Gene networks for innate immunity linked to PTSD risk

March 10 2015

Researchers at the Veterans Affairs San Diego Healthcare System and University of California, San Diego School of Medicine, with colleagues in New York and the United Kingdom, have identified genetic markers, derived from blood samples that are linked to post-traumatic stress disorder (PTSD). The markers are associated with gene networks that regulate innate immune function and interferon signaling.

The findings, published in the March 10 issue of the journal *Molecular Psychiatry*, offer novel insights into the pathophysiology of PTSD. In clinical terms, researchers say they could lead to new ways to not just improve diagnosis and treatment of persons with the mental health condition, but predict who might be more susceptible.

Previous genomic studies of PTSD have focused upon identifying differences in gene expression between persons with PTSD relative to a control group. The new study takes a broader "systems-level approach," using whole transcriptome RNA sequencing, said first author Michael S. Breen, PhD, at the University of Southampton in England.

"By comparing U.S. Marines who develop PTSD symptoms to those who do not, we can measure differences in genes, but also take into consideration the dynamic relationships between and among them, their connectivity," Breen said. "Because PTSD is thought to be such a complex disorder, measuring these dynamic relationships is crucial to better understanding the PTSD pathology."

The researchers analyzed blood samples from 188 U.S. Marines, taken before and after deployment to conflict zones. They identified modules of co-regulated genes involved in innate immune response - the body's first line of defense against pathogens - and interferon signaling, that were also associated with PTSD. Interferons are proteins released by host cells in response to the presence of pathogens and in this study are also shown to partake in the pathology PTSD.

The results were replicated with a second, completely independent group of 96 U.S. Marines.

"What's interesting is that molecular signatures of innate immunity and interferon signaling were identified both after developing PTSD as well as before developing PTSD," said Dewleen G. Baker, MD, MRS-II principal investigator, research director at the VA Center of Excellence for Stress and Mental Health, and professor in the Department of Psychiatry at UC San Diego.

The work, a sub-study of MRS-II, was co-led by Caroline M. Nievergelt, PhD, associate chief of the Neuroscience Unit at the VA Center of Excellence for Stress and Mental Health and assistant adjunct professor in the Department of Psychiatry at UC San Diego and the late Daniel T. O'Connor MD, departments of Medicine and Pharmacology at UC San Diego.

"The question to ask is what's stimulating an interferon response prior to PTSD development," said Baker. "The answer could be any number of factors, ranging from a simple explanation of increased anticipatory stress prior to deployment or more complex scenarios where individuals may have a higher viral load. It's a question for future studies."

Experts say what makes PTSD different - and more challenging to study - than other psychiatric disorders is the presence or trigger of a traumatic

event, such as serving in a combat zone.

"The odds of obtaining a sample both before and after a traumatic event are incredibly small," said co-senior author Christopher H. Woelk, PhD, reader in genomics and bioinformatics at University of Southampton and assistant adjunct professor at UC San Diego School of Medicine.

"Under this experimental design, not only can we identify differences between U.S. Marines with PTSD and without, but we can go back in time, so to speak, to see if any of the Marines who eventually developed PTSD contain prognostic signatures that might be indicative of eventual PTSD emergence. In this vein, we are able to start labeling findings as being putatively 'causal' in nature."

Woelk said the findings are intriguing because they follow upon recent studies that have demonstrated how changes in peripheral blood might lay the seeds for subsequent pathological changes in the brain.

"Since our causal (pre-deployment) and consequential (post-deployment) discoveries are based upon peripheral blood samples, these results suggest that identifying individuals at risk for PTSD development may be achievable through high-throughput profiling of molecular data."

The researchers say their results should encourage further investigation along two distinct avenues. First, development of a blood panel of predictive biomarkers to identify persons at greater risk of developing PTSD. Second, use of molecular information from blood samples to design targeted therapies to treat - or help prevent - PTSD.

Provided by University of California - San Diego