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SDSC Resources, Expertise Used in Genomic Analysis of 115 Year-Old Woman

Sequencing of blood and brain samples reveals background of somatic mutations

A team of researchers investigating the genome of a healthy supercentenarian since 2011 has found many somatic mutations – permanent changes in cells other than reproductive ones – that arose during the woman's lifetime. Led by Erik Sistermans and Henne Holstege from the VU University Medical Center in Amsterdam, the team recently published its findings in the journal *Genome Research* as reported by *GenomeWeb*.

While previous studies have examined mutations that arise in certain disease conditions such as leukemia, Sistermans said that it was not well known how many mutations might appear in the genomes of healthy cells, according to the *GenomeWeb* report.

At the time of her death at the age of 115, the subject woman, called W115 by the researchers, was the second oldest person in the world and showed no signs of vascular disease or dementia. By donating her body to science, she allowed researchers to study her organs and genome.

The researchers hypothesized that white blood cells, which divide frequently, would have many more somatic mutations than brain cells, which seldom divide. Thus the whole genomes of W115's blood and brain cells were sequenced using SOLiD technology from Life Technologies. Analyses were then done to look for mutations present in the blood cells but not the brain cells.

These analyses involved numerous computations, some of which were done by Wayne Pfeiffer on the *Triton* cluster at the San Diego Supercomputer Center at the University of California, San Diego under a National Institutes of Health grant. Pfeiffer said that the initial analyses identified thousands of putative somatic mutations, many of which were incorrect because of sequencing errors. Filters were subsequently developed to select the mutations most likely to be somatic.

Two types of mutations were considered: single nucleotide variants (SNVs) and short insertions or deletions (indels). Filtering of the latter was particularly compute-intensive and was done at SDSC. Thousands of core hours were consumed, and some steps required more than 64 gigabytes of shared memory, according to Pfeiffer.

After filtering, many of the highly likely and moderately likely somatic mutations were tested by targeted sequencing using newer Ion PGM sequencers, also from Life Technologies.

Based on these validation tests, the researchers estimated that there were about 450 somatic mutations in the non-repetitive genome of the white blood cells studied, corresponding to an average of four mutations per year. These mutations, they noted, were not present in the breast cancer that W115 had at age 100 or in the gastric tumor she had at the time of her death. About 95% of the somatic mutations were SNVs rather than indels.

“Of 376 highly likely somatic SNVs, only four mapped to regions in genes that code for proteins, whereas most were in genomic regions predicted to have neither adverse nor favorable impact on genetic fitness,” said Pfeiffer. “The message here is that one can have lots of somatic mutations and still live long, provided the mutations do not affect genetic fitness.”

“It is important to note that white blood cells differ from most other cells in the body and are especially prone to acquiring somatic mutations,” said Mark A. Miller from SDSC, who helped interpret the results. “Large numbers of white blood cells are generated from relatively few hematopoietic stem cells. Because white blood cells divide continually throughout a person’s lifetime, it is possible for non-harmful somatic mutations to accumulate.”

“These mutations accumulate in clones that comprise only some of the white blood cells, which makes their detection more difficult,” explained Pfeiffer. “For W115, about 64% of the white blood cells comprised a dominant clone, which was where the mutations were found, while about 44% of the white blood cells were in a second clone subsidiary to the larger one. The remaining cells were presumably in smaller clones that were below our detection limit.”

The researchers concluded that there is a significant somatic mutation background among white blood cells, even in healthy blood.

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