Behavior

Manic depression–DNA links

A trio of new studies describes five DNA neighborhoods where genes that contribute to manic depression may hang out, but scientists express considerable caution about whether this evidence will prove reliable.

Much of their tentativeness comes from experience with prior investigations in which excitement accompanying the announcement of apparent inheritance sites faded when further studies failed to support initial findings.

"None of the new articles by itself constitutes clear genetic linkage to manic depression," asserts Elliot S. Gershon, chief of the Clinical Neurogenetics Branch at the National Institute of Mental Health (NIMH) in Bethesda, Md. "We don't know which of these findings will wash out and which will hold up in further, independent replications."

Researchers agree on one assumption—a number of genes probably work together in as yet undetermined ways to create a predisposition to manic depression. It seems unlikely that a single gene plays a pivotal role in the alternating bouts of depression and agitated elation that typify this condition.

The first of the new reports, all of which appear in the April NATURE GENETICS, finds evidence that a gene along a segment of chromosome 4 influences manic depression. Douglas H.R. Blackwood of Edinburgh University in Scotland and his colleagues collected blood samples from 120 members of a multigenerational family, including 11 individuals diagnosed with manic depression and 16 with recurrent major depression.

Enzymes that snip DNA segments at precise spots enabled Blackwood's group to identify a particular chemical rearrangement on part of chromosome 4 in all cases of manic depression and in 14 instances of major depression.

A statistical link between the chromosome 4 variation and manic depression emerged in a further analysis of members of 11 families, 40 of whom suffer from this mental disorder.

In a second study, Edward I. Ginns of NIMH and his coworkers report that genes which may influence manic depression lie along segments of chromosomes 6, 13, and 15. The researchers used 551 genetic markers to scan all 23 pairs of chromosomes in members of five Amish families living in southeastern Pennsylvania. Of the 207 participants, 39 suffered from manic depression.

These Amish volunteers belong to an isolated population in whom rigorous psychiatric evaluations were carried out over a 19-year period, lending credence to the findings, Ginns' team contends. However, additional genes may contribute to manic depression in other populations, they add.

The third study, directed by Nelson B. Freimer of the University of California, San Francisco, encompassed members of two families from a genetically isolated population in Costa Rica. A region tagged by several markers on chromosome 18 appeared in 23 out of 26 cases of manic depression.

Previous evidence indicated that defects on chromosome 18 occur in a substantial minority of persons with manic depression (SN: 7/2/94, p. 13).

Each of the three studies reports "modest" statistical ties between manic depression and proposed inheritance sites, contend Neil Risch and David Botstein, both of Stanford University School of Medicine, in an accompanying comment.

The most promising DNA regions may emerge from a unified analysis of all genetic data on manic depression gathered so far by different research teams, Risch and Botstein state.

As yet, no statistical methods exist for conducting this type of analysis, notes Gershon. "Statisticians are attempting to develop such methods, but their job would be easier if researchers were more forthcoming in sharing their data," he holds.

Biomedicine

Protein cure for Parkinson's?

A naturally occurring protein benefits monkeys suffering from an ailment resembling Parkinson's disease, researchers report in the March 21 NATURE. The new finding raises the hope that the same protein may help people suffering from this neurodegenerative disorder, characterized by a shuffling walk, rigidity, and tremors.

Known as glial-cell-line-derived neurotrophic factor (GDNF), the protein protects and restores nerve cells damaged by Parkinson's disease in mice (SN: 1/28/95, p. 52).

Neurobiologist Don M. Gash of the University of Kentucky College of Medicine in Lexington and his colleagues focused on rhesus monkeys infused with MPTP, a street drug that produces the symptoms of Parkinson's disease. Once every 4 weeks, the researchers injected GDNF directly into the regions of the brain affected by this disorder.

After GDNF therapy, the monkeys showed measurably improved posture and balance. "We saw less rigidity," says Gash. Monthly shots of GDNF sustained these improvements. The study didn't address whether the therapy has any long-term benefits.

Scientists believe that Parkinson's disease results from injury to or death of neurons that make the chemical messenger dopamine. The monkeys given GDNF showed increased dopamine concentrations in the substantia nigra, a region of the brain affected by the disease. In contrast, dopamine concentrations did not rise in another key brain area, the striatum. Gash and his colleagues speculate that GDNF may provide some of its benefits through better regulation of dopamine in that region. They are currently working to test that theory, he said.

Before long, GDNF will get a chance to demonstrate its prowess in people with Parkinson's. Amgen, the Thousand Oaks, Calif., firm that makes GDNF, plans to launch a small safety and efficacy trial of the compound later this year.

Epilepsy gene identified

A joint U.S.-Finnish team reports nabbing a gene that, when mutated, causes an inherited form of epilepsy.

Richard M. Myers and Len A. Pennacchio of the Stanford University School of Medicine and their colleagues in Finland knew from previous work that the gene for progressive myoclonus epilepsy resides on chromosome 21. They used landmarks along the DNA to zero in on a specific region of the chromosome. Their research, which appears in the March 22 SCIENCE, identifies the culprit as a gene carrying the blueprint for a protein called cystatin B.

Progressive myoclonus epilepsy occurs when a person inherits two defective copies of this gene. A serious disorder that's relatively common in Finland but rare in the United States, the disease results in seizures and mental deterioration that eventually leads to senility.

Researchers don't know why a defect in the gene triggers the disorder. However, the team's results suggest that the mutant form of the gene leads to reduced production of cystatin B. Cystatin B is a member of a class of proteins called protease inhibitors.

This study marks the first time that a protease inhibitor has been linked to epilepsy, Pennacchio says. Moreover, scientists don't understand why a protease inhibitor would play a role in epilepsy. The finding will most likely spark investigations into whether other forms of the disease are linked to defects in genes coding for these proteins.

The discovery may also lead to a method of identifying carriers of the defect, Pennacchio says. People with a family history of the disorder may want genetic testing before having children, he adds.