Gene variants may increase risk of anxiety disorders

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Massachusetts General Hospital (MGH) researchers – in collaboration with scientists at the University of California at San Diego and Yale University – have discovered perhaps the strongest evidence yet linking variation in a particular gene with anxiety-related traits. In the March issue of *Archives of General Psychiatry*, the team describes finding that particular versions of a gene that affects the activity of important neurotransmitter receptors were more common in both children and adults assessed as being inhibited or introverted and also were associated with increased activity of brain regions involved in emotional processing.

“We found that variations in this gene were associated with shy, inhibited behavior in children, introverted personality in adults and the reactivity of brain regions involved in processing fear and anxiety,” says Jordan Smoller, MD, ScD, of the MGH Department of Psychiatry, the report’s lead author. “Each of these traits appears to be a risk factor for social anxiety disorder, the most common type of anxiety disorder in the U.S.”

It has long been recognized that the tendency to anxiety disorders can run in families and is believed to be influenced by the interaction of several genes. Because of the different forms of these disorders and their complex patterns of inheritance, identifying specific susceptibility genes has been difficult. Studies in mice have associated an area of chromosome 1 with anxious temperament, particularly the gene that codes for a protein called RGS2, which mediates the activity of neurotransmitter receptors that are also the targets of many

antidepressant and antipsychotic drugs. Mice in whom RGS2 is knocked out exhibit increased fearful behavior.

To more comprehensively investigate the role of RGS2 in humans, the researchers conducted several experiments. They analyzed blood samples from children from 119 families who had participated in an earlier study assessing their reactions to unfamiliar situations at the ages of 21 months, 4 and 6 years. The participants had been evaluated on their levels of behavioral inhibition, a form of temperament linked to increased risk of anxiety disorders.. Testing several sites in the RGS2 gene identified nine variations that appeared to be associated with inhibition.

The second experiment involved more than 700 college students who had completed questionnaires designed to measure several personality traits. Analyzing blood samples from this group, the research team genotyped the four gene markers that had demonstrated the strongest effects in the first group. They found that the versions associated with inhibited behavior in the children were also more common in the college students who scored high on measures of introversion, a personality trait that also involves social inhibition.

Another group of 55 college students had functional MRI brain imaging done after they had completed a standard interview screening for anxiety and mood disorders. While in the MR scanner, the participants viewed a series of faces expressing various emotions, a test that previously was shown to influence activity in the amygdala, a brain structure involved in emotion processing. Participants with the inhibition/introversion-associated alleles also had increased activity of the amygdala and the insula, another anxiety-related brain region.

“Now we need to investigate whether these RGS2 variants actually are associated with particular disorders and how they act on a cellular level,”

says Smoller, an associate professor of Psychiatry at Harvard Medical School. “We hope that ultimately this work will lead to new drug targets and treatment options for anxiety disorders.”

Source: Massachusetts General Hospital