Carrier Status Effects

Professor Turk's presentation at the conference last September was about carrier status effects or effects associated with carrying a premutation of fragile X. He talked about it being possible for those with a premutation/intermediate allele to have some developmental and psychological difficulties. A premutation covers those with a CGG repeat number of between about 50 and 200 with individuals with a repeat number of over 200 having a full mutation. The production of the protein FMRP is switched off in those with a full mutation and this is what gives rise to the learning disabilities. The cut-off point in terms of people who are premutation carriers of fragile X and those who are completely unaffected is not an exact science – the key thing is if the CGG repeat number or mutation is or is not stable in that individual. Hence there is a stage known as an intermediate allele. This describes those with a repeat number of between about 40 and 55.

In those with a premutation there have been incidences of the physical features and behavioural and developmental phenotypes, more usually associated with the full mutation, showing through. Females with the premutation are also at risk of premature ovarian insufficiency (POI) and an earlier than usual menopause, though it remains unclear when this is likely to occur. There is also the Fragile X Tremor Ataxia Syndrome (FXTAS), which is a condition confined solely to **some** premutation carriers of fragile X, most typically some males.

Study of Boys with a Premutation 2003 Aziz et al

Professor Jeremy Turk referred back to this study, which is still available as a publication from the society entitled "Clinical Features of Boys with Fragile X Premutations and Intermediate Alleles". There is the consideration that, as a psychiatrist, Professor Turk would inevitably see boys with difficulties, but these boys were selected using records from genetic centres and not because they had been referred to Professor Turk

The study showed that these boys, who were premutation carriers, had higher rates of delayed development, Autistic Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD) and problems with language, most noticeably social language, expressive language and intelligibility of speech. There was also found to be some testicular enlargement.

Study of Men with Fragile X Premutations Mills et al 2002

For this study all known male carriers of fragile X in the UK were approached – they were not individuals who had been referred to Professor Turk or any other health professional as a result of their difficulties. Findings showed that they tended, when compared with typical members of the population and also with members of their own family who did not have a diagnosis of fragile X syndrome, to

- Be slow, polite, precise and keen to co-operate
- Be overfriendly & over-compliant
- Have problems showing their emotions and feelings

- Have problems with understanding social situations and empathising with the feelings of others
- Have problems making & keeping close friendships
- Have poor visuo-spatial skills (the ability to perceive objects, see where objects are in relationship to each other, retrace our steps back to our car after a shopping trip, read a map etc)
- Have difficulties concentrating & sustaining attention
- Have memory problems mainly relating to accessing their memory & forgetfulness
- Have physical & psychological symptoms attributable to stress

Summary of Main Difficulties of Male Carriers following various studies

The main findings concerning male carriers of fragile X were that there may well be genetic influences, related to fragile X, on their personalities and temperaments. These difficulties were in 3 main areas

- Memory problems particularly working memory
- Stress related physical and mental symptoms
- Problems with close relationships

These symptoms were rarely severe enough to bring the person to particular professional attention. However, this information can be helpful in terms of helping individuals better understand themselves and also in helping them and their families understand why they present as they do.

Females with Fragile X Syndrome Turk and Howlin 2003

The situation with females with fragile X is further complicated because they have 2 X chromosomes and, in layman's terms, the non-fragile X can compensate for the fragile one. This means that some females with the full mutation have no learning difficulties. Some will have the range of difficulties more usually associated with males with the full mutation, whilst for others the level of learning difficulty will be milder.
The study above looked into females diagnosed with a full mutation and a premutation. It found that both those with a full mutation and a premutation can have some difficulties with learning, particularly with tasks involving numeracy; with maintaining attention and with thinking things through to enable them to solve a problem. Similarly both could have some problems in the social arena, often being very shy, socially anxious and having particular difficulties with the social use of language. Both could experience low self esteem, attributable, in part, to not having their particular needs met or understood.

FXTAS

This only affects some individuals in the premutation range. It is not a condition associated with the full mutation. Main areas of difficulty include an intention tremor (a limb shaking when it goes to do something rather than when at rest e.g. a hand shaking when the individual goes to pick up a cup of tea, but being still when rested on the arm of the chair) and gait ataxia (an instability when walking). There can also be problems with short term memory and executive

functioning skills i.e. the ability to formulate a solution to a problem and act on it. FXTAS occurs when too much messenger RNA is deposited in the central nervous system. This attracts other chemicals and can lead to cells dying. This excess of messenger RNA can be deposited anywhere in the body. POI is caused when it is deposited on the ovaries