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Researchers identify genetic signatures of human exceptional longevity

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While environment and family history are factors in healthy aging, genetic variants play a critical and complex role in conferring exceptional longevity, according to a new study by a team of researchers from the Boston University Schools of Public Health and Medicine and the Boston Medical Center.

In a study released July 1 online by the journal *Science*, the research team identified a group of genetic variants that can predict exceptional longevity in humans with 77 percent accuracy - a breakthrough in understanding the role of genes in determining human lifespan.

Based upon the hypothesis that exceptionally old individuals are carriers of multiple genetic variants that influence their remarkable survival, the team conducted a genome-wide association study of centenarians. Centenarians are a model of healthy aging, as the onset of disability in these individuals is generally delayed until they are well into their mid-nineties.

Researchers led by Paola Sebastiani, PhD, a professor of biostatistics at the BU School of Public Health and Thomas Perls, MD, MPH, associate professor of medicine at the BU School of Medicine and a geriatrician at Boston Medical Center, built a unique genetic model that includes 150 genetic variants, known as single nucleotide polymorphisms (SNPs). They found that these 150 variants could be used to predict if a person survived to very old ages (late 90s and older) with a high rate of accuracy.

In addition, the team's analysis identified 19 genetic clusters or "genetic signatures" of exceptional longevity that characterized 90 percent of the centenarians studied. The different signatures correlated with differences in the prevalence and age-of-onset of diseases such as dementia and hypertension, and may help identify key subgroups of healthy aging, the authors said.

Notably, the team found that 45 percent of the oldest centenarians - those 110 years and older - had a genetic signature with the highest proportion of longevity-associated genetic variants.

"These genetic signatures are a new advance towards personalized genomics and predictive medicine, where this analytic method may prove to be generally useful in prevention and screening of numerous diseases, as well as the tailored uses of medications," said Dr. Perls, founder and director of the New England Centenarian Study.

The researchers developed a novel Bayesian statistical approach to analyze genotype data from more than 1,000 centenarians and several control groups, and to identify those SNPs that were most predictive of being centenarians or controls. The team began by using the SNPs that were most likely associated with exceptional longevity, and once the researchers identified 150 SNPs, they found that adding more variants did not further improve the ability to predict whether a person was a centenarian or a control subject.

Dr. Sebastiani noted: "The methodology that we developed can be applied to other complex genetic traits, including Alzheimer's disease, Parkinson's, cardiovascular disease and diabetes. It reinvigorates the potential high utility of collecting and analyzing such data."

Besides looking at which genetic variants were associated with longevity, the authors looked into whether the absence of disease-associated

variants also played an important role. They did this by analyzing how many disease-associated variants each centenarian had, compared to each of the controls. Their analysis found little difference between the two groups, suggesting that the presence of genetic variants associated with longevity is of more importance than the absence of disease-associated variants.

If these findings are confirmed, they would suggest that "predicting disease risk using disease-associated variants may be inaccurate and potentially misleading, without more information about other genetic variants that could attenuate such risk" the authors commented.

Overall, the authors said, their preliminary data "suggest that exceptional longevity may be the result of an enrichment of longevity-associated variants that counter the effect of disease-associated variants and contribute to the compression of morbidity and/or disability towards the end of these very long lives." They added that "further investigation is needed to understand how and why these variants collectively predispose for exceptional longevity."

The researchers noted that the 77-percent accuracy rate of predictions "shows that genetic data can indeed predict exceptional longevity without knowledge of any other risk factor."

But they added: "This prediction is not perfect, however, and although it may improve with better knowledge of the variations in the human genome, its limitations confirm that environmental factors (e.g., lifestyle) also contribute in important ways to the ability of humans to survive to very old ages."

Drs. Sebastiani and Perls also cautioned that they developed this genetic risk model as a way to dissect the complex genetic bases of exceptional longevity and to discover the different genetic paths to age 100 and

older. An understanding of the implications of this model's use in the general population would be necessary before this test is marketed, they said.

The study was funded by grants from the National Institute of Aging (NIA) and the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH).

"This is a novel approach to studying genetic contributions to exceptional longevity," said Winifred K. Rossi, deputy director of the NIA's Division of Geriatrics and Clinical Gerontology. "It adds to a growing set of analytical tools that aim to identify and understand the complex genetic and environmental factors that lead to healthy long life."

More information: "Genetic Signatures of Exceptional Longevity in Humans," *Science*.

Provided by Boston University Medical Center