MOLECULAR GENETICS

False start on manic depression

Miranda Robertson

MOST of the presentations at *Nature*'s conference in Boston, held last week, were a startling reflection of the pace of progress in the understanding of the genetic mechanisms of complex processes. The one conspicuous reversal, candidly acknowledged by Ken Kidd (Yale University), was in the genetics of psychiatric disease.

Readers of *The New York Times* may already be aware that the linkage reported in *Nature* two years ago[1] between manic depression and a locus on chromosome 11 is now acknowledged probably to have been spurious. The events that led to this conclusion are described, by a group including many of the authors of the original report, on page 238 of this issue[2], and were discussed at the meeting by Kidd who is co-author on both papers. At the end of his presentation, David Baltimore (Whitehead Institute) voiced the question that must have been left in many people's minds: "Setting myself up as an average reader of *Nature*", he asked, "what am I to believe?". What follows is an attempt to enable readers to answer the question for themselves.

A picturesque feature of the original study was the choice of the Amish community of Pennsylvania for analysis. The Amish are no more prone to psychiatric disease than other groups, but they have three advantages as subjects for the investigation of complex genetic traits. First, they have large families whose members do not disperse. Second, the restrictive rules they live by reduce confounding environmental variables such as drugs and drink. Third (and crucially), the Amish are relatively inbred, which increases the probability that an abnormal phenotype running in a family will be traceable to the same gene in all affected members.

The claim of the 1987 paper was that manic depression in a large Amish pedigree was linked to two marker genes, the *Harvey ras* oncogene and the insulin gene, known to be in the same region of the short arm of chromosome 11. Neither of these genes was itself implicated in the disease, nor was any other gene actually identified as the cause of the disorder: the claim rested upon the consistent inheritance of specific and recognizable variants of the two marker genes with the propensity to develop manic depression, and on a calculation of the probability that this co-inheritance could occur purely by chance. The traditional measure of this probability is the LOD score (LOD standing for the log-of-the-odds ratio), and the traditionally acceptable LOD value is 3, corresponding to a probability of 0.05 against the chance occurrence of the observed pattern of co-inheritance. The LOD score for the linkage of a chromosome 11 locus to manic depression was comfortably more than 4.

For any disorder, the assessment of linkage is complicated by the possibility of recombination events that may separate the marker from the gene and that become more likely the greater the distance between the two (this distance being of course unknown). For psychiatric disorders the calculation is further complicated by the likelihood of incomplete penetrance, which means that some individuals with the predisposing gene will fail to develop the disorder. Both factors must be taken into account in calculating linkages to psychiatric diseases.

Thus the conclusion that a gene on chromosome 11 could predispose to manic depression was calculated on a delicate balance of uncertainties. Two developments have now upset that balance. First, two people in the original Amish pedigree have become manic depressive in the absence of the putative markers of predisposition; second, an additional branch of the original pedigree shows negative evidence of linkage. This could mean that there are two genes instead of one predisposing to manic depression in the pedigree; but the simplest explanation is that the apparent linkage to a chromosome 11 locus was in fact just chance.

According to Kidd, chance may also account for a second genetic linkage, more recently reported by Hugh Gurling's group[3] which has published evidence implicating a locus on chromosome 5 in predisposition to schizophrenia. The conclusion in that case was based on two markers which, as Lander[4] remarked at the time, were uninformative for many members of the five families analysed, where the same marker variants were carried by both the affected and the unaffected parent.

In an attempt to find a marker that will distinguish the parental chromosomes in these cases, Gurling has since tested a third chromosome 5 marker which, as it turns out, shows less evidence of linkage than either of the other two. This could mean that the third marker is more distant from the putative schizophrenia locus than the others, allowing more recombination between the marker and the gene; but in fact Kidd maps the third marker in between the other two, ruling out that explanation. This leaves us with no persuasive evidence linking any psychiatric disease to a single locus and brings us back to Baltimore's question.

It is neither necessary nor justified to conclude from these reversals that there simply is no single gene capable of predisposing some individuals to psychiatric disease. Studies of identical twins have already provided very strong evidence, especially in the case of schizophrenia, for an important genetic component. There is on the other hand every reason to expect the predisposing genes to be hard to identify, for reasons that can be illustrated by the remarkably successful recent attempts at analysing the complex multifactorial genetics of predisposition to coronary heart disease.

The work on cholesterol metabolism in particular was discussed by Gerd Utermann (University of Innsbruck), who has been investigating the effects of plasma lipoprotein polymorphisms on coronary heart disease in people already known to be at risk through a mutation in one of their low-density lipoprotein (LDL) receptor genes. People who are homozygous for such mutations never escape heart attack. Heterozygotes on the other hand may have heart attacks by the age of 40, or they may be quite unaffected. What Utermann has been able to show is that polymorphisms in plasma proteins that affect cholesterol levels can account for much of the variation in effect of the LDL receptor mutation on heterozygotes.

In this case several interacting genes affecting the uptake and disposition of lipids can be seen to contribute to the risk of heart disease in such a way that no one mutant gene or polymorphic variant would reliably be inherited with the disease. We may expect the genetics of psychiatric disease to be at least as complex as those of cholesterol metabolism. But in the absence of a good biochemical clue to what genes may be involved, they will be much harder to trace. The hope has been that the high incidence of specific psychiatric disorders in inbred families reflects the existence of a single, strong, predisposing allele. If in fact it is necessary to seek linkage to more than one gene in such families, there are techniques that would make this possible[5]; but a high-resolution linkage map of polymorphic markers for the human genome would be needed for a reasonable chance of success, and in the view of many this should be a priority for the human genome project.

In the meantime, readers of *Nature* are entitled to be sceptical about reports of psychiatric disease linkages at LOD scores of less than 6. But they should have no reason to doubt the existence of genetic predisposition to psychiatric disease, nor the ability of molecular geneticists eventually to identify the genes responsible. □

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1. Egeland, J. A. *et al. Nature* **325**, 783–787 (1987).
2. Kelsoe, J. R. *et al. Nature* **342**, 238–242 (1989).
3. Sherrington, R. *et al. Nature* **336**, 164–170 (1988).
4. Lander, E. S. *Nature* **336**, 105–106 (1988).
5. Lander, E. S. & Botstein, D. *Cold Spring Harb. Symp. quant. Biol.* **LI**, 49–62 (1986).