Annotation

Fragile X mental retardation

It used to be said that diabetes was a geneticist's nightmare. The number one nightmare position may well have been taken over by fragile X mental retardation, which behaves deceptively as if it is caused by a standard X linked gene, but can be passed through completely normal males, and although it can be diagnosed by cytogenetic techniques, it has to be on a good day when all the laboratory conditions are optimal! It has also been mapped on the X chromosome by extensive efforts using the new molecular genetic techniques—although the map is only about as good as saying that Birmingham is somewhere between London and Manchester.

This is not to say that progress has been lacking in the understanding of this elusive condition or that the level of research activity is not intense. The incidence of the condition is so high that it is thought to be the second most common genetic cause of mental retardation after Down's syndrome. Reliable estimates of prevalence read like the sort of over-exaggeration seen in grant applications: 0.3–1/1000 in males and 0.2–0.6/1000 in females, but these numbers have been verified by several studies.^{1–3}

The term fragile X retardation derives from the unusual appearance of the distal portion of the long arm of the X chromosome in a proportion of cells of affected individuals. At metaphase the two chromatids appear to be thinned to a thread with the terminal tips hanging on like a pair of inverted commas (figure). Such thinning of the chromatin is termed a fragile site. Special culture conditions are needed for the cells to express the fragile site—low folate and thymidine or treatment with fluorodeoxyuridine or methotrexate. Even then the fragile X chromosome is not seen in every cell. In affected males 4–50% of cells may show the fragile site, in female gene carriers of the condition the proportion is less, and in about 50% of these females the fragile X chromosome cannot be detected at all.⁴

The condition causes a non-specific form of mental retardation—that is, without major dysmorphic features or severe neurological abnormalities. Before puberty it is probably impossible to make a confident diagnosis clinically, although affected children may be slightly taller than average, with a larger than average head circumference, and

Figure Fragile X syndrome—what the cytogeneticist sees. In this unbanded chromosome preparation from one cell of an affected male the arrow points to the fragile site on the X chromosome. The end of the chromosome is separated from the proximal part by a thinned segment of chromatin—the fragile site itself.

perhaps loose joints. Developmental assessment in boys ranges from 20–70 and speech may be particularly affected. A characteristic speech pattern has been noted—so called 'cluttering' or hurried, repetitive sentences that come out in a rush. The incidence of the condition has been found to be increased in children with autistic features and ranges from 0–15% of males in different studies.⁵ The incidence in autistic females may be lower.⁶ After puberty the testes are usually significantly enlarged and the face is long with a large, squared off mandible and large ears.

Approximately 30% of female gene carriers have mild to moderate developmental delay, with occasional severely affected individuals. There is some correlation between the percentage of cells expressing the fragile X chromosome and the degree of retardation in females.

Treatment with high doses of folic acid has been tried, but no significant improvement of behaviour or performance has been recorded in blind trials.⁷

Prenatal diagnosis can be carried out by cytogenetic techniques. The most reliable method is to look at the chromosomes of fetal lymphocytes obtained by fetal blood sampling. Cells from amnio-

tic fluids or a chorionic villus sample can also be studied; however, techniques for encouraging the expression of the fragile site are at present less reliable in these tissues.⁷ A further complication arises if a female fetus is detected that shows a significant proportion of cells with a fragile X chromosome. In this case there may be a 30% chance of mild to moderate developmental delay—a situation that makes decision about termination difficult for the parents and clinicians.

One of the alternative names for the condition, Martin-Bell syndrome, comes from a report of a very large pedigree studied before the fragile X chromosome was discovered.⁸ Subsequent cytogenetic analysis has shown the fragile X chromosome in affected members. The family reported illustrates some of the unusual genetic features of the condition. A cursory look at the pedigree reveals affected males linked by normal or mildly retarded females—standard 'semi-dominant' X linked inheritance. However, closer inspection shows that there are also completely normal males in the family who appear to have passed on the gene to their normal daughters, who then go on to have affected sons. These 'normal transmitting males' must carry an abnormality at the fragile X locus but it is not certain whether this is the full mutation, which is masked by genes at separate loci or by other genetic interactions, or whether they carry a premutation that predisposes to the generation of the full mutation when it is passed through their normal daughters to their grandsons. In any event, it seems as though there must be novel genetic mechanisms operating at the fragile X locus to explain the unusual inheritance pattern.

Molecular genetic studies have shown polymorphic DNA markers close to the fragile X locus that might potentially be used for prenatal diagnosis or for carrier detection, however, even here there are difficulties. There is evidence that some DNA markers are closely linked in some families (or parts of families) but not in others, making them unreliable for clinical use. When new, closer markers are discovered, many families will have to be studied before the risk of similar 'linkage heterogeneity' can be ruled out and the probes can be used clinically.⁴ Meanwhile, the only reliable means of prenatal diagnosis is by additional examination of fetal chromosomes and there is no completely reliable

method of excluding carrier status in females who don't express the fragile X chromosome.

The general paediatrician must suspect the condition in a child of either sex with non-specific mental retardation, even in the absence of a family history. Requests for cytogenetic analysis must mention the possibility of fragile X syndrome and cases must be selected carefully. Appreciable microcephaly, dysmorphic features, or abnormal neurological features make the diagnosis very unlikely and the cytogenetic laboratory should not normally be asked to carry out fragile X analysis on these cases. Even with careful selection, complete ascertainment of all cases eligible for fragile X analysis in a region would overwhelm most cytogenetic laboratories without special resources. A planned programme, giving initial priority to cases where family members are envisaging further children, may be necessary.

Families of affected children should be referred to genetic centres as the complex inheritance pattern and problems with carrier detection and prenatal diagnosis make genetic follow up far from straightforward.

References

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