Psychiatric genetics: **A genetic basis for health?**

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Attempts to map the genes for psychotic illnesses have been fraught with problems. Studying why some family members do not become ill might prove to be a more successful strategy.

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Current Biology 1999, 9:R326–R328
http://biomednet.com/elecref/09609822009R0326

 ISSN 0960-9822

One of the few well accepted pieces of evidence we have about the biology of psychiatric illnesses is that there is a genetic component to (almost) all of them, but very little is yet known about the number of genes, where they are on the genome or what they are doing to produce illness. Ten years ago, a breakthrough was announced with a report in *Nature* [1] that a gene, or genes, on chromosome 11 was associated with the development of manic depressive psychosis. Manic depressive psychosis, also known as bipolar affective disorder, is a condition characterized by debilitating fluctuations in mood. In mania, patients experience elation or euphoria, which may spill into psychotic grandeur. There is a reduced need for sleep, boundless optimism and, too often, hopelessly flawed judgement in the sexual and financial spheres. In depressive episodes, patients experience profound sadness and a depressed affect of almost painful intensity. Action and thinking are slowed and there is significant impairment of concentration and memory. In depression, there may be persistent thoughts of suicide and as many as 15% of patients who require hospitalisation eventually do kill themselves.

It was with heavy hearts that those of us committed to a scientific psychiatry read, a couple of years later, that the claim of a breakthrough in manic depressive psychosis was wrong [2]. It was overturned by the incidence of only a few new cases in apparently unaffected members of the original families. This, and other false positive findings in the field, led to a greater caution among the research community in their approach to the declaration of positive results. There was also a wider pessimism. A curious consensus was formed by scientists who thought all psychiatry unscientific and an anti-psychiatry lobby who still regard all efforts to be scientific about psychiatry as inhumane.

The burden of disability that mood disorder imposes guarantees, however, the importance of the clinical problem. Cautious enthusiasm for mapping genes for manic depressive psychosis has been sustained, and a number of groups have reported linkages to mood disorders (see Table 1). To put the table in perspective, the standard measure of the likelihood that a specific chromosomal position is linked to a disorder given a set of segregation data, the 'log of the odds ratio' or LOD score, is reckoned to be significant if it exceeds 3.6. To find significance is not to establish confidence that a linkage is real, however. Such studies are simply too small to achieve that, so convincing evidence for linkage to any one chromosome is still lacking. The authors of the largest survey — 319 markers on 540 subjects — admitted that no chromosomal area met criteria for significant or even suggestive linkage [3].

Three years ago Risch and Botstein [4], commenting on a series of linkage reports for manic depressive psychosis in *Nature Genetics*, asked if the field had advanced and concluded that "compared to other fields to which genetics has been applied, one would have to argue not". They suggested that the genetics of manic depressive psychosis was much more complex than anyone had anticipated. Genetics can be complex for a number of reasons. In disorders caused by mutations in a single gene, the situation can be bad enough; consider the difficulties in understanding the inheritance of fragile X syndrome [5,6], or the complex series of different phenotypes that arise from mutations of fibroblast growth factor receptors [7]. When we deal with disorders that are likely to be due to mutations in more than one gene, the ways in which complexity can arise are legion: there may be different genes in different populations, different combinations of genes producing different phenotypes, variable interactions between genes and environment and so on.

How complex is the genetics of manic depressive psychosis likely to be? The answer appears to be that it is very complex indeed. Consider first how the genetic analyses are done. The basic methodology of genetic linkage and association studies is to ask what affected individuals have in common, genetically speaking. Thus, if all affected individuals share some segment of chromosome 5 and this is rare or non-existent in unaffected individuals, we have evidence for a gene predisposing to the disorder somewhere in the shared segment of chromosome 5.

Perhaps the sole uncontested result from linkage studies of manic depressive psychosis is that the disorder is not, at least commonly, the result of a mutation in a single gene. Assume that mutations in any ten of a hundred different genes can give rise to the disorder. In outbred populations, if we picked 200 affected individuals, the chance that they all have at least one common mutated gene is

very low. Our genetic test is therefore not going to have much power to detect an effect, unless we study many thousands of individuals. One way to simplify things is to study inbred populations, or those where all affected individuals are genetically related (inhabitants of small islands tend to attract the interest of geneticists for this reason). In a population where all affected individuals are descended from a single progenitor, then all will have the same set of susceptibility genes.

This is one reason why the Old Order Amish community in Pennsylvania — who inhabit a virtual island bounded by their culture — were selected for one of the largest genome screens undertaken for any disorder. They have large extended families with well-documented genealogies dating back to the 30 progenitors who arrived from Europe in the 18th century. All affected pedigrees trace back to a very small number of individuals with the disorder (perhaps even a single affected founder). Despite such remarkably propitious circumstances for a gene hunt, the results have been disappointing: no single chromosome region stands out as a convincing place to look for the genes that predispose to this psychiatric illness. This is why Risch and Botstein [4] concluded that the genetics of manic depressive psychosis are complex.

There is now a new twist to the Amish story. Hitherto, no one has thought to look at the absence of illness as a genetically determined trait in high risk families. Why not see what the *well* relatives have in common, genetically speaking? You might think, from the arguments given above, that such a strategy would only make things more complicated. If finding evidence of genetic susceptibility for manic depressive psychosis is complex, then surely finding evidence of genetic predisposition to health will be equally complex? Yet the results indicate otherwise [8].

Ginns *et al.* [8] have recently reported evidence of linkage to good mental health at a locus on chromosome 4p, with a P value in favour of linkage of 5.22×10^{-4} (LOD score of 4.05), and a locus on chromosome 4q, with a P value of 2.57×10^{-4} (LOD score of 3.29). In comparison, the most encouraging result of their search for loci linked to manic depressive psychosis, in the same population, was one at chromosome 6p with a LOD score of 2.5. Of course, the size of the LOD score is not everything: an earlier report [9] of apparent linkage to Xq28 reported a LOD of 7.5 that was never replicated. But the new result is certainly more encouraging than most. Furthermore, the use of simulated data to obtain empirical P values and an analysis relatively free of assumptions about the mode of inheritance gives the result a certain authority.

But why should 'wellness' be easier to study than disease? In families with manic depressive psychosis members, wellness means either the absence of manic depressive psychosis predisposing genes, or the presence of protective alleles. Assuming that the latter is the case, then one reason why wellness loci have been found might be because they are rarer than disease loci. In other words, for the family members studied, health is just a cover-up of the effects of disease genes. This is not to say that disease is more common than health within these families: there may be fewer wellness loci, but each has a larger effect, and it is this larger effect that has made them easier to find, relative to disease loci. This would also explain why, when the investigators increased the age-at-risk cut-off for defining the wellness phenotype from 25 to 45, the number of mentally healthy members decreased, while the P values in favour of linkage increased.

Table 1

Candidate genetic linkages to mood disorders.

Location	LOD	Reference	Year
Xq28	7.5	[9]	1987
11p15	4.9	[1]	1987
21q22	3.4	[12]	1994
	2.76	[13]	1999
12q23	2.1	[14]	1994
18p/18q	2.38	[15]	1994
	1.7–3.1	[16]	1995
16p13	2.7	[17]	1995
4p16	4.8	[18]	1996

There are certainly plenty of examples of protective alleles in other conditions: a classic finding in mouse genetics is that a mutation may lose or radically alter its phenotype when transferred onto a different genetic background [10] and similar moderating effects have been reported for a few complex human disorders ([11] for example). The discovery of protective alleles might make it easier to find the disease genes. By allowing for the effect of the protective alleles the genetics of manic depressive psychosis can be simplified, a little at least. Theoretically, the linkage analyses will have more power to find effects of disease loci.

Studying wellness rather than ill health has other advantages too. Although linkage of genes for particular receptors or enzymes to the illness may offer clues to develop treatments, it might be more fruitful to investigate what neurobiological processes keep individuals well in high-risk families. Attempts to mimic or stimulate the molecular actions of the products of such genes might lead

to protective treatments that can transform high risk individuals into low risk individuals. A similar strategy is already being pursued in relation to apolipoprotein E and susceptibility to Alzheimer's dementia. At the very least, wellness alleles might prove to be predictive of differential responsiveness to the variety of treatments we already have. Too often, claims for the molecular genetic approach to human disease are couched in revolutionary terms: there is much reference to new dawns and fresh horizons. To improve the modest benefits of existing treatment would actually represent a major public health gain. Let us look forward to it being achieved, along with more breakthroughs, of course.

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