Molecular genetics of the mind

The use of DNA markers has shown that manic-depressive illness can be caused by a single gene. These markers will not be useful for screening but may lead to fundamental insight into the disease.

THERE has for some time been good evidence that individuals in some families may be genetically predisposed to a spectrum of mental diseases of which the most distinctive is manic-depressive psychosis. About two years ago, Daniela Gerhard and colleagues published an abstract suggesting that manic-depressive disease among the Old Order Amish of Pennsylvania might be traceable to a single gene on the short arm of chromosome 11 (Gerhard *et al. Am. J. hum. Genet.* **36**, 35; 1984). Evidence in support of this suggestion is reported by Egeland *et al.* on page 785 of this issue. On pages 805 and 806 the assiduous reader will find persuasive evidence from two other research groups for an inherited predisposition to manic-depressive disease that is not linked to the short arm of chromosome 11. None of these groups has actually identified the predisposing gene.

It is not in principle surprising that a defect in a single gene may cause a complex and variable disorder of human behaviour, or that the predisposition is apparently attributable to different genes in different families. It is, however, remarkable that it has been possible to establish the linkage to chromosome 11 in one of them, for reasons connected partly with the nature of the disease and partly with the more general obstacles presented by the human species to the study of genetics.

For much the same reasons, there are strict limits on the practical uses to which the new genetic markers for manic depression could be put. Manic-depressive illness (also known as bipolar affective disorder) is relatively common, affecting an estimated 0.5 to 1.0 per cent of people. Although manic-depressives characteristically undergo alternating cycles of wild excesses and profound depression, the age of onset, frequency and severity of the mood changes vary considerably, and some individuals in affected families manifest only depression. Moreover, while the effect of the gene is dominant — that is, an individual carrying only one copy can be affected — it has incomplete penetrance, which means that some fraction of those carrying it will never develop the disorder.

Genetic analysis of such a disease faces obvious difficulties. First, the diagnosis of the disorder necessarily requires subjective assessment; second, if more than one gene is involved, genetic evidence from different families cannot necessarily be pooled; and third, incomplete penetrance may make it very difficult to establish a clear link between the inheritance of a given gene and the inheritance of the disease. In any case, the unequivocal establishment of such linkages requires large and generally rather inbred families, which are rare in Europe and North America.

These last conditions are however met by the Old Order Amish whose religious convictions moreover forbid alcohol and drugs, thus eliminating one serious obstacle to the accurate ascertainment of psychiatric disease. What Egeland *et al.* have been able to establish, in brief, is that in one large Amish family, two genes known to lie close together on chromosome 11 are frequently inherited together with affective disorder, which in their study was rather stringently defined and independently diagnosed by five independent assessors.

They were able to establish this linkage because the cloned genes they used as markers lie adjacent to highly variable regions of DNA, making it extremely unlikely that a given individual will inherit identical variants of this region from both parents. By tracing the inheritance of different variants of the two marker genes, and of affective disorder, through the affected family, Egeland and colleagues were able to show that a gene predisposing to manic depression lies close to the two marker genes on chromosome 11.

What are the implications of this linkage, especially in the light of the evidence of the other two groups, Hodgkinson *et al.* and Detera-Wadleigh *et al.*, that in three Icelandic families and three North American families respectively the chromosome 11 markers used by Egeland and collaborators are not associated with affective disorder? First, although mistakes in diagnosis could more easily lead to a false negative conclusion than a false positive, all three research groups used the same standard diagnostic criteria and the negative evidence is quite convincing. This means there are at least two different genes predisposing to affective disorder.

In fact there are probably at least three: a large Israeli survey using traditional genetic markers provides strong support for earlier suggestions that some cases may be due to a gene on the X chromosome (M. Baron *et al. Nature*, in the press). Although it seems quite likely that most cases of manic-depressive disorder arise from a genetic predisposition, it is clearly impossible to tell at this stage how many will be linked to chromosome 11. Genetic heterogeneity alone will thus limit the usefulness of the chromosome-11 markers in identifying individuals at risk in the general population. But in any case the use of linked markers for this purpose is generally impossible without unusually extensive family data, as the particular variant of each marker that is linked to the disease will differ from one family to another. Moreover because of the incomplete penetrance of the gene (Egeland *et al.* estimate maximum penetrance at 63 per cent), there is no guarantee that an individual carrying the predisposing gene will ever develop the disorder.

Finally, what kind of single gene might produce the spectrum of complex disorders that seem to arise in affected families? Egeland *et al.* point out the highly suggestive recent finding that their two marker genes on chromosome 11 are closely linked to the gene encoding tyrosine hydroxylase, which is the principal enzyme in the synthesis of the catecholamines. The catecholamines comprise a major class of neurotransmitters, disturbances in whose function are implicated in a wide range of mental disorders.

It is not difficult to imagine ways in which abnormalities in the regulation of either the enzyme or the gene encoding it might lead to imbalances in neural activity that could, by inducing delayed compensatory changes in other systems, result eventually in periodic oscillations expressed as manic-depressive cycles. Nor is it hard to see how such regulatory defects might occur either through mutations in the tyrosine hydroxylase gene itself or in genes encoding (perhaps) tissue specific regulators of the gene or the enzyme.

At this stage, so little is known about either the gene or the development and regulation of neural-signalling systems as to leave the imagination dangerously unfettered. However, Moss *et al.* (*Nucleic Acids Res.* **14**, 9927; 1986) have recently reported variable regions of DNA in the vicinity of the tyrosine hydroxylase gene. Hodgkinson *et al.* used the variation to look for linkage with manic-depression in the Icelandic families and drew a blank. It is a very safe bet that a similar investigation will soon be reported in the Amish; and that the genomic organization and regulation of the tyrosine hydroxylase gene will not be left to the imagination for long.

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