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Longevity scores show signs of resilience to certain diseases

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Using data from four studies that connect genetic variants to lifespan, scientists have developed 11 different polygenic longevity scores (PLS) that predict both long life and resilience to some age-related conditions

such as Alzheimer's disease and heart disease.

The researchers, led by scientists from the Translational Genomics Research Institute (TGen), part of City of Hope, constructed the scores and tested them with genome data collected by UK BioBank, which represents around 480,000 people from the United Kingdom who were between the ages of 40 and 69 at the time the BioBank study was underway.

In their report published in *GeroScience*, TGen researchers Janith Don, Ph.D. and Nicholas Schork, Ph.D. and their colleagues found that the PLS were strongly associated with the lifespan of the parents of the UK BioBank individuals. They calculate that the average lifespan of people with the highest PLS was 0.31 to 1.98 years longer than those with the lowest PLS scores.

The scientists also discovered that the higher a person's PLS score, the less likely they were to be at risk for non-cancerous diseases such Alzheimer's, coronary artery disease, heart attack, diabetes and even COVID-19.

The PLS scores did not predict a resilience to any of the cancers the researchers studied, most likely because cancer has a strong random component, said Schork, TGen Deputy Director and Distinguished Professor of Quantitative Medicine. "Aspects of cancer have less to do with the environment, less to do with inheritance, and more to do with bad luck."

"We think these polygenic longevity scores are associated with longer life, and longer healthier life, not because they reflect resilience to every disease out there, but resilience to enough diseases to affect the average lifespan and health span of the people who have these high scores," he added.

The increasing number of genome-wide association studies (GWAS), which look for genetic variants related to a certain trait or disease across hundreds or thousands of genomes, has led to the creation of polygenic risk scores (PRS). PRS are built from summing up the risk of disease-related variants in the GWAS.

The TGen researchers decided to "turn this idea on its head," Schork said, and instead construct scores that sum up the "risk" of long life, based on GWAS that examined genetic variants related to longevity.

The four GWAS studies used in developing the 11 PLS scores "don't all have the same variants, but there is some overlap," said Don, a TGen postdoctoral fellow, who noted that the definition of "long-lived" individuals in the GWAS studies ranged from people in their 90s to "super-centenarians" living past 100 years old.

No matter what definition of longevity was used, the researchers said, the PLS scores they created "all seemed to correspond or replicate with the [BioBank] dataset," Don said.

The scores "reflect health and lifespan in such a strong way that we also see it reflected in the lifespan of their parents," Schork added, "which is a step removed from looking at it in the BioBank participants themselves."

Schork, Don and colleagues are now looking more closely at the genetic variants that make up the PLS, to discover how they might be protective against some diseases. "The genes that are causing susceptibility or causing a propensity to live a long time are doing something fundamental," said Schork, "and we want to find out what that is."

For instance, the PLS might be able to aid Schork and TGen researchers working as part of the national Precision Aging Network (PAN) to better

predict who is resilient to cognitive decline, with the ultimate goal of developing more effective treatments and interventions targeted to individuals.

More information: Janith Don et al, The relationship between 11 different polygenic longevity scores, parental lifespan, and disease diagnosis in the UK Biobank, *GeroScience* (2024). DOI: 10.1007/s11357-024-01107-1

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