weaknesses were found. 80% of FraX-A patients have been reported to have an IQ below 70. Thus, it may be that intellectual functioning in FraX-E is better than in FraX-A, consistent with the hypothesis that FraX-E is associated with borderline to mild learning disability (Harris-Schmidt, 2005).

Impact

All three participants and their mothers reported substantial lifelong difficulties in several areas of psychological functioning. Nonetheless, they all came from supportive, emotionally warm, loving and nurturing families, suggesting that psychosocial deprivation or disadvantage were not major contributors to psychological state for them. Furthermore, all the boys scored well on sociability scales. This appears to have had a positive knock-on effect on friendships and leisure activities. Therefore their psychological difficulties arising from their having FraX-E were not having substantial social impacts. The main setting where adversities were experienced was at school. All three individuals experienced problems with inattention and distractibility making it very difficult for them to prosper in academic environments. All of the boys had received extra help at school but they all commented that if their difficulties had been better understood by teachers and peers then their problems could have been reduced.

ADHD features

Responses to the SDQ, DISCO and the PACS questionnaires were consistent with all three participants qualifying for the diagnostic label of the DSM-IV attention deficit hyperactivity disorder (ADHD) inattentive subtype, and participant C qualifying for ADHD combined type earlier in life. These findings suggest that FraX-E, similar to FraX-A (Turk, 1998), may play a role in the aetiology of mild to moderate ADHD. Our findings agree with previous studies in which most individuals with FraX-E were reported as having ADHD or at least showing multiple features of the clinical syndrome.

Participants A, B and C currently fulfil diagnostic criteria for the inattentive subtype of ADHD and not the combined type. This is in stark contrast to some reports of the phenotype of FraX-A where the combined type is reportedly predominant, suggesting the possibility of attentional deficits being caused by different mechanisms in the two conditions (Harris-Schmidt, 2005).

Behaviour

None of the participants showed significant levels of behavioural problems on the SDQ or the

DISCO, although all three of them reportedly had temper tantrums when younger. This is in agreement with the findings of Mulley *et al* (1995), Knight *et al* (1996), Abrams *et al* (1997), Barnicoat *et al* (1997) and Russo *et al* (1998) all of whom found temper tantrums to be frequent in individuals with FraX-E.

Emotional problems
All participants showed some evidence of worrying and nervousness. Participant A reportedly worried a lot, whereas participants B and C reportedly worried only sometimes according to both the SDQ and the DISCO. Since this has not been reported on in other studies it is difficult to make a firm statement as to the validity of the finding and it needs to be investigated further to confirm any possible characteristic pattern of emotional difficulty.

Autistic features
FraX-A is known to be associated with a set of autistic behaviours (Turk & Graham, 1997). These are:

- gaze aversion
- unusual speech patterns (jocular litanic phraseology)
- lack of imaginary and symbolic play
- dysfunction in peer play
- echolalia and repetitive speech
- verbal perseveration
- insistence on routine
- hand-flapping
- hand-biting.

Although participant C demonstrated most of these traits when he was younger, and indeed qualified for a diagnosis of childhood autism using the DSM-III on the Autistic Behaviour Checklist (Krug, Arick & Almond, 1980), he reportedly doesn't show many of these behaviours any more. Participant B echoes this pattern as, according to the DISCO, he qualified for a diagnosis of childhood autism, but the vast majority of these behaviours have disappeared over time. Participant A however showed very few autistic traits at any time of his life, although he does have the ability to draw at a level that is far above his cognitive level, which is especially striking as he has a slight intention tremor.

The major difference of note between FraX-A and FraX-E is that none of the FraX-E individuals had any social problems and actively sought to be around others including their peers and families. All of them are extremely polite and sociable boys. They have no problems with maintaining eye contact and have many friends. These qualities have helped them immensely as they have a good social network structure, so that they don't suffer much bullying and when they do they have the resilience and social skills to cope with it.

The companionable nature of the individuals studied appears to be the most definite finding which is in stark contrast to the behavioural phenotype of FraX-A. The boys studied had good social confidence and it was evident that they preferred to be with company. All of the participants were kind to younger children and those that were hurt. They all have a good theory of mind and care about the feelings of animals (Harris-Schmidt, 2005).

These results appear to be somewhat different to previous findings in this area. However all of the boys, in their earlier life, experienced some autistic features in the areas of social

development, obsessional and repetitive tendencies. It is possible that FraX-E predisposes to certain autistic traits, but not necessarily to autism itself. Another possibility is that these features may only be present in childhood in cases of FraX-E and that these decrease over time, which is again in contrast to the tendency in FraX-A for autistic features to increase in number and intensity over time.

Conclusion

Since the discovery in 1992 of the FraX-E locus by Sutherland and Baker, most of the information concerning a possible behavioural phenotype comes from just four papers (Abrams *et al*, 1997; Barnicoat *et al*, 1997; Russo *et al*, 1998; Turk, Callias & Taylor, 2000). Although others have written on the subject, little is known about specific behavioural aspects of the syndrome.

The behavioural phenotype of FraX-A is already well researched. This has helped patients and their families as:

- doctors find it easier to make a diagnosis and so help is found for a child at a younger age
- knowledge of behaviour has aided in establishing teaching techniques that can maximise concentration and learning potential (Dew-Hughes, 2004)
- knowledge has enabled families to learn effective ways of dealing with behavioural problems and other developmental challenges.

It is therefore important that if there is a behavioural phenotype for FraX-E it is identified and defined in order to give those with the condition the same psychological and educational benefits as those with FraX-A. It is also important for families so they can know what to expect from the syndrome as well as possible ways of developing appropriate plans for the future.

The results of this study revealed many behavioural similarities among the participants in the areas of attention, distractibility, impulsivity and fidgeting. It has also showed that although some autistic features are evident, the participants did not have autism and that furthermore the autistic tendencies they had diminished with age. This is a good first step on the way to characterisation of a possible behavioural phenotype. However it is somewhat futile to discover a behavioural phenotype if there is no substantial population who can be helped. From our research we have calculated that if the prevalence found in scientific papers is reflective of the true rate of FraX-E then there could be up to 600 people in the UK affected with this condition. Therefore it is important to consider FraX-E when referrals for FraX-A testing are made in order to give those who are affected as much help as they need. Further investigation in the form of longitudinal research is required to ascertain autistic and other psychological symptomatology over lifetime. This will add to the current knowledge of possible intellectual and social progress that people with FraX-E can make and will increase their options for later life. This study has taken the first steps towards this and shows where further research is needed.

What do we already know?

- Fragile X syndrome (FraX-A) is the most common, identifiable, inherited cause of intellectual disability worldwide.
- FraX-A is well documented as being associated with learning disability, marked social

and communication difficulties frequently consistent with an autistic spectrum disorder, speech and language anomalies and attentional deficits.

- There is a rarer condition known as FraX-E which is caused by a similar unusual expansion of DNA just above the X chromosome's tip. This is different from FraX-A and is not just 'a milder form of FraX-A'.
- FraX-E, like FraX-A, can be diagnosed extremely reliably and sensitively with DNA testing technology. However, unless the request is made for the condition to be tested for, it is highly unlikely that it will be done.
- FraX-E, like FraX-A, can be carried by individuals without any apparent effects, the condition only becoming evident when a child is born with developmental difficulties.

What more does this study contribute?

- Physical consequences of having FraX-E are, at best, extremely subtle and unremarkable compared to members of the general population.
- Intellectual functioning can be in the mild learning disability, and even within the low average, range without any clear discrepancy between verbal and performance skills.
- Because of this, delayed development and poor academic, social and language progress can be misattributed to parenting and other environmental deficiencies rather than a genetically determined neurodevelopmental disability.
- Social and communication difficulties occur, but marked attentional deficits, impulsiveness and distractibility are most common, even in the absence of gross motor overactivity.
- Given early identification, understanding, and appropriate multidisciplinary intervention, treatment and support to the individual and family, positive outcomes with a good quality of life and ability to contribute meaningfully to society, are entirely possible.

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