Mutations in neurons accumulate as we age: The process may explain normal cognitive decline and neurodegeneration

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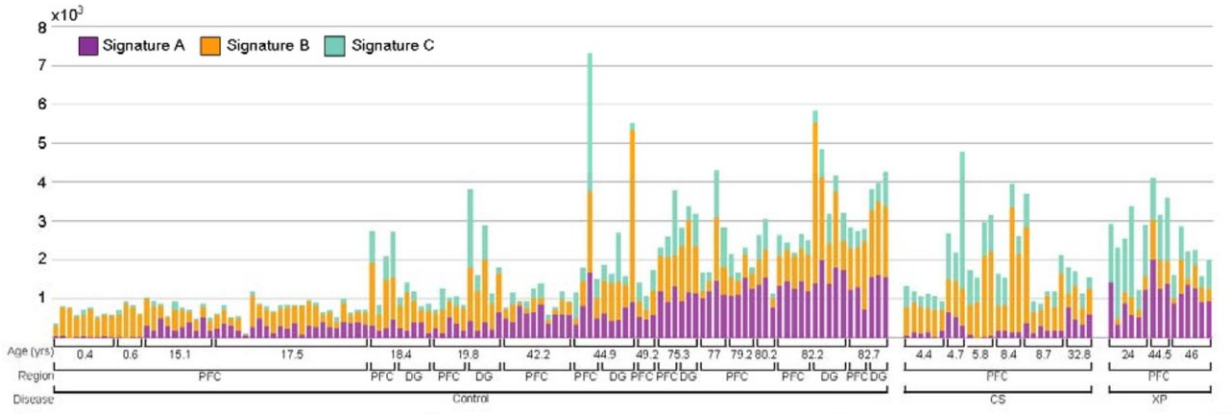


This graph of all 161 neurons in the dataset, sampled at different ages, shows the quantity and type of mutations they carry. From left to right, by ascending age in each group, are neurons from normal controls, people with Cockayne syndrome (CS) and people with xeroderma pigmentosum. Color indicates the type of mutation: Signature A (purple), correlates closely with aging; Signature B (orange), is apparent soon after birth; and signature C (blue) is related to oxidative DNA damage. Brain areas are also designated: PFC, prefrontal cortex; DG, dentate gyrus of the hippocampus. The highest numbers of mutations are in neurons from the older controls and the two disease groups. Credit: Reprinted with permission from MA Lodato et al., *Science* Dec. 7, 2017, DOI: 10.1101/221960

Scientists have wondered whether somatic (non-inherited) mutations play a role in aging and brain degeneration, but until recently there was no good technology to test this idea. A study published online today in *Science*, led by researchers from Boston Children's Hospital and Harvard Medical School, used whole-genome sequencing of individual neurons and found strong evidence that brain mutations accumulate as we age. They also found that mutations accumulate at a higher rate in people with genetic premature aging disorders causing early brain degeneration.

"It's been an age-old question as to whether DNA mutations can accumulate in neurons—which usually don't divide—and whether they are responsible for the loss of function that the brain undergoes as we get older," says Christopher A. Walsh, MD, PhD, chief of the Division of Genetics and Genomics at Boston Children's and co-senior author on the paper. "It hasn't been possible to answer this question before, because we couldn't sequence the genome of a single cell, and each mutation accumulated is unique to each cell."

Testing neurons one by one

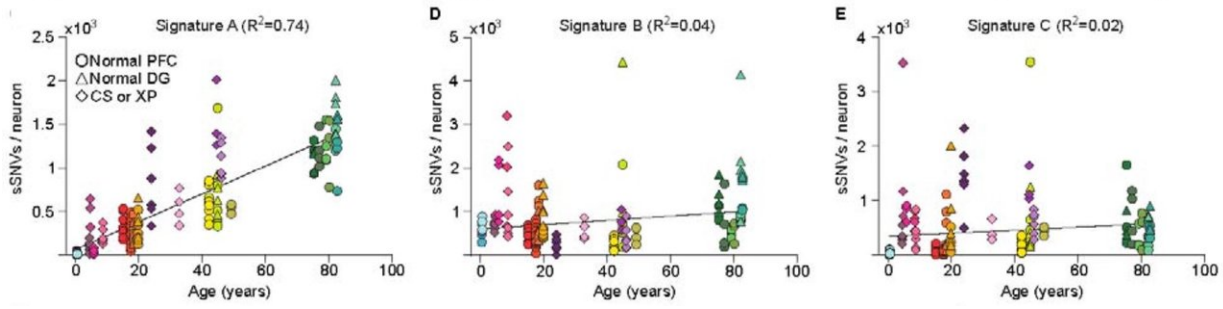
The research team tested DNA from 161 single neurons, taken from postmortem samples from the NIH NeuroBioBank. They came from 15 neurologically normal people of different ages (4 months to 82 years) and nine people with one of two accelerated aging and early-onset neurodegenerative disorders: Cockayne syndrome and xeroderma pigmentosum.

Using the latest experimental and data analysis techniques, the team was able to detect mutations as small as single-letter changes in each neuron's genetic code. Each cell had to have its genome amplified—by generating a multitude of copies—before its DNA sequence could be determined, and a large amount of data had to be analyzed.

"Because many experimental artifacts arise during the single-cell experiments, a new computational method that can distinguish true mutations from the experimental noise was critical to the success of the project," says Peter J. Park, PhD, of Harvard Medical School's Department of Biomedical Informatics (DBMI), the paper's other co-senior author.

The neurons tested came from two areas of the brain implicated in age-related cognitive decline: the prefrontal cortex (the part of the brain most highly developed in humans) and the dentate gyrus of the hippocampus (a focal point in age-related degenerative conditions like Alzheimer's).

In neurons from neurologically normal people, the number of genetic mutations increased with age in both brain areas. However, mutations accumulated at a higher rate in the dentate gyrus. The researchers think this may be because the neurons have the ability to divide, unlike their counterparts in the prefrontal cortex.



In these graphs, the number of mutations per neuron are grouped by age for each mutation category (similar ages are grouped by color). The circles represent individual neurons from the normal prefrontal cortex (PFC); triangles represent the normal dentate gyrus; diamonds denote neurons from people with neurodegenerative disease: Cockayne syndrome (CS) or xeroderma pigmentosa

(XP). Signature A strongly correlates with age, regardless of disease status or brain region, while Signatures B and C do not. Credit: Reprinted with permission from MA Lodato et al., *Science* Dec. 7, 2017, DOI: 10.1101/221960

In neurons from people with Cockayne syndrome and xeroderma pigmentosum, there was an increase in mutations in the prefrontal cortex over time—more than two-fold compared to the normal rate. Additionally, the researchers found that the portions of the genome that neurons used the most accumulated mutations at the highest rate, with help from collaborators at WuXi NextCODE.

The aging genome

The researchers coined the term "genosenium"—combining the concepts of genome and senescence/senility—to capture the idea of gradual and inevitable accumulation of mutations contributing to brain aging.

The mutations themselves fell into three categories. "We were able to take all the mutations we found and use mathematical techniques to deconstruct them into different types of DNA changes," says Michael Lodato, PhD, one of six co-first authors on the paper. "It's like hearing an orchestra and teasing out the different instruments."

One category of "clocklike" mutations was strictly aging-related, accumulating like clockwork in both brain areas, and independent of disease status. Another type did not correlate with age, except in the dentate gyrus, where mutation numbers in dividing neurons did increase over time.

A parallel with cancer?

The third type was associated with oxidative damage to DNA and faulty DNA repair; it increased with age and was seen in high numbers in Cockayne syndrome and xeroderma pigmentosum neurons, and to a lesser extent in normal neurons.

"This last finding convinced me I need more anti-oxidants," quips Walsh, who is also a Howard Hughes Medical Institute Investigator and the Bullard Professor of Pediatrics at Harvard Medical School. "Overall, it raises a question as to whether neurodegenerative diseases are like cancer, relating ultimately to DNA mutation."

The researchers are now turning their sights on other neurodegenerative disorders. "The technology we used can be applied to any degenerative disease of the brain," says Walsh.

More information: M.A. Lodato el al., "Aging and neurodegeneration are associated with increased mutations in single human neurons," *Science* (2017). science.sciencemag.org/lookup/ … 1126/science.aao4426

Provided by Children's Hospital Boston