Largescale brain epigenetics study provides new insights into dementia

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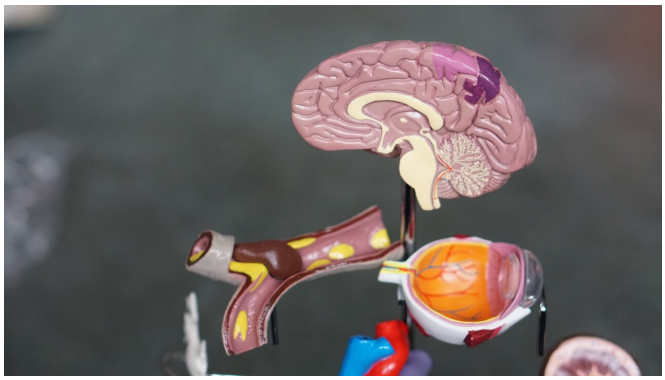

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The largest study of its kind has unveiled new insights into how genes are regulated in dementia, including discovering 84 new genes linked to the disease.

Led by the University of Exeter, the international collaboration combined and analyzed data from more than 1,400 people across six different studies, in a meta-analysis published in *Nature Communications*. These studies had used brain samples from people who had died with Alzheimer's disease. The project, funded by Alzheimer's Society and supported by the Medical Research Council and the National Institutes for Health, looked at an epigenetic mark called DNA methylation at nearly half a million sites in the genome. Epigenetic processes control the extent to which genes are switched on and off, meaning they behave differently as needed across the different cell-types and tissues that make up a human body. Importantly, unlike our genes, epigenetic processes can be influenced by environmental factors, making them potentially reversible and a possible route to new treatments.

The study looked at epigenetic patterns across the genome, in a number of different regions of the brain. The team then related the amount of DNA methylation to the amount of neurofibrillary tangles within the brain, which is an important hallmark of the severity of Alzheimer's disease.

The team looked in different regions of the brain, which are affected in Alzheimer's disease before looking for common changes across these cortical regions. They identified 220 sites in the genome, including 84 new genes, which showed different levels of DNA methylation in the cortex in individuals with more severe Alzheimer's disease, which weren't seen in another area of the brain called the cerebellum.

The team went on to show that a subset of 110 of these sites could distinguish in two independent datasets whether a brain sample had high or low levels of disease, with more than 70 percent accuracy. This suggests that epigenetic changes in the brain in Alzheimer's disease are very consistent. The findings were subsequently confirmed in an independent set of brain samples from the Brains for Dementia Research cohort funded by the Alzheimer's Society and Alzheimer's Research UK.

Professor Katie Lunnon, of the University of Exeter, who led the research, said: "Our study is the largest of its kind, giving important insights into genomic areas that could one day provide the key to new treatments. The next step for this work is to explore whether these epigenetic changes lead to measurable changes in the levels of genes and proteins being expressed. This will then allow us to explore whether we could repurpose existing drugs that are known to alter the expression levels of these genes and proteins, to effectively treat dementia."

The study included a number of international collaborators from the US (Columbia University and Mount Sinai School of Medicine in New York, Rush

University Center in Chicago, Arizona State University), and Europe (Maastricht University in Netherlands, University of Saardland, Germany). The paper is titled "A meta-analysis of epigenome-wide association studies in Alzheimer's disease highlights novel differentially methylated loci across cortex," published in *Nature Communications*.

Dr. Richard Oakley, Head of Research, Alzheimer's Society said: "Epigenetics is a flourishing area of dementia research. Work like this, led by the University of Exeter, is another step forward in our understanding of the incredibly complex role our genes play in Alzheimer's disease.

"It's now important to delve into the specific impact of these epigenetic changes and the associated genes on the changes in the brains of people with Alzheimer's disease. This work is in early stages but breakthroughs in research begins with work like this, and it brings us a step closer to developing new treatments for Alzheimer's disease.

"Alzheimer's Society is delighted to have part-funded this work and 'Brains for Dementia Research', which provided the tissue samples to this research team. Without the support of charities, this work simply would not be possible—we are committed to investing in, and accelerating, dementia research. However, dementia research remains hugely underfunded. We need public support now more than ever to help us continue our ground-breaking research to make a world without dementia a reality."

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