Genes for age-linked brain deterioration identified

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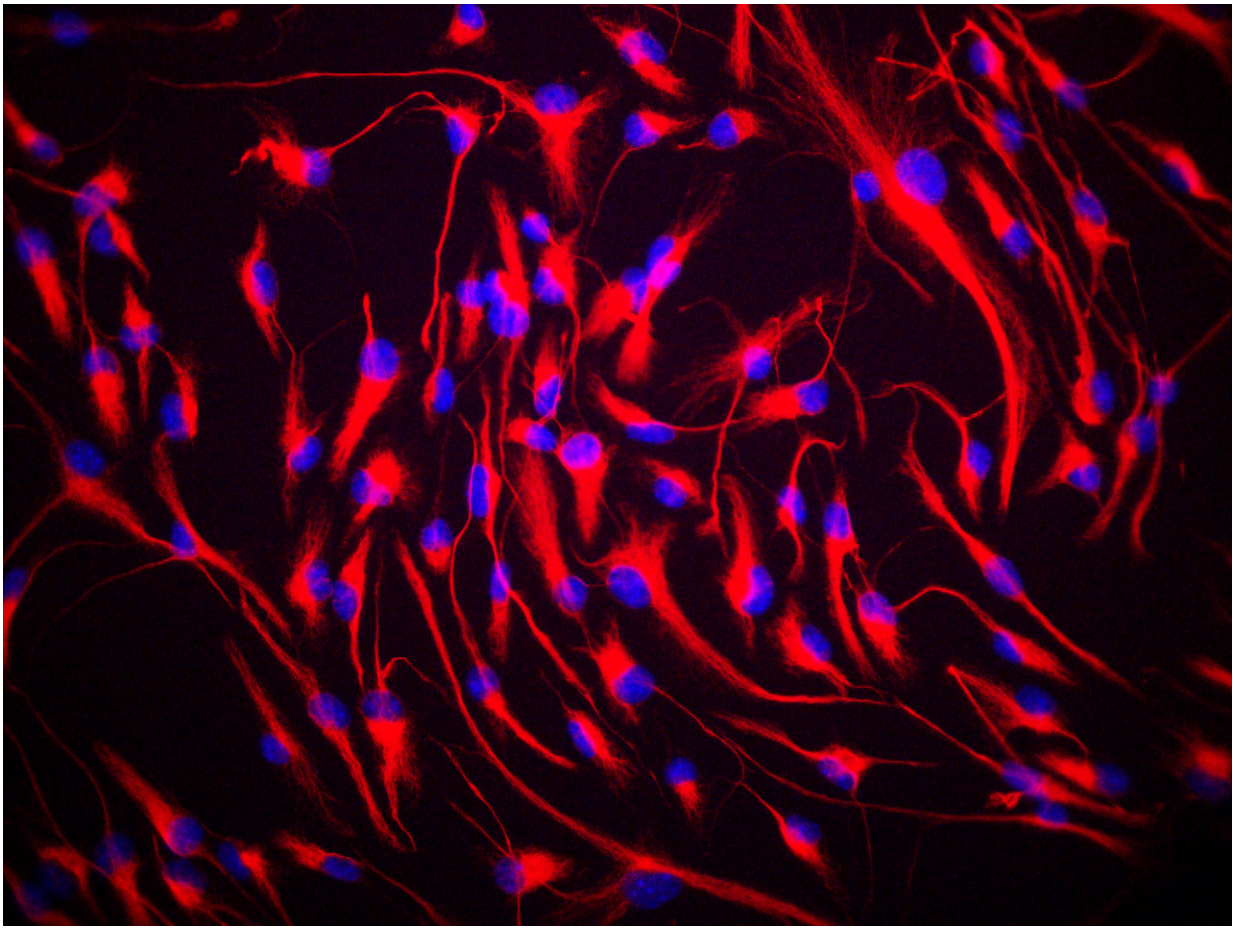


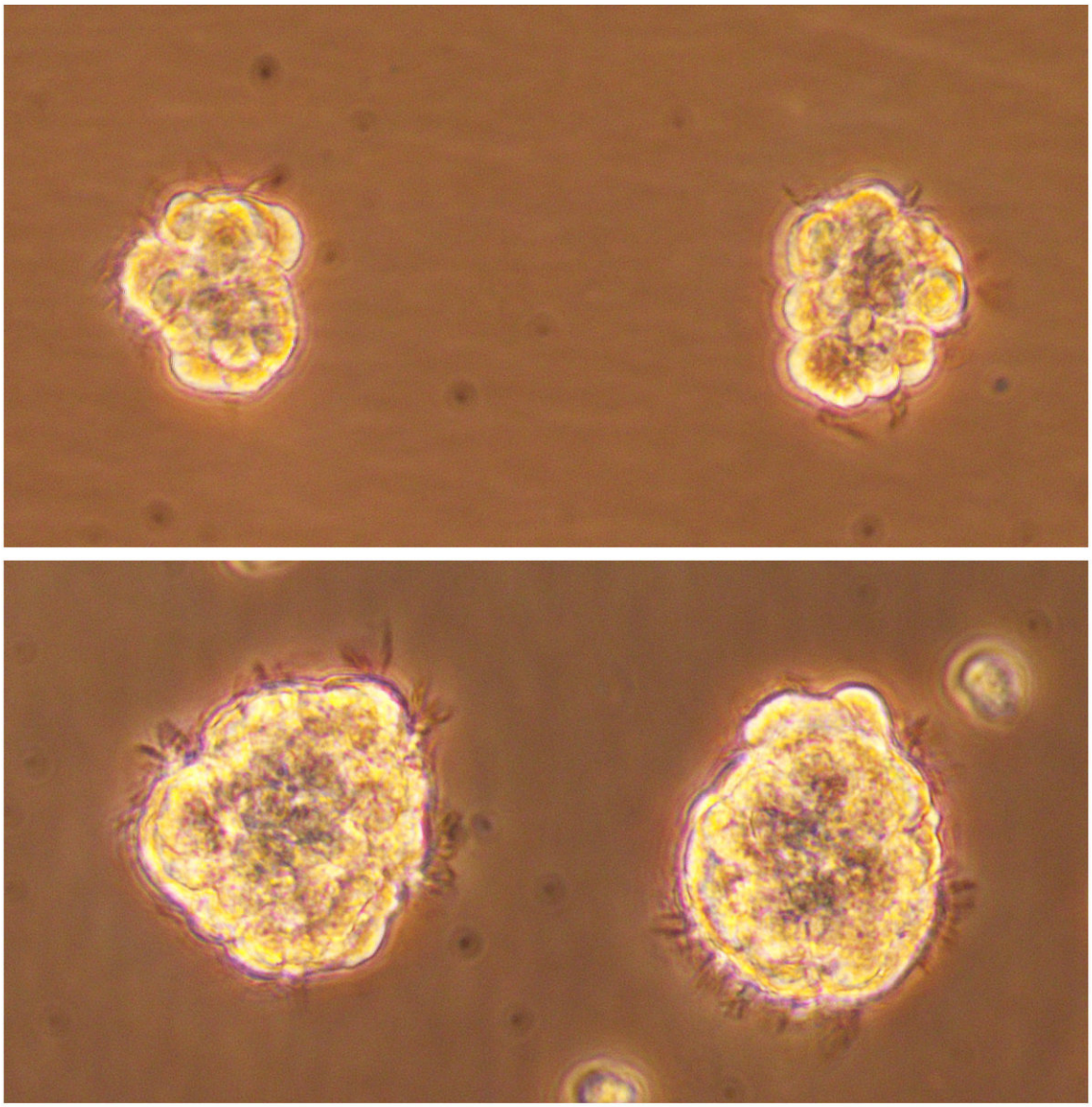
Stem cells from the brain. Cells were labelled using a stain that detects a protein called nestin, found in neural stem cells. Credit: Dr. Giuseppe Lupo

A group of genes and genetic switches involved in age-related brain deterioration have been identified by scientists at the Babraham Institute, Cambridge and Sapienza University, Rome. The research, published online today (5th March) in *Aging Cell*, found that changes to one of these genes, called Dbx2, could prematurely age brain stem cells, causing them to grow more slowly. The study was led jointly by Giuseppe Lupo and Emanuele Cacci in Italy and Peter Rugg-Gunn in the UK.

Cells in the brain are constantly dying and being replaced with new ones produced by brain stem cells. As we age, it becomes harder for these stem cells to produce new brain cells and so the brain slowly deteriorates. By comparing the genetic activity in brain cells from old and young mice, the scientists identified over 250 genes that changed their level of activity with age. Older cells turn some genes, including Dbx2, on and they turn other genes off.

By increasing the activity of Dbx2 in young brain stem cells, the team were able to make them behave more like older cells. Changes to the activity of this one gene slowed the growth of brain stem cells. These prematurely aged stem cells are not the same as old stem cells but have many key similarities. This means that many of the genes identified in this study are likely to have important roles in brain ageing.

The research also identified changes in several epigenetic marks - a type of genetic switch - in the older stem cells that might contribute to their deterioration with age. Epigenetic marks are chemical tags attached to the genome that affect the activity of certain genes. The placement of these marks in the genome change as we age and this alters how the cells behave. The researchers think that some of these changes that happen in the brain may alter causing brain stem cells to grow more slowly.



Stem cells from the brains of old an young mice grown into balls of cells called neurospheres. The slower growth of cells from older mice produces smaller spheres (lower image). Credit: Dr. Giuseppe Lupo

First author on the paper, Dr Giuseppe Lupo, Assistant Professor at Sapienza University said: "The genes and gene regulators that we

identified are corrupted in neural stem cells from older mice. By studying the Dbx2 gene we have shown that these changes may contribute to ageing in the brain by slowing the growth of brain stem cells and by switching on the activity of other age-associated genes."

Co-lead scientist Dr Peter Rugg-Gunn at the Babraham Institute said: "Ageing ultimately affects all of us and the societal and healthcare burden of neurodegenerative diseases is enormous. By understanding how ageing affects the brain, at least in mice, we hope to identify ways to spot neural stem cell decline. Eventually, we may find ways to slow or even reverse brain deterioration - potentially by resetting the epigenetic switches - helping more of us to stay mentally agile for longer into old age."

Co-lead scientist Dr Emanuele Cacci at Sapienza University said: "We hope this research will lead to benefits for human health. We have succeeded in accelerating parts of the ageing process in neural stem cells. By studying these genes more closely, we now plan to try turning back the clock for older cells. If we can do this in mice, then the same thing could also be possible for humans."

More information: Giuseppe Lupo et al, Molecular profiling of aged neural progenitors identifies Dbx2 as a candidate regulator of age-associated neurogenic decline, *Aging Cell* (2018). DOI: 10.1111/acel.12745

Provided by Babraham Institute