Is There a Gene for Depression?

Two investigators say they have found a link to HLA markers, but their unorthodox approach elicits skepticism from other researchers

A team of investigators headed by Lowell R. Weitkamp of the University of Rochester Medical School and Harvey C. Stancer of the University of Toronto last month presented evidence that a gene confers susceptibility to depression, the most common form of mental illness.* Their report, combined with a supportive editorial in the same issue of the journal, initiated a flurry of press reports about "major progress in understanding the genetics of depressive disorders." It also detonated a controversy that seems likely to reverberate for quite some time. The quarrel revolves around the unorthodox manner in which they have demonstrated a genetic linkage.

The hypothetical gene for depression cannot be observed directly. It must thus be traced through its linkage with some gene for which there is such a marker. The most commonly used markers are the HLA genes, which control the human leukocyte antigens that appear on the surface of blood cells and other tissues. These antigens are immunologically defined, genetically determined characteristics of tissues which, among other things, determine the compatibility of organs for transplantation. Certain HLA markers have been shown to be associated with, for example, Graves' disease and idiopathic Addison's disease; the association is most often noted where viral infection and autoimmune processes are involved.

The most common way to demonstrate a genetic component of a disease is to demonstrate that an affected parent and an affected child, or two or more affected siblings, share the same pattern of HLA markers. Such a finding suggests that the gene in question is located physically near the HLA genes on chromosome 6 and is transmitted with them. Several investigators, particularly Elliot S. Gershon and his colleagues at the National Institute of Mental Health, have tried to demonstrate such a linkage for depressive disorders, but their data appear to rule out such a linkage. Weitkamp and Stancer claim only that the HLA-linked genes contribute to the risk, not that they are necessary or sufficient. If this is so, linkage may be detected by haplotype sharing among siblings, even when it cannot be observed by conventional pedigree analysis. The one previous success was achieved in 1978 when Enrico Smeraldi and his colleagues at the University of Milan in Italy reported a slightly increased sharing of HLA haplotypes (specific gene markers) among pairs of siblings who both had depressive disorders.

Weitkamp and Stancer began their study on the assumption that two or more genes are responsible for susceptibility to depression—a reasonable assumption based on the fact that depression does not follow the classic Mendelian pattern for either dominant or recessive inheritance. They assume that the genes could be one or more alleles (separate segments of DNA at the same site) or completely separate genes on different chromosomes.

This assumption, Weitkamp and Stancer say, leads to two predictions. The first is that pairs of affected siblings in families with only two affected siblings should share HLA haplotypes more often than expected by chance and more often than haplotypes are shared among three or more affected siblings. The second is that affected pairs of siblings should have the greatest possibility of sharing haplotypes if neither parent is affected, a lower probability if only one is affected, and the lowest probability if both are affected.

In essence, they are saying that if a large number of siblings are affected, each parent is probably homozygous for the depression susceptibility genes (that is, has inherited genes from each of his or her parents), and thus can pass on to the child one of two possible genes at each locus, minimizing the possibility that sharing will be observed. If there are only a small number of affected children, however, then one parent (presumably the unaffected parent) is likely to be heterozygous for the depression susceptibility genes (has inherited them from only one parent); those genes must be transmitted to the child for depression to occur, and there should be sharing. The division between two affected siblings and three or more reflects the fact that most families studied are small.

Weitkamp, using available data on families, first applied this approach to insulin-dependent (juvenile-onset) diabetes. He found [*Am. J. Hum. Genet.* **33**, 776 (1981)] that 60 percent of diabetic siblings shared HLA haplotypes when there were only two affected siblings, but less than 40 percent shared them when there were three or more affected siblings.

He and Stancer also began a prospective study of families located in the Toronto area and combined their data with data from the literature. They found that 44 percent (15 of 34) of clinically depressed siblings shared haplotypes when there were only two affected siblings, while only 16 percent (5 of 31) shared haplotypes when there were three or more affected siblings. Similarly, in families with one affected or one unaffected parent and two affected siblings, the affected children shared HLA haplotypes from the unaffected parent more often than predicted by chance, while sharing of the haplotypes from the unaffected parent in larger families occurred only about as often as predicted by chance. The *American Journal of Human Genetics* paper contains similar, but more limited, data showing the same effect in multiple sclerosis.

In the accompanying editorial in the *New England Journal of Medicine*, Steven Matthysse of Harvard Medical School and Kenneth K. Kidd of the Yale University School of Medicine praise Weitkamp and Stancer's findings without qualification. They also argue that the strength of the technique is demonstrated by the "remarkable" fact that linkage was observed even though the depressed patients were not divided into unipolar (simple depression) and bipolar (manic-depression) subtypes. Weitkamp is a bit more cautious, and concedes that the results obtained for depression might "seem a bit unlikely" had he not observed similar results in diabetes. Other investigators are unconvinced.

Gershon, for example, argues that Weitkamp and Stancer have not approached the experiment in the right way. "They don't have an explicit genet-

*L. R. Weitkamp, H. C. Stancer, E. Persad, C. Flood, S. Guttormsen, *N. Engl. J. Med.* **305**, 1301 (1981).

0036-8075/81/1218-1330$01.00/0

ic model in their paper," he says, and their decision to separate the two groups of siblings in that manner seems "arbitrary and does not correspond to any precise genetic hypothesis." Of course, he adds, "even if it were after the fact and arbitrary, there could still be something to it. But if we look at our own data in the same way, [their theory] doesn't seem to hold up. We have other data that we weren't going to publish because our initial results were so resoundingly negative, but we're putting it together now because of this article and we'll publish it. We find just a completely random distribution of data."

C. Robert Cloninger of the Washington University School of Medicine concedes that Weitkamp and Stancer have an "important hypothesis, but the experimental support for it is questionable." He is particularly concerned by the fact that their overall data for haplotype sharing agrees with a distribution that would be predicted by chance, and that the increased sharing occurs only in one small subgroup. He and his colleagues at Washington University have conducted computer simulations of several types of potential inheritance, and they find that the type of associations observed by Weitkamp and Stancer can occur only under very special conditions, depending upon the frequency of occurrence of the susceptibility genes and their degree of expression. The observed linkage thus could have occurred solely by chance. "In their defense," he adds, they also found an increased sharing among well siblings. He thinks that their report is "not a compelling argument," but concludes that "the body of data is not at a stage where we can either accept it or reject it."

Interestingly, Weitkamp's earlier paper on diabetes has not provoked nearly as much reaction, perhaps because there is already strong evidence of genetic linkage in that disease. Françoise Clerget, a French geneticist visiting at the National Institutes of Health, considers that Weitkamp's work confirms results already known, but argues that his method does not give any more information than other approaches and does not seem to provide any advantage. Other investigators seem to have reached much the same conclusion. Weitkamp concedes that his results are not critical in proving a linkage in diabetes, but argues that the results in diabetes are critical in proving the case for HLA linkage of the depression susceptibility gene. But as far as the hypothetical depression susceptibility gene is concerned, everyone agrees on only one point: the study needs to be replicated before any more firm conclusions can be drawn.

—THOMAS H. MAUGH II

Palmdale Bulge Doubts Now Taken Seriously

Researchers were skeptical of the claim that the bulge never existed, but new data have many wondering about its true size

The Palmdale Bulge, that ominous swelling of 83,000 square kilometers of southern California real estate, had been all too real to geophysicists. Immediately upon the bulge's discovery in 1975 (it apparently sprang into existence around 1960), they had to consider whether its appearance meant that a great earthquake was imminent. Addressing an earthquake prediction meeting in the spring of 1980, Wayne Thatcher of the U.S. Geological Survey (USGS) in Menlo Park spoke for many when he said that "honest investigators may disagree on details [of the bulge], but so many separate pieces of data support its existence that something like this must have happened." But now, Thatcher and many other researchers are much less certain of the bulge. The existence of a bulge as high and as extensive as the one claimed "is up in the air," he says. "A number of sources of error once thought to be unimportant need serious consideration."

Thatcher and others are most concerned about the effects of optical distortion on the measurement of the height of the bulge (apparently 30 to 45 centimeters). David Jackson of the University of California at Los Angeles (now temporarily at the Goddard Space Flight Center, Greenbelt, Maryland) had mentioned 2 years ago that error due to the atmospheric refraction of light could have helped make the bulge seem much larger than it was, if it ever existed at all. But the controversy had not included serious consideration of the atmospheric refraction problem until some researchers went back to the field to see just how accurate the century-old measuring technique really is.

Precise elevation determination, or geodetic leveling, is deceptively simple. Two 3-meter-long rods are erected about 60 meters apart. A surveyor stands midway between them, peering at first one and then the other rod through a small, horizontally mounted telescope. But this simple system can be used to measure some astonishingly small differences. In the case of the bulge, Robert Castle and his colleagues at the USGS in Menlo Park reported that an area of southern California 250 kilometers by 100 kilometers had risen a mere 25 to 45 *centimeters* above the surrounding land. Even the steepest part of the uplift spanned a distance of 70 kilometers (7 million centimeters) and included a 1000-meter (100,000-centimeter) climb up the Transverse Range. In order to measure such subtle changes over large expanses, the setup of two rods and a leveling instrument is moved one 60-meter step at a time from areas unlikely to move up or down quickly to the less stable, more mountainous areas.

It is this repetition and the consequent accumulation of error that concerns researchers. During the first setup, the surveyor looks back along a horizontal line toward the precisely ruled scale on the first rod, which is standing on a permanent elevation marker, and ahead at the scale of the second rod. The difference between the heights sighted on the two rods is the difference in elevation between their two locations. The first rod is then moved ahead of the second, and the surveyor makes the same kind of sightings from between the two rods. This gives the second increment of elevation difference along the leveling line. A surveying team will repeat this process as many as 1000 times to determine the difference in elevation over a leveling route 50 kilometers long.

Engineers have used these leveling lines to create a network of precisely determined elevation markers that are reference points in the construction of railroads, pipelines, and highways. Castle and his group looked instead at differences in elevation that showed up between relevelings at the same site. Be-

0036-8075/81/1218-1331$01.00/0