Nature Reviews Neurology | Published online 22 Dec 2017; doi:10.1038/nrneurol.2017.181

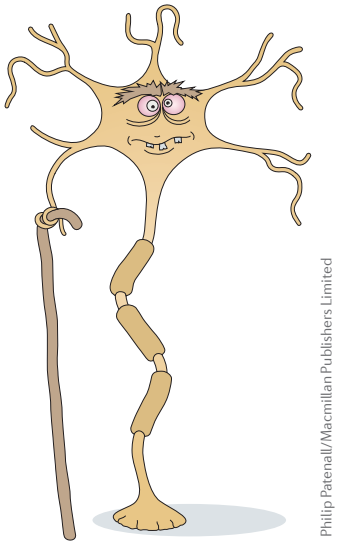
AGEING

Somatic mutations accumulate in ageing and diseased neurons

Ageing and neurodegeneration are associated with accumulation of somatic mutations in neurons, according to a new report in *Science*.

Ageing increases the incidence of neurodegenerative diseases and also increases the occurrence of markers of DNA damage in the brain. However, due to methodological constraints, it has been unclear whether somatic mutations accumulate in mature neurons of the human brain. In the new study, Lodato and colleagues used single-cell whole-genome sequencing to compare the genomes of single postmitotic neurons.

The researchers analysed 93 neurons from the prefrontal cortex of 15 neurologically normal individuals (aged between 4 months and 82 years), 26 neurons from the hippocampal dentate gyrus of 6 of the same individuals and 42 neurons from the prefrontal cortex of 9 individuals with early-onset neurodegenerative disease (either Cockayne syndrome or xeroderma pigmentosum). Single neuronal nuclei were isolated by flow cytometry before whole-genome sequencing analyses, and a new bioinformatics pipeline called Linked-Read Analysis (LiRA) was used to identify somatic single-nucleotide variants (sSNVs).



Philip Patenall/Macmillan Publishers Limited

Neurons from neurologically normal individuals had sSNV counts that correlated with age, a phenomenon that the researchers define as 'genosenium'. Furthermore, there was a twofold faster rate of accumulation of somatic mutations in the hippocampal dentate gyrus than in the prefrontal cortex.

Neurons from the brains of individuals with early-onset neurodegenerative diseases had a ~2.3–2.5-fold excess of sSNVs relative to the age-adjusted count of neurologically normal individuals. This finding suggests that the defective nucleotide excision repair that characterizes these disorders can accelerate neuronal ageing.

Interestingly, mutational signature analysis identified three distinct mutational signatures associated with human neurons: signature A, which comprised C>T and T>C mutations and was associated with normal ageing; signature B, which comprised C>T mutations and might represent a developmental signature; and signature C, which comprised C>A mutations (associated with oxidative DNA damage) and was associated with both disease and age.

"Further elucidating the mechanistic basis of the clock-like accumulation of mutations across brain regions and other tissues would increase our knowledge of age-related disease and cognitive decline," the researchers conclude.

Shimona Starling

> "mutational signature analysis identified three distinct mutational signatures associated with human neurons"

ORIGINAL ARTICLE Lodato, M. A. *et al.* Aging and neurodegeneration are associated with increased mutations in single human neurons. *Science* http://dx.doi.org/10.1126/science.aao4426 (2017)