Strictly embargoed until 10am UK time on Thursday June 10

Largescale brain epigenetics study provides new insights into dementia

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 analysed 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 the Alzheimer's Society and the Medical Research Council and supported by 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 per cent accuracy. This suggests that epigenetic changes in the brain in Alzheimer's disease are very consistent.

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 Saarland,

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*.

Once the embargo lifts, the paper will be available at http://dx.doi.org/10.1038/s41467-021-23243-4

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As part of a Russell Group university, we combine this world-class research with very high levels of student satisfaction. Exeter has over 19,000 students and is ranked 12th in The Times and Sunday Times Good University Guide 2020.

The University of Exeter Medical School's Medicine course is in the top 10 in the Complete University Guide 2020.

The College's Medical Imaging programme is ranked in the top 5 in the Guardian Guide 2020 and the Complete University Guide 2020.

The University of Exeter entered the world top 20 for Biomedical and Health Sciences in the CWTS Leiden Ranking 2019, based on the percentage of publications ranked in the top 10 per cent most cited.

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