Single-Cell Approaches Reveal Brain Cell Mutations During Aging, Development

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NEW YORK (GenomeWeb) – A pair of single-cell-based studies by independent research teams has documented genetic changes that arise in cells from developing and aging brains.

"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," Christopher Walsh, chief of the Boston Children's Hospital's genetic and genomics division, said in a statement.

For one of two papers published today in *Science*, Walsh and his colleagues used single-cell sequencing to look for somatic mutations in 161 individual neurons from the prefrontal cortex and a hippocampus area called the dentate gyrus, which has been implicated in Alzheimer's disease and other age-related degenerative conditions.

The cells came from post-mortem brain samples in neurologically healthy individuals across the age spectrum and in individuals with Cockayne syndrome or xeroderma pigmentosum (early-onset neurodegenerative conditions that involve DNA damage repair defects).

Using flow cytometry-based cell isolation, multiple displacement amplification, and single-cell whole-genome sequencing, the team analyzed 93 prefrontal cortex neurons from 15 neurologically healthy individuals between the ages of four months and 82 years old, along with 26 neurons from the dentate gyrus in half a dozen of these individuals. A similar single-cell sequencing strategy was used to assess 42 prefrontal cortex neurons from the neurodegenerative disease-afflicted individuals.

To deal with errors arising during the amplification and sequencing process, the team came up with the Linked-Read Analysis, or LiRA, informatics pipeline to weed out experimental "noise" and focus in on authentic somatic changes, co-senior author Peter Park, a biomedical informatics researcher at Harvard Medical School, explained in a statement.

The researchers saw single-nucleotide somatic mutations in both brain regions considered, though the alterations were roughly twice as common in the dentate gyrus than the more complex prefrontal cortex — at least in the neurologically healthy individuals. In the latter brain region, 40 somatic single-base variants

arose per year, on average, compared to 23 single-nucleotide variants appearing annually in the prefrontal cortex samples.

That pattern shifted in the individuals with early-onset neurodegenerative conditions. In samples from individuals with Cockayne syndrome, the team identified around 2.3 times as many somatic mutations in the prefrontal cortex, on average. Those with xeroderma pigmentosum had roughly 2.5 times as many prefrontal cortex somatic mutations as their neurologically healthy counterparts.

Of the three somatic mutation signatures they detected in the brain samples, the researchers attributed increases in one "clocklike" signature to aging. The remaining two signatures seemed to stem from development and oxidative DNA damage, respectively. The so-called signature B appeared to reflect rampant mutation in young individuals and showed some ties to age in the dentate gyrus.

The authors noted that the 300 to 900 or so somatic single nucleotide variants (sSNVs) appearing in neurons over the first year after birth seems to be "strikingly dovetailing with the 200-400 sSNVs estimated to be present in human progenitor cells at 20 weeks gestation or earlier."

The latter estimate came from a related study, also appearing online in *Science*. There, researchers from Yale University, the Mayo Clinic, and elsewhere used clonal cell populations established from individual brain cells to profile mutational patterns in forebrain samples from three human fetuses at 15 to 21 weeks post-conception. They sequenced clonal populations representing 31 individual cells from the frontal cortex, parietal cortex, or basal ganglia, along with spleen samples.

From variants observed in these samples and analyses done to adjust for false-positive mutations and the like, the team estimated that the brain cells contained between 200 and 400 single nucleotides apiece, on average, including some mutational signatures resembling those described in cancer genomic studies. And comparisons done across single-cell culture and spleen samples suggested that mosaic mutations frequently arise in the developing brain.

Based on these and other findings, Yale neuroscience researcher Flora Vaccarino and the Mayo Clinic's Alexej Abyzov, co-corresponding authors on that study, and their colleagues concluded that "the prenatal period is intrinsically highly mutagenic, likely the consequence of oxidative damage coupled with more frequent cell divisions."

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