BOB WOODRUFF FOUNDATION

STAND SMART FOR HEROES

SPOTLIGHT PARTNER: Cohen Veterans Bioscience

New Treatment Opportunities from Genetic Markers for Post-Traumatic Stress Disorder Susceptibility and Risk

ISSUE/CHALLENGE

More than eight million people in the United States suffer from post-traumatic stress disorder (PTSD), which can cause symptoms as varied as irritability, physical pain, anxiety, depression, and suicide. PTSD is 13.5 times more prevalent amongst veterans (RAND 2015).

Individuals vary widely in their responses to traumatic and life-threatening events, such as combat, sexual assault, and natural disasters (Kilpatrick, et al. 2013; Kessler, et al. 1995). Many factors, including the intensity of the event and the strength of their social support network, affect a person's risk of developing PTSD. But initial research indicates that genetics is critical in determining whether a person develops PTSD: inheritance accounts for nearly 70 percent of the risk of the disease (Stein, et al. 2002). This is not surprising; most psychiatric diseases are highly heritable. The estimated heritability for bipolar disorder, schizophrenia, and autism are all 80 percent or higher – much higher than for diseases like breast cancer (12 percent) and hypertension (30 percent) (Burmeister, 2008). A 2017 study broke new ground by confirming that PTSD has a genetic component, and that it shares characteristics with other psychiatric disorders, including schizophrenia (Duncan, 2017). However, genetic studies require extremely large samples, and even 20,000 patients was not enough for that study to identify specific PTSD genetic risk markers.

Current PTSD treatments include behavioral therapy and selective serotonin reuptake inhibitors, a class of drugs typically used as antidepressants. Unfortunately, individuals respond differently to these interventions, and no tools exist to identify predict how patients will respond to each treatment (Steenkamp et al, 2015; Friedman and Bernardy, 2015).

KEY FINDINGS

In May 2017, Cohen Veterans Bioscience and the Broad Institute's Stanley Center for Psychiatric Research, along with researchers from the PGC-PTSD Work Group, announced initial findings from the largest study to date of markers for PTSD.

- The study identified the first three loci, or chromosomal points, involved in PTSD risk. This is a pivotal milestone as it provides the first significant evidence that researchers can expect to identify dozens, if not hundreds, of new markers with additional sample size.
- One of the PTSD loci is also implicated in the genetics of another psychiatric disorder, bipolar disorder, suggesting that these conditions may share common causal mechanisms (etiology).
- This analysis was one of the most ethnically/racially diverse genetic studies to date, and indicates that genetic susceptibility may differ by population (Caucasian, Asian, African).

IMPLICATIONS

Finding genetic markers of risk is a pivotal first step to understanding how an experience like trauma interacts with an individual's biological pathways to rewire the brain and cause symptoms of disease. Understanding the pathways involved will accelerate new approaches to predict, identify, treat, and maybe even prevent, PTSD. Clearly, understanding the genetic risk factors for PTSD could have profound implications for patient care. Not all individuals exposed to a traumatic event will develop PTSD. Genetic tests could be used to predict who is most susceptible and triage trauma patients for intensive monitoring and tailored care. For patients with PTSD, insights from the genetic pathways could lead to new biomarker tests of treatment response to individualize effective treatment. And in advance of potential trauma, baseline genetic tests could target PTSD-susceptible individuals for pre-emptive resiliency training. More intensive study of these genes could also provide insight into the biological mechanisms that trigger PTSD, allowing more targeted drug, device and alternative therapeutic discovery for individualized, precision medicine.

STRENGTH OF FINDINGS

This study was the largest meta-analysis to date of PTSD, and included analysis of 4 times more cases and controls than its predecessor. PTSD is a "complex" disease comprised of multiple traits (phenotypes) that may, in turn, be affected by multiple genes, and each gene may only have a weak association with this phenotype. Even with 80,000 cases, this study had sufficient overall statistical power only to identify the first three loci associated with PTSD risk and will need to be independently replicated. Adding more ethnic and racially diverse samples will increase the power to detect more variants within each population and identify potential overlaps.

RESEARCH CONDUCTED

Previous studies confirmed the genetic basis of PTSD but were unable to identify any genetic variants associated with the disorder. In 2016, Cohen Veterans Biosciences partnered with the Stanley Center for Psychiatric Genetics and researchers around the world to conduct a global genome-wide association study (GWAS) of trauma patients, aimed at identifying genetic factors linked to PTSD. This research collaborative provided more than $3 million in funding and project management to support the collection, extraction, and genotyping of DNA samples in many PTSD cohorts. The project screened over 80,000 trauma-exposed patients, consisting of 58,769 controls and 21,845 PTSD cases from 56 contributing groups.

Significantly, this research used the newest next-generation gene sequencing technology, which expanded coverage of non-Caucasian population genetics, reduced the cost of screening, and increased the number of samples that could be analyzed in this GWAS of PTSD, thus increasing the statistical power of the analysis. The global collaboration allowed the research team to add patients from Asian and African background to the original database of primarily Caucasian patients.

GOALS FOR THE FUTURE

- The global team will continue to build sample size both to replicate results and identify new loci.
- New insights and targets for treatment: As research identifies each genetic loci, the goal is to map downstream effects on an individual's pathways and function. These will help identify precision targets for therapeutic intervention.
- New diagnostics: Once additional loci have been identified and replicated, we can develop a diagnostic test where a saliva or blood sample can be tested in the ER or clinician's office to inform clinical practice, post-trauma exposure.

REFERENCES

Abdallah, Chadi G., Steven M. Southwick, and John H. Krystal. "Neurobiology of posttraumatic stress disorder (PTSD): A path from novel pathophysiology to innovative therapeutics." Neuroscience Letters 649 (May 2017): 130-132. https://doi.org/10.1016/j.neulet.2017.04.046.

Burmeister, Margit, Melvin G. McInnis, Sebastian Zöllner. "Psychiatric genetics: progress amid controversy." Nature Reviews Genetics 9 (July 2008): 527–540. https://doi:10.1038/nrg2381.

Duncan, LE, et al. "Largest GWAS of PTSD (N=20070) yields genetic overlap with schizophrenia and sex differences in heritability." Molecular Psychiatry 23 (April 2017): 666–673. https://doi.org/10.1038/mp.2017.77.

Friedman, Matthew J., and Nancy C. Bernardy. "Considering future pharmacotherapy for PTSD." Neuroscience Letters 649 (May 2017): 181-185. https://doi.org/10.1016/j.neulet.2016.11.048.

Kessler, Ronald C., et al. "Posttraumatic Stress Disorder in the National Comorbidity Survey." Archives of General Psychiatry. 52 (12) (December 1995): 1048-1060. https://doi:10.1001/archpsyc.1995.03950240066012.

Kilpatrick, Dean G., et al. "National Estimates of Exposure to Traumatic Events and PTSD Prevalence Using DSM-IV and DSM-5 Criteria." Journal of Traumatic Stress 26 (5) (2013): 537-547. https://doi: 10.1002/jts.21848.

RAND Health. Current and Projected Characteristics and Unique Health Care Needs of the Patient Population Served by the Department of Veterans Affairs. Santa Monica: Rand Corporation, 2015. Accessed March 5, 2018. https://www.rand.org/content/dam/rand/pubs/research_reports/RR1100/RR1165z1/RAND_RR1165z1.pdf.

Schizophrenia Working Group of the Psychiatric Genomics Consortium. "Biological insights from 108 schizophrenia-associated genetic loci." Nature 511 (July 2014): 421–427. https://doi:10.1038/nature13595.

Steenkamp, Maria M., et al. "Psychotherapy for military-related PTSD: A review of randomized clinical trials." JAMA 314 (5) (August 2015): 489-500. https://doi:10.1001/jama.2015.8370.

Stein, Murray B., et al. "Genetic and Environmental Influences on Trauma Exposure and Posttraumatic Stress Disorder Symptoms: A Twin Study." American Journal of Psychiatry 159 (10) (October 2002): 1675-1681. https://doi:10.1176/appi.ajp.159.10.1675.

ABOUT STAND SMART FOR HEROES

The Bob Woodruff Foundation is proud to partner with best-in-class scientific organizations to provide important research findings to the community of organizations that represent and serve post-9/11 veterans, service members, families, and caregivers. For more information on the Bob Woodruff Foundation and Stand SMART For Heroes, please see bobwoodrufffoundation.org.

ABOUT COHEN VETERANS BIOSCIENCE

Cohen Veterans Bioscience is a 501(c)(3) non-profit research organization dedicated to fast-tracking the development of diagnostic tests and personalized therapeutics for the millions of veterans and civilians who suffer the devastating effects of brain trauma. More information is available at www.cohenveteransbioscience.org.

BOB WOODRUFF FOUNDATION

Cohen Veterans Bioscience