THE FRAGILE X SOCIETY

FRAGILE X SYNDROME:
MALE CARRIERS OF FRAGILE X

INTRODUCTION

This booklet reports the findings of a UK study of men who carry a fragile X premutation. Over fifty fragile X families from all areas of the United Kingdom participated and to date this research represents one of the world's largest studies of adult men who have a fragile X premutation.

The aim of the study was to discover whether there are any consequences for adult men who have a fragile X premutation, in addition to their passing on their fragile X premutation to all their daughters.

The Fragile X Society gratefully acknowledges the authors of this booket, Professor Kim Cornish and Professor Jeremy Turk who, with Dr. Ann Dalton, were the lead researchers on the UK study.

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WHAT IS FRAGILE X SYNDROME?

Fragile X syndrome is the most common identifiable cause of inherited intellectual disability. It can cause a wide range of difficulties with learning, as well as social, language, attentional, emotional and behavioural problems.

The gene that causes fragile X syndrome is found at the end of the X chromosome. When viewed down a microscope this part of the X chromosome appears fragile, hence the condition's name.

In 1991 the gene, which causes fragile X, was identified. This gene, called FMR1, is present in all of us and it must work properly for normal intellectual development to take place. In people affected by fragile X syndrome there is an increase in size of DNA adjacent to the FMR1 gene, which prevents it from working properly. This change in the gene is called a mutation. Men and women affected by fragile X syndrome usually have a large change, called a full mutation, in their FMR1 gene.

Some people have a small change, called a premutation, in their gene. Men and women with premutations in the FMR1 gene are described as "carriers" and up until now have not been believed to be affected by fragile X although they are at risk of passing on their "fragile" X chromosome to their children. When the fragile X gene is passed on from a carrier woman the adjacent DNA may increase in size to a full mutation which means there is a chance her children will be affected by fragile X. When the fragile X gene is passed on from a carrier man the gene does not increase in size which means that his children will not be affected by fragile X, although they too will be carriers. The carrier man's daughters, who will <u>all</u> inherit their father's premutation, will <u>all</u> be carriers with a chance that their children will be affected. The sons of a fragile X male carrier will all receive their father's Y chromosome, and all will be clear of fragile X.

Approximately one in 4,000 males and one in 6,000 females have a fragile X full mutation. Approximately one in 250 females and one in 800 males have a fragile X premutation.

Diagnosis is made in a genetic laboratory by a DNA test on an individual's blood sample. There are two common reasons why such a test is done. Firstly, the individual may have been identified as having developmental or other psychological difficulties for which a cause has yet to be identified. Secondly, a relative may have been identified as having fragile X syndrome, thereby prompting a search for its presence in other family members - including those without any obvious developmental or psychological difficulties who may be unknowing carriers of the syndrome.

Importance of genetic counselling for carriers

Genetic counselling is important for everyone who carries fragile X, including carrier men who are not at risk of having children with learning difficulties themselves. Genetic counsellors can give up to date information about how fragile X is passed on, and about our understanding of any possible effects on carriers.

BACKGROUND TO THE STUDY

Recent reports from families who have fragile X syndrome, and clinicians who work with them, have suggested that having a premutation may in itself have important psychological and developmental impacts on males who are carriers of fragile X.

The profile of developmental and psychological challenges faced by boys and men who have full mutation fragile X syndrome is now well understood. There is good evidence that in addition to causing generalized intellectual disability, there is a characteristic profile of intellectual, social, language, emotional and behavioural functioning. This profile comprises varying abilities across differing aspects of psychological functioning.

There are often relative strengths in language and comprehension, short-term memory for language-related issues, and long-term memory. Conversely there are relative special needs in concentration span, restlessness, fidgetiness, impulsiveness and distractibility, as well as short-term memory for more "abstract" concepts, problems in dealing with sequences of information, problems with number work, and difficulties with "visuo-spatial skills", for example thinking in 3D, giving directions, and finding your way around places. In addition, there is good evidence for specific problems with certain sorts of short term (so-called "working") memory, and organizing one's thoughts.

Shyness and social anxiety are common as are an aversion to eye contact with others, self injury in the form of hand biting, hand flapping in response to anxiety or excitement, and delays in the ability to play imaginatively with toys. Up to 30% of young people with full mutation fragile X syndrome qualify for a diagnosis of autistic spectrum disorder in one or other of its guises. There are suggestions that the proportion of individuals with full mutation fragile X syndrome who qualify for a diagnosis of autistic spectrum disorder increases with age. However, more often, it is the seemingly contradictory situation of a friendly and socially aware (albeit shy and socially anxious) individual with a range of social, language, and obsessional "autistic-like" traits, which characterizes those who have a fragile X full mutation.

These problems can persist into adulthood yet there are a range of medical, psychological, educational and social interventions and supports, which can minimize handicaps as well as maximizing potential and quality of life.

The question remains as to whether individuals who have premutations may be vulnerable to milder versions of the above challenges. To date few studies have explored this important aspect sufficiently systematically and scientifically. Very little is known about the range of abilities in individuals with a fragile X premutation in contrast to the above descriptions of strengths and needs in individuals who have a fragile X full mutation. In the following section we outline our major findings of clinical importance from the national UK Fragile X Male Premutation study.

WHO PARTICIPATED IN THE STUDY?

Three groups of adult males participated with families located throughout the United Kingdom.

- Adult males with a *fragile X premutation* ("carrier") were recruited through UK Regional Genetic Centres and the UK Fragile X Society. These men had DNA expansions (so-called "CGG repeats") in the 55-200 repeat range. None of these men had been recruited via clinical (including psychiatric) services.

  However, in order to control for variability that may arise from other genetic and socio-cultural factors, in addition to more individual differences in basic perceptual and intellectual capacities, selecting appropriate comparison groups was therefore crucial. Here we adopted two.

- The first comparision group was recruited from genetically "normal" male relatives (6 - 39 CGG repeats) in fragile X families who, in general, would share similar socio-economic and cultural backgrounds with the premutation participants.

- A second comparison group of males was also needed because of the possibility that the familial comparison males - through having an affected relative or through showing subtle problems themselves - may under-represent the difficulties faced by the premutation group in any comparison. Accordingly, we recruited our second group of males from members of the general population with no family history of fragile X who were matched on age and intellectual functioning with the premutation males.

The table below outlines the main characteristics of our sample.

	Number in group	Average age	Age range
Premutation	49	47.04	18-69
Family Controls	22	40.82	20-67
Non-family Controls	49	45.73	20-69

FINDINGS OF THE UK FRAGILE X MALE CARRIER STUDY

GENERAL INTELLECTUAL FUNCTIONING

Most fragile X carrier boys and men, who have a fragile X premutation, do not have any intellectual impairment. They usually progress through the mainstream education system with no major academic or other concerns.

Occasionally, academic difficulties may require special attention. In these instances outcome is substantially improved by early identification of problem areas and appropriately targeted interventions and supports.

Over 70% of participants with fragile X premutations in our study had left school with academic qualifications. Many had progressed to further education or other training schemes. The range and types of adult occupation were similar to those of the general population.

Decision-making skills

The ability to plan ahead, organise one's thoughts and behaviours, and to change these with ease as necessary in order to get on in life is an important part of our everyday activities. Decision making ranges from simple actions such as deciding in what order to put your clothes on or when it is safe to cross the road, to more sophisticated procedures such as deciding between financial budgetary options or long-term career and other lifestyle choices. There is evidence that adult men with a fragile X premutation can experience difficulties in these areas of planning, organising thoughts, problem-solving and switching between topics of interest - so-called "executive function" skills. Such difficulties can be present throughout life and may even begin in adolescence.

Short-term memory skills

Memory difficulties in people who have a fragile X premutation usually relate to tasks that require dealing with sequences of information, such as remembering a list of instructions to order. Again, difficulties can emerge early in development.

Spatial awareness skills

Skills that require good spatial awareness (e.g. the ability to find your way about a building or neighbourhood, or being able to think in 3D or give directions to others) can be a relative strength in men who have a fragile X premutation. Performance is especially good on tasks that involve making a whole from its parts (as in jigsaw puzzles) and on tasks that require a "motor-construction" component (as in building a constructional model). These skills appear to be maintained throughout life.

Focusing and switching attention

The ability to stay focused on task and to select relevant and useful information from that available to you can be an area of considerable weakness in men with fragile X premutations. Problems are particularly noticeable on skills that require inhibition (i.e. not being impulsive) and good concentration. Conversely, a number of men with fragile X premutations demonstrated a tendency to be over-rigid in their focus of attention with problems shifting from one topic to another.

The association between CGG repeat length and cognitive abilities

Our findings suggest some link between higher CGG repeat expansion sizes and greater difficulty in abilities that require one to stay 'on task' (short-term memory) and require the ability to inhibit thoughts or behaviours. These findings indicate that higher CGG lengths might be predictive of some cognitive difficulties in adulthood and possibly childhood that are similar to those found in individuals who have the fragile X full mutation. Further research will be needed to substantiate this link.

Aging and cognitive abilities

As mentioned above, difficulties in inhibition and short-term memory have been highlighted in men with the premutation. Our findings suggest that these problems increase disproportionately with age, and are not related to intellectual functioning. From the mid 30's onwards we found a decline in performance that was not present in men who were the same age but without the premutation. This decline appears to become more severe with age and may be an early clinical indication of the premutation status. In contrast, other cognitive skills such as IQ, spatial ability, verbal and visual memory followed the same expected age trajectory as for men without the premutation.

EDUCATIONAL IMPLICATIONS FOR BOYS AND YOUNGER MEN WHO HAVE FRAGILE X PREMUTATIONS

Generally, men with a fragile X premutation appear to do as well as other people academically. Results from our study suggest that most men with a fragile X premutation have managed to navigate the school system without major difficulties. However, there remain the possibilities of subtle yet important functional impairments capable of interfering significantly with quality of life and achievement of potential, yet of an insufficient number or severity in boys and young men with a premutation to trigger referral to clinical or other support services.

Skills dependent on good abilities to process sequences of information, for example learning the days of the week or months of the year, or trying to tie one's shoe laces, may prove problematic. In later childhood, demands on these "sequential information processing skills" increase so that children have to follow more complex instructions that often require the "holding on-line" of information whilst processing other pieces of data (e.g. mental arithmetic). Such situations are helped by breaking down sequences of commands into more manageable chunks of information that can be processed more efficiently.

Tasks involving problem-solving strategies and planning ahead can also prove to be problematic. Being faced with an array of options, without expertise in working through which is the best to pursue, can be a highly distressing and anxiety provoking experience. Lack of "inhibitory control" may result in inappropriate, over-rapid and impulsive "knee-jerk" responding with potentially adverse consequences academically and socially.

SOCIAL DIFFICULTIES

Data analysis from our study suggests a number of subtle but potentially debilitating difficulties experienced by men with fragile X premutations. Their nature suggests that it should be possible to treat these effectively with psychological, educational and social strategies if they are identified early enough.

The ability to use "working memory" as a tool to help in solving problems, concentrating and focussing in on issues, and planning ahead, may be an area of special need. As a consequence self-esteem often appears to suffer. There may also be a link between these issues, common witnessed difficulties with the social use of language, and frequently reported lack of any close friends.

In addition, stress seems to show itself in terms of physical and mental symptoms such as aches and pains, tiredness, lethargy, malaise, anxiety and low mood.

Other tentative findings suggest a number of social, language and even obsessional tendencies similar to those witnessed in the autistic spectrum but of insufficient intensity and impact on day to day functioning to warrant such a diagnostic label. Such tendencies included difficulties in discerning peoples' emotional state ("feelings") from the look on their face - in particular subtle or ambiguous feelings. Similarly participants often found it difficult to show their own feelings to others either because of shyness and social anxiety, and/or because of more basic problems in expressing their feelings and being able to label them.

TREMOR AND GAIT PROBLEMS

A number of recent clinical studies have indicated that in a subgroup of older men (over 55 years) with fragile X premutations there may be an increased risk of developing problems in walking (gait) and of having a tremor. This condition is now known as 'fragile X-associated tremor/ataxia syndrome' (FXTAS) and appears to develop in the late 50s or early 60s. It begins by interfering gradually with daily living activities including handwriting, eating and personal care. There are an increasing number of published studies on FXTAS, but almost all are based on clinic samples of older men whose symptoms were sufficiently severe for them to request medical attention.

Our study is unique because it represents men with the fragile X premutation who come from the general population and represent different ages. The findings from our study were based on a self-reported neurological symptoms questionnaire that included questions on the presence, characteristics, and time-of-onset of tremors, and questions related to the onset of balance problems, recent falls, and walking distance. The questionnaire was completed over the phone or in person.

Our findings showed that of the forty completed questionnaires received, approximately 50% of men over the age of 50 years displayed some symptoms of FXTAS. Only 2 men aged less than 50 reported symptoms. Intellectual impairment in men with FXTAS symptoms was quite subtle, especially when we compared their performance to men with the fragile X premutation who were the same age. Thus areas of concern that might serve as indicators of possible FXTAS are difficulties in inhibition of mental activity and working memory, especially if they begin early in adulthood. For example, problems may show as acting impulsively when responding to a question or an item on a test, or forgetting to stay 'on-line' when performing a task or forgetting complex instructions.

These findings have also been reported in other studies in America and Australia. More detailed studies are now needed to investigate how such difficulties impact on everyday life and functioning rather than just in a scientific testing environment, and how one can recognise the presence of these problems as early as possible in development.

CONCLUSION

In summary, there do seem to be a number of subtle yet important influences on personality, temperament and psychological functioning generally in men who have a fragile X premutation. Furthermore, the findings from our carefully controlled investigation suggest that these may well be attributable to having a fragile X premutation. There is no reason to suspect that these difficulties cannot be helped effectively by already available evidence-based medical, psychological, educational and social interventions.

We found these issues to be real, common and of genuine concern to participants and their families. Participants expressed how useful it felt to them to have greater understanding of their psychological challenges and why they are the way they are. Nonetheless, almost without exception, the developmental and psychological challenges faced were insufficient for individuals to have ever come to the attention of psychological, psychiatric or other relevent clinical services. Even when they had done, it was not the case that useful intervention strategies, or even self-help advice, had been offered.

We conclude that it is important for all concerned to recognize that having a fragile X premutation may, in itself, lead to subtle yet often critical developmental and psychological difficulties which, if identified and helped early enough, need not cause long term intellectual, social, emotional and behavioural disability and handicap.

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THE FRAGILE X SOCIETY

was formed in May 1990 and our aims are to:

- provide support and information to fragile X familes
- raise awareness of fragile X
- encourage research into all aspects of fragile X

HOW DO WE ACHIEVE THESE AIMS?

through our

- National Support and Information Service
- National Helplines and Family "Link" members
- Newsletters, publications, book and DVD
- Conferences, talks and presentations
- Media campaigning and distribution of literature
- Arranging for our family members to take part in research

MEMBERSHIP OF THE SOCIETY

is FREE to fragile X familes and carers and we welcome as associate members those with a professional interest in fragile X.

FURTHER INFORMATION ABOUT FRAGILE X

If you would like more information about any aspect of fragile X contact:

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