Can a human microglial atlas guide brain disorder research?

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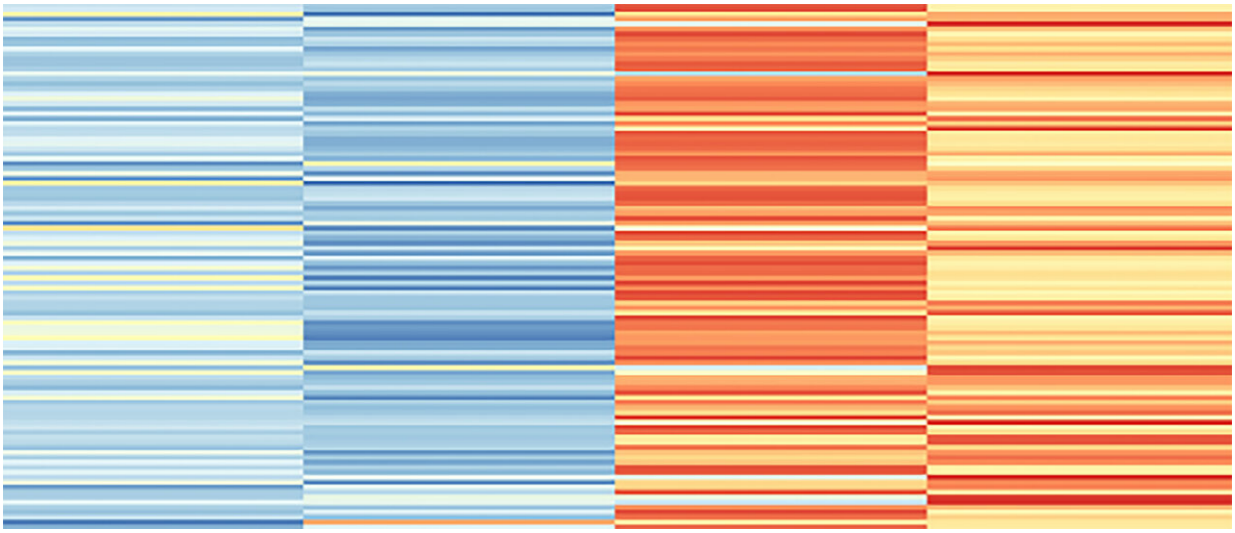

Researchers at the Icahn School of Medicine at Mount Sinai analyzed the genetic activity of thousands human microglia, the brain's immune cells. Their results support the idea that microglia may play critical roles some brain disease. Credit: Raj and de Witte labs, Mount Sinai, N.Y., N.Y.

Certain subtle differences in DNA sequences are known to raise the chances a person may develop Alzheimer's or Parkinson's disease. Some of these differences may work by altering the genetic activity of microglia, the brain's immune cells. Those are just a few of the findings from a study led by scientists at the Icahn School of Medicine at Mount Sinai.

The researchers analyzed thousands of microglia from different brain regions of deceased patients who had been diagnosed with a variety of neuropsychiatric and neurodegenerative disorders. Their results, published in *Nature Genetics*, support the idea that microglia may play critical roles in some cases of brain disease while also providing a potentially valuable guide for future studies.

The study was led by Katia de Paiva Lopes, Ph.D., Gijsje Snijders, MD, Ph.D., and Jack Humphrey, Ph.D., working in the laboratories of Towfique Raj, Ph.D., Associate Professor of Neuroscience, and Lotje D. De Witte, MD, Ph.D., Assistant Professor of Psychiatry at Icahn Mount Sinai.

Shaped like octopi, microglia can be found sprinkled throughout the brain. For nearly a century after they were first spotted, scientists thought that these cells served as both the brain's infection-fighting immune system and clean-up crew. They also thought that microglia strictly played a reactive, rather than causative, role in brain disorders.

Recently this view has started to change. For instance, experiments in rodents have shown that microglia may actively shape how the brain is wired. Meanwhile, genomic studies identified potential links between microglia and the risk that certain DNA sequences are associated with developing several brain disorders, including Alzheimer's disease and multiple sclerosis. However, tying these results to specific genes has proved elusive.

In this study, scientists used advanced genomic techniques to take an in-depth look at the many roles that microglia may play in the brain. To do this, they created the largest and most thorough high-resolution microglial genomic atlas of its kind. Microglia were extracted from samples of human brain tissue and then underwent a series of gene activity experiments. A total of 255 samples representing four different

brain regions were obtained from 100 donors, who were part of the Netherlands Brain Bank and the Neuropathology Brain Bank Research CoRE at The Mount Sinai Hospital. The average donor was about 73 years old, spanning a range of 21 to 103 years of age. Ninety-six samples came from control donors whereas the rest came from donors who had been diagnosed with a neurological or psychiatric disorder.

Overall, the results both supported previous findings and made new discoveries. For example, microglia gene activity changed with age or in different brain regions, reinforcing the idea that the roles microglia play can vary throughout the brain and at different stages of life. Moreover, aging appeared to alter primarily the activity of genes associated with the immune system.

The results strengthened the evidence that microglia may be linked to some cases of Alzheimer's and Parkinson's diseases while also finding links to other disorders, including multiple sclerosis, schizophrenia, and bipolar disorder. Finally, the researchers identified two new genes that may be associated with brain disorders. One gene, called *USP6NL*, was associated with Alzheimer's disease while the other one, called *P2RY12*, was associated with Parkinson's disease. According to the authors, these results support the idea that the atlas provides the kind of comprehensive guide needed to fully understand the roles microglia may play under healthy and disease states.

More information: Lot Witte, Genetic analysis of the human microglial transcriptome across brain regions, aging and disease pathologies, *Nature Genetics* (2022). DOI: 10.1038/s41588-021-00976-y. www.nature.com/articles/s41588-021-00976-y

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