Learning to Care for Those in Harm's Way

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Release No. 21-02-15
Feb. 15, 2021
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USU's Genome Center Helps Identify Genes That Can Open New Avenues in Dementia Research

Bethesda, Md. – Five genes may play a key part in influencing if a person will contract Lewy body dementia, and possibly dementia from Parkinson's and Alzheimer's diseases, according to a study published in Nature Genetics Feb. 15. The genes, BIN1, TMEM175, SNCA, APOE, and GBA, were identified by a team of scientists at the National Institute of Neurological Disorders and Stroke and the National Institute on Aging, National Institutes of Health, and sequenced by The American Genome Center (TAGC), a series of state-of-the-art laboratories at the Uniformed Services University of the Health Sciences.

Patients with dementia have impaired cognitive abilities, such as memory loss and difficulty in problem-solving. Alzheimer's is the most common cause of dementia. Lewy body dementia, a disease associated with abnormal protein deposits in the brain called Lewy bodies, is the second most common form of progressive dementia. Lewy bodies, made of a protein called alpha-synuclein, affect several different brains regions that control memory, movement and thinking. Lewy bodies are also found in brains of patients with Parkinson's disease who develop dementia.

There is an increased prevalence of dementia among veterans. Military service risk factors, like post-traumatic stress disorder, traumatic brain injury and depression, increase dementia risk and subsequent health outcomes associated with dementia.

"The genetic findings in this study of Lewy body dementia, and its intersections with Alzheimer's and Parkinson's disease, provides key insights into the potential targets for therapeutic strategies against all dementias that may affect veterans and non-veterans alike," said Dr. Clifton Dalgard, director of TAGC and associate professor, Department of Anatomy, Physiology & Genetics at USU.

The study was led by Sonja Scholz, MD, PhD, investigator at the NIH's National Institute of Neurological Disorders and Stroke (NINDS), along with her team and researchers in the lab of Bryan J. Traynor, MD, PhD, senior investigator at the NIH's National Institute on Aging (NIA).USU's TAGC generated genomic data for analysis of the dementia genetic study.

The team's results not only support the connection of Lewy body dementia with Parkinson's disease but also suggest that people who have Lewy body dementia may share similar genetic profiles to those who have Alzheimer's disease.

"Lewy body dementia is a devastating brain disorder for which we have no effective treatments.Patients often appear to suffer the worst of both Alzheimer's and Parkinson's diseases. Our results support the idea that this may be because Lewy body dementia is caused by a spectrum of problems that can be seen in both disorders," said Dr. Scholz, the senior author of the study. "We hope that these results will act as a blueprint for understanding the disease and developing new treatments."

Lewy body dementia affects those who are over 65 years old. Men are at greater risk than women of developing the disorder, and those with a family history of Lewy body dementia or Parkinson's disease are also at an increased risk. Symptoms can include visual hallucinations, movement disorders, poor regulation of body functions, cognitive problems, sleep difficulties, fluctuating attention, depression, and apathy.

Genetics may play a role in the disorder, according to emerging scientific evidence, and some cases may be inherited. A mutation in the gene for alpha-synuclein (SNCA), the main protein found in Lewy bodies, may be the cause of some rare cases. Variants in the gene known to factor into Alzheimer's disease, apolipoprotein E (APOE), may also have a tie to Lewy body dementia.

"Compared to other neurodegenerative disorders, very little is known about the genetic forces behind Lewy body dementia," said Dr. Traynor. "To get a better understanding we wanted to study the genetic architecture of Lewy body dementia."

To do this, they worked with Dalgard and researchers at TAGC to sequence every DNA letter in the chromosomes obtained from 2,981 Lewy body dementia patients and of 4,931 healthy, age-matched control participants. Samples were collected from participants of European ancestry at 44 sites: 17 in Europe and 27 across North America and sequenced at TAGC.

Initially, they found that the sequences of the five genes from the Lewy body dementia patients were often different from those of the controls, suggesting that these genes may be important. It was the first time that two of the genes, BIN1 and TMEM175, had been implicated in the disease. These genes may also have ties to Alzheimer's and Parkinson's diseases. The other three genes, SNCA, APOE, and GBA, had been implicated in previous studies, and thus, strengthened the importance of the genes in Lewy body dementia.

The researchers also saw differences in the same five genes when they compared the DNA sequences of another 970 Lewy body dementia patients with a new set of 8,928 control subjects, confirming their initial results.

Extending upon confirmation of previous genetic variants associated with Lewy body dementia, the identification of novel candidate genes that may influence the disease provides new therapeutic strategies for Lewy body dementia and neurodegenerative disease processes in general. The finding that the GBA gene, which encodes a protein, beta-glucosylceramidase, that acts in lysosomes to break down glycolipids that may accumulate as garbage products within cells, provides a new target for further investigation.

Building from known clinical links between Lewy body dementia and other neurodegenerative diseases, the study team further analyzed genetic data from previous Alzheimer's and Parkinson's disease genetic studies. Interestingly, genetic risk factors for Alzheimer's or Parkinson's Disease were greater but distinct for individual Lewy body dementia patients in this study.

"While neurodegenerative diseases such as Alzheimer's and Parkinson's Disease present as distinct cellularly and clinically, our study suggests genetic influences for these diseases overlap with Lewy body dementia. The complex intersection of these diseases allows us to focus and select potential preventative approaches for military service members and veterans with risk factors of neurotrauma, stress and depression. We are enthusiastic to share this genomic data and its findings to the research community," said Dr. Dalgard.

“Although Alzheimer’s and Parkinson’s disease are molecularly and clinically very different disorders, our results support the idea that the problems that cause those diseases may also happen in Lewy body dementia,” said Dr. Scholz. “The challenge we face in treating these patients is determining which specific problems are causing the dementia. We hope studies like this one will help doctors find precise treatments for each patient’s condition.”

To help with this effort, the team published the genome sequence data from the study on the “dbGaP Portal,” a website that researchers can freely search for new insights into the causes of Lewy body dementia.

Article: Chia, R., et al. Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into the complex genetic architecture. Nature Genetics, February 15, 2021 DOI: 10.1038/s41588-021-00785-3

This study was supported in part by the NIH Intramural Research Programs at the National Institute of Neurological Disorders and Stroke (NS003154) and the National Institute on Aging (AG000935).

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