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The yin and yang of genes for mood disorders

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Individual genes do not cause depression, but they are thought to increase the probability of an individual having a depression in the face of other accumulating risk factors, such as other genes and environmental stressors.

One gene that has been shown to increase the risk for depression in the context of multiple stressful life events is the gene for the serotonin transporter protein. This gene is responsible for making the protein that is targeted by all current drug treatments for depression. In a number of studies it has been shown that people who inherit one form of this gene, called SLC6A4, are at up to four times the risk of depression if they experience unusual stresses in their lives.

Basic science experiments and imaging studies in normal people suggest that the way this form of the gene affects risk for depression is by impacting on the development of a system in the brain that mediates how negative environmental stresses and threats feel. The effects of this serotonin gene on this brain system are thought to occur early in development, where the shaping of brain systems related to how the environment is experienced emotionally is critically determined.

Basic science experiments have shown that another gene, called BDNF, regulates the expression of a protein that is important for the ability of the serotonin gene to cause these developmental effects. The BNDF gene plays a critical role in allowing the serotonin gene to have its affect on brain development.

Interestingly, the BDNF gene also has been found to be a risk factor for mood disorders and is thought to be important in mediating the effects of antidepressant drugs. Thus, given the basic molecular link between SLC56A4 and BDNF, and the potential that risk for depression might be better understood in the context of these two genes together rather than any one of them alone, investigators now have looked at how inheriting different combinations of forms of these two gene would impact on the development of this emotion regulation system in the brain.

They found that in normal subjects the deleterious impact of the serotonin gene on the development of this brain system was critically dependent on which form of the BDNF gene was also inherited. If an individual inherited one form of the BDNF gene, they were particularly susceptible to the deleterious form of the serotonin gene but if they inherited the other form of the BDNF gene, they were completely protected against it.

This study is the first to show the complex interactions that occur between mood disorder related genes and their impact on mood disorder related brain circuitry. The study makes it clear that individual genes have to be viewed in a context, both a genetic and an environmental context.

But the results also illustrate that no one gene is an island unto itself, and the impact that any gene will have on complex condition like mental illnesses will depend on how that gene interacts with other genes sharing biological overlap. This study also makes it clear why individuals genes do not show stronger effects on predicting complex illnesss like depression, because risk is based on the combinatorial effects of interacting risk factors.

Source: Molecular Psychiatry