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Connection between genetic variation and immune system, risk for neurodegenerative and other disease

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Researchers from Brigham and Women's Hospital (BWH), Harvard Medical School (HMS), the Broad Institute of MIT and Harvard, Massachusetts General Hospital (MGH), and University of Chicago report findings demonstrating how genetic variations among healthy, young individuals can influence immune cell function. Many of those variants are also genetic risk factors for common diseases such as Alzheimer's disease, diabetes, and multiple sclerosis later in life, offering new insight into disease pathology.

The study will be published in the May 2, 2014 issue of *Science*.

"Over the last decade, geneticists have identified hundreds of genetic risk factors for several human diseases, but the functional consequences of those factors on relevant cells are largely unknown," said Towfique Raj, PhD, BWH Department of Neurology and a postdoctoral scholar at the Broad Institute, lead study author. "Our study highlights the potential role of immune system cells in human diseases."

The study was conducted as part of the ImmVar Project, which leveraged BWH's PhenoGenetic Project, a "living biobank" of healthy volunteers willing to contribute blood samples to understand how human genetic variations affect how the human body functions.

The researchers recruited a subset of 461 volunteers from the

PhenoGenetic Project of African American, East Asian American, or European American ancestry. Two different types of immune cells—T cells and monocytes—were purified from each individual's blood, representing the adaptive and innate arms of immunity, respectively. The researchers profiled these cells to measure the expression of 19,114 genes in each cell type. They then examined genetic variants throughout the human genome for their effects on gene expression in these two representative populations of immune cells.

They discovered that genetic variation influencing a person's risk for multiple sclerosis, rheumatoid arthritis, and type 1diabetes is more likely to control gene activity in T cells than in monocytes. In contrast, genetic variation that increases one's risk for neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, shows a striking enrichment of functional effects in monocytes.

"This study shows that our genomes introduce changes in the immune system early on," said Christophe Benoist, MD, PhD, HMS, Broad Institute associate member, and study author. "These changes influence how a person responds to additional risk factors that he or she may encounter over the course of their life, making them more or less susceptible to triggering a disease process such as type 1, or juvenile, diabetes."

"The study focuses our attention on a particular part of the immune system that already exhibits changes caused by Alzheimer risk factors in people in their 20s and 30s," said Philip L. De Jager, MD, PhD, director, BWH Program in Translational NeuroPsychiatric Genomics, associate member at the Broad Institute, senior study author. "Functionally, we cannot say that blood-derived immune cells are the key cell type for Alzheimer's disease. They are likely to be proxies for the infiltrating and resident cells found at the sites of neuropathology. However, these exciting insights encourage us to explore how manipulating these

immune cell types may one day slow or contribute to stopping the accumulation of Alzheimer's disease pathology that occurs as each of us ages."

By including volunteers of different genetic ancestries, the researchers also found that genetic variation that alters immune function is highly shared across human populations of different ancestry.

"Our multi-ethnic exploration of innate and adaptive immunity highlights a remarkable level of sharing across human populations of genetic variation influencing immune function, while identifying interesting instances of genetic effects on immune function that are specific to a population," said Nir Hacohen, PhD, MGH and the Broad Institute, study author.

"This study extends the narrative that many of the effects of disease-related genetic variation are specific to a certain context, such as a given immune cell type," said Barbara Stranger, PhD, University of Chicago, senior study author. "Thus, it is clear that further studies must investigate an increasingly complex matrix of cell types and conditions to fully understand the role of human genetic variation in disease."

More information: "Polarization of the Effects of Autoimmune and Neurodegenerative Risk Alleles in Leukocytes" *Science*, 2014.

Provided by Brigham and Women's Hospital