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Genetic predisposition to disease common in two supercentenarians: study

January 3 2012

The first-ever published whole-genome sequences of not just one, but two supercentenarians, aged more than 114 years, reveal that both unusual and common genetic phenomena contribute to the genetic background of extreme human longevity.

Data from the study -- led by researchers from the Boston University Schools of Public Health and Medicine and Boston Medical Center -- will be available to researchers around the world at the NIH data repository.

In the study, published Jan. 3 in the open-access journal *Frontiers in Genetics*, researchers at BU, the University of Florida, Gainesville, and The Scripps Research Institute report a comprehensive analysis of the whole genome sequences of a man and a woman, both of whom lived past the age of 114. Supercentenarians (age 110+ years) are very rare, occurring at a rate of one person per five million in developed countries, and there is growing evidence supporting a strong genetic influence in survival to such ages.

The study, led by Paola Sebastiani, professor of biostatistics at the BU School of Public Health, shows that the overall genomic architecture of these two subjects is comparable to that of other published full genomes, in terms of rates of novel variants, functional variants, and variants that predispose to common age-related diseases and common cancers. But while the two carried as many disease-associated genes as the general population, their longevity suggests other protective mechanisms at

work.

For example, the male subject had 37 genetic mutations associated with increased risk for colon cancer -- indicating that he was in no way immune to that age-related disease. "In fact, he had presented with an obstructing colon cancer earlier in his life that had not metastasized and was cured with surgery. He was in phenomenal cognitive and physical shape near the time of his death," said Dr. Thomas Perls, director of the New England Centenarian Study and senior author of the article.

The female supercentenarian also had numerous genetic variations associated with age-related diseases, including those related to increased risks for Alzheimer's, cancer and heart disease. She did have congestive heart failure and mild cognitive impairment, but these diseases did not become evident until after the age of 108 years.

"The presence of these disease-associated variants is consistent with our and other researchers' findings that centenarians carry as many disease-associated genes as the general population," Perls said. "The difference may be that the centenarians likely have longevity-associated variants that cancel out the disease genes. That effect may extend to the point that the diseases don't occur -- or, if they do, are much less pathogenic or markedly delayed towards the end of life, in these individuals who are practically living to the limit of the human lifespan."

In support of this conjecture, Sebastiani and colleagues identified more than 50 putative longevity-associated variants in genes that determine two forms of progeria (an accelerated aging disease), and genes linked to cardiovascular disease and Alzheimer's disease. The authors highlighted the importance of performing follow-up studies to determine the impact and function of these genetic variants and their role in regulating health span, as well as life span.

The findings of the study suggest that unusual genetic phenomena and a combination of rare and common genetic variants contribute to the genetic background of extreme human longevity, the authors said.

"The study of these two supercentenarians is just the beginning, and genetic study of many more such subjects needs to be performed," said Perls. A number of such endeavors are underway, on a larger scale, including the Archon Genomics X Prize and a collaboration between Complete Genomics, Inc., The Scripps Translational Science Institute, and other institutions.

More information: www.frontiersin.org/Genetics_o …
.2011.00090/abstract

Provided by Boston University Medical Center

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