# Maryland scientists research gene linked to depression

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Although there are medications to treat depression, many scientists aren't sure why they're effective and why they don't work for everyone.

Researchers at the University of Maryland School of Medicine believe they may have found a key to the puzzle of major depression that could lead to therapies for those who don't respond to medications already on the market.

A study by the researchers has identified the central role a gene known as Slc6a15 plays in either protecting from stress or contributing to depression, depending on its level of activity in a part of the brain associated with motivation, pleasure and reward seeking.

Published in the *Journal of Neuroscience* in July, the study is the first to illuminate in detail how the gene "works in a kind of neuron that plays a key role in depression," the according to the medical school.

Specifically, the researchers found that mice with depression had reduced levels of the gene's activity, while those with high levels of the gene's activity handled chronic stress better.

Though senior researcher Mary Kay Lobo's primary studies were done with mice, she also examined the brains of people who had committed suicide and found reduced levels of the gene's activity, confirming a likely link.

She hopes now that drugs could be developed that would encourage the gene's activity.

"I thought it was fascinating we had this system in place that allows us to go after things or be motivated or have pleasure and I was interested in how it becomes dysfunctional in certain diseases like depression," Lobo said. "I hope that we can identify molecules that could potentially be therapeutically treated or targeted to treat depression."

Lobo and her colleagues have been examining the gene for years. In

2006, they discovered that it was more common among specific neurons in the brain that they later learned were related to depression. Five years later, other researchers learned that the gene played a role in depression and Lobo and her research colleagues decided to investigate what that role is in those specific neurons.

About 15 million adults, or 6.7 percent of all U.S. adults, experience major depression in a given year, according to the Anxiety and Depression Association of America. It is the leading cause of disability for Americans ages 15 to 44. It is more prevalent in women and can develop at any age, but the median age of onset is 32.5.

David Dietz, an associate professor in the Department of Pharmacology and Toxicology at the State University of New York at Buffalo, said little was known previously about the biological basis of depression in the brain. Many drugs used to treat depression were discovered "serendipitously," he said, and it wasn't clear why they worked.

"We're starting to really get an idea of what does the depressed brain look like," Dietz said. "When you put the whole puzzle together, you see where the problem is. For too long we've been throwing things at individual pieces. It's so complex and we have so little information that it was almost bound to be that way. For the first time this is one of those bigger pieces you can slide into the jigsaw puzzle."

Lobo said it's not clear yet how Slc6a15 works in the brain, but she believes it may be transporting three types of amino acids into a subset of neurons called D2 neurons in a part of the brain called the nucleus accumbens. The nucleus accumbens and D2 neurons are known to play a role in pleasure, activating when one eats a delicious meal, has sex or drinks alcohol.

The amino acids would then be synthesized into neurotransmitters.

Depression previously has been linked to imbalances of the neurotransmitters serotonin, norepinephrine and dopamine.

So even though people may have proper levels of amino acids in their bodies, the neurons in their brains that need them may not be getting enough if the transporter is not working as it should.

"This gene is critical for putting very specific amino acids in the right place so that neurotransmitters can be synthesized," said A.J. Robison, an assistant professor in the Department of Physiology at Michigan State University. "It's the location, location, location idea. It's not the amino acids, it's where they're at and in which cells."

Robison said Lobo's next step would be discovering more about how the transporter gene works.

"The fact that this transporter seems to be important is what the paper shows and how it does it is not shown, and that's a challenge for her," he said. "Figuring out the how of it is the next step and Dr. Lobo is particularly positioned to do it."

Lobo's team was able to use gene therapy, a form of therapy in the early stages of being studied in humans, in the mice to boost the gene's activity. The mice were exposed to larger, more aggressive mice, which usually causes depressive symptoms. But the gene therapy helped protect the mice against the stress, the team found. When the team reduced the gene's activity in the mice, just one day of exposure to the aggressive mice was enough to cause symptoms of depression.

Gene therapy is starting to be used in the treatment of some types of cancers, but Lobo said science had not yet advanced to the point where it can be used for treating neurological issues in human patients. A more likely treatment would be a drug that targets the gene's activity directly,

she said.

"I think this is a major step toward our understanding of the precise maladaptive changes that occur in response to stress," said Vanna Zachariou, an associate professor in the Department of Neuroscience at the Icahn School of Medicine at Mount Sinai. "It can be a more efficient way to target depression because it's not simply targeting monoamine receptors or dopamine but targeting molecular adaptations that occur. It doesn't act necessarily as the drugs we have available, so it might create an alternative avenue to treat depression."

Lobo said she wouldn't refer to Slc6a15 as a "depression gene," saying the disease was complex and could have many factors.

"I wouldn't say there's one depression gene" she said. "A number of things play a role, and also there's no depression neuron, there's multiple depression neurons."

There also may be different types of depression with different symptoms, she said. With the disease, some sufferers sleep a lot, while others sleep a lot less, for example.

"With all these complex diseases, it's hard to link it to something," she said. "Like Huntington's disease, we know there's a specific gene that causes Huntington's disease. For depression we don't have that.