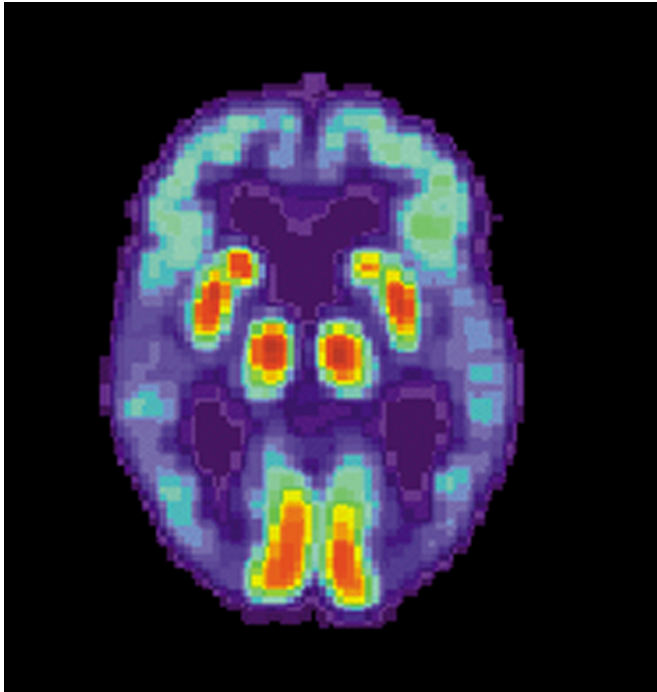# Team gains insights into genetic and molecular machinery that predisposes individuals to Alzheimer's disease

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PET scan of a human brain with Alzheimer's disease. Credit: public domain

Mount Sinai researchers have achieved an unprecedented understanding of the genetic and molecular machinery in human microglia—immune cells that reside in the brain—that could provide valuable insights into how they contribute to the development and progression of Alzheimer's disease (AD). The team's findings were published in *Nature Genetics*.

Working with fresh human brain tissue harvested via biopsy or autopsy from 150 donors, researchers identified 21 candidate risk genes and highlighted one, SPI1, as a potential key regulator of microglia and AD risk.

"Our study is the largest human fresh-tissue microglia analysis to date of genetic risk factors that might predispose someone to Alzheimer's disease," says senior author Panos Roussos, MD, Ph.D., Professor of Psychiatry, and Genetic and Genomic Sciences, at the Icahn School of Medicine at Mount Sinai and Director of the Center for Disease Neurogenomics. "By better understanding the molecular and genetic mechanisms involved in microglia function, we're in a much better position to unravel the regulatory landscape that controls that function and contributes to AD. That knowledge could, in turn, pave the way for novel therapeutic interventions for a disease that currently has no effective treatments."

Microglia are primarily responsible for the immune response in the brain, and are also critical to the development and maintenance of neurons. While previous studies, including some at Mount Sinai, have identified microglia as playing a key role in the genetic risk and development of Alzheimer's disease, little is known about the epigenetic mechanics of how that occurs. Because microglia are challenging to isolate within the human brain, most previous studies have used either animal- or cell-line-based models which do not reflect the true complexity of microglia function in the brain. Another challenge has been relating AD genetic risk variation to specific molecular function because these risk factors are frequently found in the non-coding part of the genome (what used to be called "junk DNA"), which is more difficult to study.

The Mount Sinai team's solution was to access fresh brain tissue from biopsies or autopsies made possible by a collaboration between four brain bio-depositories, three at Mount Sinai and the other from Rush University Medical Center/Rush Alzheimer's Disease Center. "Using a total of 150 samples from these sources, we were able to

isolate high-quality microglia, which provided unprecedented insights into genetic regulation by reflecting the entire set of regulatory components of microglia in both healthy and neurodegenerative patients," explains Dr. Roussos.

That process—comparing epigenetic, gene expression, and genetic information from the samples of both AD and healthy aged patients—allowed researchers to comprehensively describe how microglia functions are genetically regulated in humans. As part of their statistical analysis, they expanded the findings of prior genome-wide association studies to link identified AD-predisposing genetic variants to specific DNA regulatory sequences and genes whose dysregulation is known to directly contribute to the development of the disease. They further described the cell-wide regulatory mechanisms as a way of identifying genetic regions involved in specific aspects of the microglial activity.

From their investigation emerged new knowledge about the SPI1 gene, already known to scientists, as the main microglial transcription factor regulating a network of other transcription factors and genes that are genetically linked to AD. Data the team is generating could also be important to deciphering the molecular and genetic mysteries behind other neurodegenerative diseases in which microglia play a role, including Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis.

Dr. Roussos concedes that much work remains for his team to fully understand how the identified genes contribute to the development and progression of Alzheimer's disease, and how they could be targeted with new therapeutics. He is greatly encouraged, though, by the results of single-cell analysis by his lab of microglia using highly sophisticated instruments that are uncovering the unique interactions between different types of immune cells in the brain and its periphery that are related to neurodegenerative disease. "We're seeing very exciting results through our single-cell data," Dr. Roussos reports, "and that's bringing us ever closer to understanding the genetically driven variations and cell-specific interactions of inheritable diseases like Alzheimer's."

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