GNN Genome News Network

THE CENTER FOR THE ADVANCEMENT OF GENO

GNN Home | About GNN | Subscribe | Contact Us | Archives |

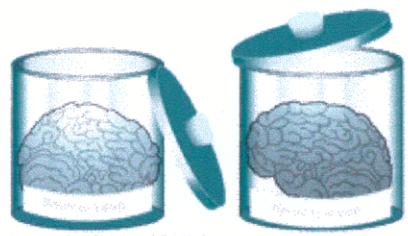
Riches of the Brain Bank

Seeking clues to mental illness, gene hunters discover proteins

By
Edward R. Winstead

June 2, 2000

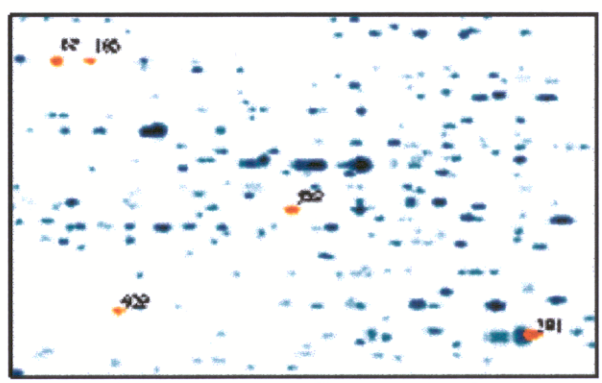
featured article



Mary S. Gibbs [GNN]

Safely stored in 52 freezers in a federal building outside Washington, DC, are the Brain Bank's holdings: brain tissue from hundreds of individuals with schizophrenia, bipolar disorder, and severe depression. Scientists in a dozen countries have analyzed tissue from this collection, but the genes involved in these diseases remain at large. Now, a leading gene hunter says that proteins—and what they reveal about the diseased brain—may be the bank's greatest asset.

In the last five years, the Brain Bank has provided some 70 laboratories worldwide with postmortem brain tissue at no cost to researchers. The roughly 350 specimens currently in the bank were collected by medical examiners and always with the permission of the family. The Brain Bank is part of the Stanley Foundation, which will spend $21 million this year for research on schizophrenia and bipolar disorder, also known as manic depression.



Detail from 2-D electrophoresis of human brains. Orange spots indicate disease-related variation in protein levels.
Courtesy Dr. Nancy Johnston-Wilson

One of Brain Bank's best customers is Robert H. Yolken, who runs the Stanley Neurovirology Laboratory at Johns Hopkins School of Medicine. Yolken's team is trying to identify disease-related changes in the brains of people with schizophrenia and bipolar disorder. The approach used by this and other groups—to compare the activity of certain genes in normal and affected brains—has yielded many promising leads but no specific genes.

Advances in protein technology and the frustrations of the gene search recently persuaded Yolken to investigate proteins as disease markers. Lacking expertise in the latest tools, his laboratory teamed up with researchers at Large Scale Biology, a Maryland corporation that specializes in isolating and identifying proteins—what is now called proteomics.

The collaborators compared the levels of hundreds of proteins in the postmortem tissue of 89 Brain Bank specimens. The analysis revealed that eight proteins in the brains of affected individuals had significantly higher or lower levels than those in the control group. The sample included 24 schizophrenics, 23 individuals with bipolar disorder, 19 with major depression, and 23 who were unaffected by these diseases.

More interesting than the specific findings, says Yolken, is the fact that protein differences in postmortem tissue were detected. Although some colleagues had predicted success, Yolken was surprised by the quality of the results.

"We've done both genomics and proteomics with postmortem tissue in these diseases," says Yolken, "and the more useful information has come from proteomics."

Finally, the right approach for schizophrenia?

In fact, the two approaches are complementary, because each offers a glimpse of brain cells at a different point in time. With genomics, a gene's activity in the cell is estimated using 'messenger RNA,' the chemical that signals the cell to produce a protein when a gene is expressed. But Yolken points out that the half-life of this chemical is relatively short. "Protein lasts longer in the cell than messenger RNA, so proteomics allows us to go farther back in time," he says.

A related advantage of proteomics is the potential for detecting changes that occur after the messenger-RNA step. "The concept," explains Yolken, "is that a cell makes protein and then something happens to the protein related to disease. In theory, proteomics will be able to pick up these changes." These changes are likely to be critical in the anatomy of brain disease and could be a diagnostic tool if they show up in spinal fluid.

This year marks the 10th anniversary of Stanley Foundation Research Programs

The main disadvantage of proteomics is that getting results takes time. Although the basic techniques are not new, protein analysis is laborious and requires separating proteins and determining their molecular weight and electric charge. Researchers in this study used a method called 2-D gel electrophoresis that employs gels and electric fields to isolate and sort proteins by weight and charge. Their results appear in the latest issue of *Molecular Psychiatry*.

Despite drawbacks, proteomics may be the right approach for schizophrenia, says E. Fuller Torrey, executive director of the Stanley Foundation Research

Programs. The field is known for a long string of failures to replicate findings. "About half the human chromosomes have been linked to schizophrenia," says Torrey, who collaborated on the study. "But the pattern has been that three months after a gene is proposed a contradictory study appears."

Investigating the virus as trigger in mental illness

The study's most interesting finding involved a protein called GFAP (glial fibrillary acidic protein), which is thought to play a role in the brain's ability to adjust to certain insults. The researchers detected abnormal GFAP in the diseased brains, a discovery consistent with Yolken's hypothesis that viruses can trigger mental illness. The Stanley Neurovirology Laboratory at Johns Hopkins is the world's only laboratory focused on infectious agents as the cause of schizophrenia and bipolar disorder.

The reason that proteomics may be more useful in discovering disease-related markers than genomics is that any set of brains will have greater variation in its messenger RNA than proteins, according to Yolken. The key to finding markers is spotting deviations from the norm, and abnormalities are more likely to stand out when the normal range is relatively small, as with proteins.

'Grandiose' bank pays dividends

All research on Brain Bank specimens is performed with the researcher blind to the diagnosis. More than 20 variables are known about each brain, including the donor's diagnosis, medical history, and how the individual died, but brains are sent to researchers coded. Once a study is complete, the researchers and the Stanley Foundation exchange information: The researchers get the key to the code and the Foundation gets the results, which are entered into a database.

The practice of using coded brains has fostered a kind of cross-fertilization, with schizophrenia researchers generating information that has helped researchers in other fields and vice versa. "The Brain Bank is a grandiose undertaking, but it has been very successful," says Torrey.

For more information visit the Stanley Foundation Research Programs at
www.stanleyresearch.org