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New approach to study depression may lead to new marker for risk

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Scientists at the Texas Biomedical Research Institute and Yale University have identified a new target area in the human genome that appears to harbor genes with a major role in the onset of depression.

Using the power of Texas Biomed's AT&T Genomics Computing Center (GCC), the researchers found the region by devising a new method for analyzing thousands of potential risk factors for this complex disease, a process that led them to a new biomarker that may be helpful in identifying people at risk for major depression.

"We were searching for things in psychiatric disease that are the equivalent of what cholesterol is to heart disease," said John Blangero, Ph.D., director of the GCC and a principal investigator in the study. "We wanted to find things that can be measured in everybody and that can tell you something about risk for major depression."

The study was directed by Blangero and David Glahn, Ph.D., of Yale University. It was published online in October in the journal *Biological Psychiatry* and supported by the National Institutes of Health.

Major depressive disorder is one of the most common and most costly mental illnesses. Studies have estimated that up to 17 percent of Americans will suffer depression at some point in their lives. The disorder has proven to be a tough challenge for geneticists. Despite strong evidence that people can inherit a susceptibility to major depression, years of study have failed to locate any of the key genes that

underlie the illness. The scientists used blood samples from 1,122 people enrolled in the Genetics of Brain Structure and Function Study, a large family study that involves people from 40 extended Mexican American families in the San Antonio area.

Blangero and his colleagues looked at more than 11,000 endophenotypes, or heritable factors, and searched for the ones that were linked with the risk of major depression. They found that disease risk correlated most strongly with expression levels of a gene called RNF123, which helps regulate neuron growth.

Once they found this risk factor, further analysis directed scientists to an area on chromosome 4 containing genes that appear to regulate RNF123.

Because the RNF123 expression levels can be measured relatively easily in the blood, this finding could lead to a way of identifying people at risk for major depressive disorder, Blangero said.

"We might be able to know in advance that a person will be less able to respond to the normal challenges that come about in life," he said. "Then doctors may be able to intervene earlier after a traumatic life event to remove some of the debilitation of depression."

The study also shows the potential for using this method of analyzing a multitude of heritable traits as a way to zero in on disease-causing gene variants.

The research capitalized on the newest 'deep sequencing' technology that enables Texas Biomed scientists to search through more genetic variables. The GCC has 8,000 linked computer processors that are capable of analyzing millions of genetic variables drawn from thousands of research subjects.