

New research points to better way to treat depression

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Professor Kirill Martemyanov, PhD, co-chair of the Department of Neuroscience, led the new study on the Florida campus of The Scripps Research Institute. Credit: The Scripps Research Institute

Scientists on the Florida campus of The Scripps Research Institute (TSRI) have discovered a new target for treating major depressive disorder, a disease that affects more than 16 million American adults. Their research shows that individuals with high levels of an enigmatic receptor called GPR158 may be more susceptible to depression following chronic stress.

"The next step in this process is to come up with a drug that can target this receptor," says Kirill Martemyanov, PhD, co-chair of the TSRI Department of Neuroscience and senior author of the new study, published recently in the journal *eLife*.

The researchers say there is an urgent need for new drug targets in [major depressive disorder](#). Current pharmacological treatments for [depression](#) can take a month to start working—and they don't work in all patients.

"We need to know what is happening in the brain so that we can develop more efficient therapies," says Cesare Orlandi, PhD, senior research associate at TSRI and co-first author of the study.

The researchers zeroed in on GPR158 as a player in depression after discovering that the protein is elevated in people with major depressive disorder. To better understand GPR158's role, the scientists studied male and [female mice](#) with and without GPR158 receptors.

Behavioral tests revealed that both male and female mice with elevated

GPR158 show signs of depression following [chronic stress](#). On the flip side, suppression of GPR158 protects mice from developing depressive-like behaviors and make them resilient to [stress](#).

Next, the researchers examined why GPR158 has these effects on depression. The team demonstrated that GPR158 affects key signaling pathways involved in mood regulation in the region of the brain called prefrontal cortex, though the researchers emphasized that the exact mechanisms remain to be established.

Martemyanov explains that GPR158 is a so-called "orphan receptor" (which gets its name because its binding partner/partners are unknown) with a poorly understood biology and mechanism of action. GPR158 appears to work downstream from other important brain systems, such as the GABA, a major player in the brain's inhibitory control and adrenergic system involved in stress effects.

"This is really new biology and we still need to learn a lot," says Martemyanov.

The study also offers a potential clue to why some people are more susceptible to mental illness. Because mice without GPR158 don't alter their behavior after chronic stress, the researchers concluded these mice were naturally more resilient against depression. Their genetics, or gene expression, offer a layer of protection.

Laurie Sutton, PhD, a research associate at TSRI and co-first author of the study, says this finding matches what doctors have noticed in people who have experienced chronic stress. "There's always a small population that is resilient—they don't show the depressive phenotype," says Sutton.

As the search goes on for additional targets for depression, Martemyanov says scientists are increasingly using new tools in genome

analysis to identify orphan receptors like GPR158. "Those are the untapped biology of our genomes, with significant potential for development of innovative therapeutics," he says.

More information: Laurie P Sutton et al, Orphan receptor GPR158 controls stress-induced depression, *eLife* (2018). [DOI: 10.7554/eLife.33273](https://doi.org/10.7554/eLife.33273)

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