Annotation

X-linked mental retardation

It has long been known that there are more men than women affected by non-specific mental retardation and over the years families with clearly X-linked pedigrees have been reported by, for example, Martin and Bell¹ and Renpenning *et al.*² Davison³ first suggested that X-linked genes should be considered in the aetiology of non-specific mental retardation as a whole, but it was Turner and Turner⁴ who stressed the importance of this. They found that if 2 siblings were mentally retarded both were boys in 58 families and both girls in only 22 families; these figures are similar to those of Davison.³ Further calculation led Turner and Turner to conclude that X-linked genes might be responsible for the condition of 20% of affected males in New South Wales, and from this they extrapolated that the risk of recurrence for a woman who had had a son with non-specific mental retardation was 10%. More recent studies in British Columbia⁵ gave an incidence of at least 1.83 per 1000 males for X-linked non-specific mental retardation, so this may be second only to Down's syndrome in prevalence.

A chromosome marker rediscovered

In 1969 Lubs⁶ described the presence of a marker X-chromosome in affected males belonging to a family whose pedigree indicated X-linked mental retardation. Although the clinical significance of the finding was recognised, no further progress was made until 1977 when Harvey *et al.*⁷ reported an identical marker X chromosome in a proportion of metaphases from males of 4 such families. Sutherland⁸ showed that this marker was in fact a 'fragile site' occurring at band q 27 or q 28 (that is, towards the end of the long arm) of the X-chromosome. He pointed out that the culture conditions were critical if the fragile site on the X-chromosome were to be expressed consistently and it was because enriched media came into general use in the 1970s that Lubs's⁶ original discovery took so long to bear fruit.

Now that further family studies have been done it is clear that not all males with what is apparently X-linked mental retardation have this fragile site on the X-chromosome. Turner *et al.*⁹ found it was

present in 7 of 23 families, but Jacobs *et al.*¹⁰ found it in 6 of 7 families so more data are required before the proportion can be reliably estimated. From the practical aspect it must be stressed that absence of the fragile site does not exclude X linkage and, in addition, one must take into account the technical difficulties associated with demonstrating its presence. When one affected family member exhibits the marker other affected males can be expected to do the same.

Clinical features

There appear to be at least 3 distinct forms of X-linked mental retardation which seem to breed true within families and may or may not be allelic (that is, variants at the same locus).

(1) Boys with the marker X-chromosome do not have dysmorphic features and were originally⁹ described as being of average height, with head circumference tending to be above the mean, large simple helices to their ears, and large lower jaws and blue eyes. However these features are not present in all such families.¹⁰ A recent finding, which seems to be specific to this group, is a macro-orchidism;⁹ the testes are either clearly enlarged, or are in the upper normal range.¹¹ This sign is generally present only after puberty but it is sometimes noticed at birth. Mental retardation ranges from severe to mild and the degree of retardation may vary within a family. Initial studies were all in boys with IQ 30-55 but, in a study in progress in Sweden, Gustavson (personal communication) has found the marker in a proportion of mildly subnormal boys. Specific speech delay is common and the boys often have a characteristic rhythmic intonation labelled as litany speech.⁹ Epilepsy occurs only in the most severely retarded.

(2) Members of families who do not show the marker chromosome have clinical features which can only be distinguished from the above by the absence of macro-orchidism.

(3) Renpenning *et al.*² seem to have described a separate syndrome. Affected individuals tend to have microcephaly, small testes, are more severely retarded, and do not show the marker chromosome.¹²

Studies in carrier females

As with any X-linked condition the implications of such a diagnosis are important for female relatives. In families carrying the fragile site it may be detected in a proportion of cells in female carriers and this proportion is generally considerably smaller than that found in affected males. It may be difficult to demonstrate the marker in carrier women, particularly in those over age 30¹³ but as experience accrues with different culture media the test should become more reliable. Recently Turner *et al.*¹⁴ published the results of a study on mildly retarded girls which suggests that the gene contributes significantly in girls also. She found a fragile site in 5 of 128 girls and 4 of them had retarded male relatives, convincing evidence for their heterozygosity. The most simple explanation would be to relate such retardation to non-random X inactivation, especially in the CNS. However further studies are required and it must be stressed that many obligate carriers are of normal intelligence.

Technical aspects and prenatal diagnosis

Fragile sites are known to occur on a number of autosomes and are generally of no clinical significance. It is therefore important that the X chromosome should be positively identified by banding and, in particular, is distinguished from chromosome 6.¹⁵ The fragile site is present in 5–75% of metaphases in affected males so that many cells must be examined. All fragile sites are expressed more readily if the medium is deficient in folic acid so that special culture medium—such as TC 199, supplemented with only 5% serum—must be used. The pH is also critical.

Initial attempts to demonstrate the fragile sites in cells other than lymphocytes were unfruitful, but recently Jacky and Dill¹⁶ described a method of inducing the marker in fibroblasts, and this raised the possibility of using the marker X for prenatal diagnosis by amniocentesis. Fetal blood sampling would be a more direct but more hazardous alternative but no prenatal diagnosis has as yet been reported using either of these techniques, so we are not sure that the fragile site is expressed in the fetal chromosomes.

Conclusion

The contribution of X-linked genes must clearly be taken into account when families of boys (and perhaps of girls too) with non-specific mental retardation request genetic counselling, and when the clinical features are present in a boy with no family history a recurrence risk of 10% seems about

right. Chromosome analysis to demonstrate the fragile site on the X chromosome would be desirable but at present most laboratories could not cope with the work load if all such boys were examined, particularly as fastidious techniques are required. The discovery seems likely to make an appreciable contribution to our knowledge of the causes of non-specific mental retardation.

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