Fear factor: A new genetic candidate for treating PTSD

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Researchers at The Saban Research Institute of Children's Hospital Los Angeles have identified a new genetic candidate for testing therapies that might affect fear learning in people with PTSD or other conditions. Results of the study have been published in the *Journal of Neuroscience.*

Individuals with trauma- and stress-related disorders can manifest

symptoms of these conditions in a variety of ways. Genetic risk factors for these and other psychiatric disorders have been established but do not explain the diversity of symptoms seen in the clinic - why are some individuals affected more severely than others and why do some respond better than others to the same treatment?

"People often experience stress and anxiety symptoms, yet they don't usually manifest to the degree that results in a clinical diagnosis," says Allison T. Knoll, PhD, post-doctoral fellow at The Saban Research Institute of Children's Hospital Los Angeles. "We felt that if we could understand differences in the severity of symptoms in a typical population, it might provide clues about clinical heterogeneity in patients."

The strategy was simple. Instead of focusing on a single gene identified for a given condition, the team at CHLA tried a different approach to discover genes that may impact symptom severity. Using a population-based mouse model, they studied normal variation in how well the mice detected threats and fears. They used mice that are well-characterized for learning behavior, and also exhibit a wide range of "high" and "low" anxiety, modeling the range found in humans. The investigators tested to see how well the mice learned to detect threats, a form of fear learning that all humans and animals do. When this learning is exaggerated in children or adults, symptoms of PTSD and anxiety are expressed.

"By understanding the biological origins of individual behavioral differences - in this case a measure of anxiety - we can move beyond a single disorder diagnosis and treat the dimensions that produce a behavior spanning a multitude of diagnoses," said Knoll.

Using genetic tools, the researchers found a number of candidate genes that might influence learning of fear, and ultimately narrowed down to a single gene, Hcn1. The researchers were able to further demonstrate the

impact of the Hcn1 gene on fear learning by interfering with the function of this gene before the learning challenge. They found that the mice did not learn fear. Even when the researchers disrupted gene function after the mice learned the fear, the mice were unable to express it.

"We're suggesting that instead of focusing only on the genes that are thought to cause a disorder - for example, PTSD or anxiety disorder - it is important to discover those genes that can have a profound effect on how severely an individual is impacted by their disorder," said Pat Levitt, PhD, Principal Investigator of the study, and the Simms/Mann Chair in Developmental Neurogenetics at CHLA. Levitt is also provost professor of Pediatrics, Neuroscience, Psychiatry and Pharmacy at the Keck School of Medicine of USC.

More information: A. T. Knoll et al, Quantitative Trait Loci and a Novel Genetic Candidate for Fear Learning, *Journal of Neuroscience* (2016). DOI: 10.1523/JNEUROSCI.0177-16.2016

Provided by Children's Hospital Los Angeles

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