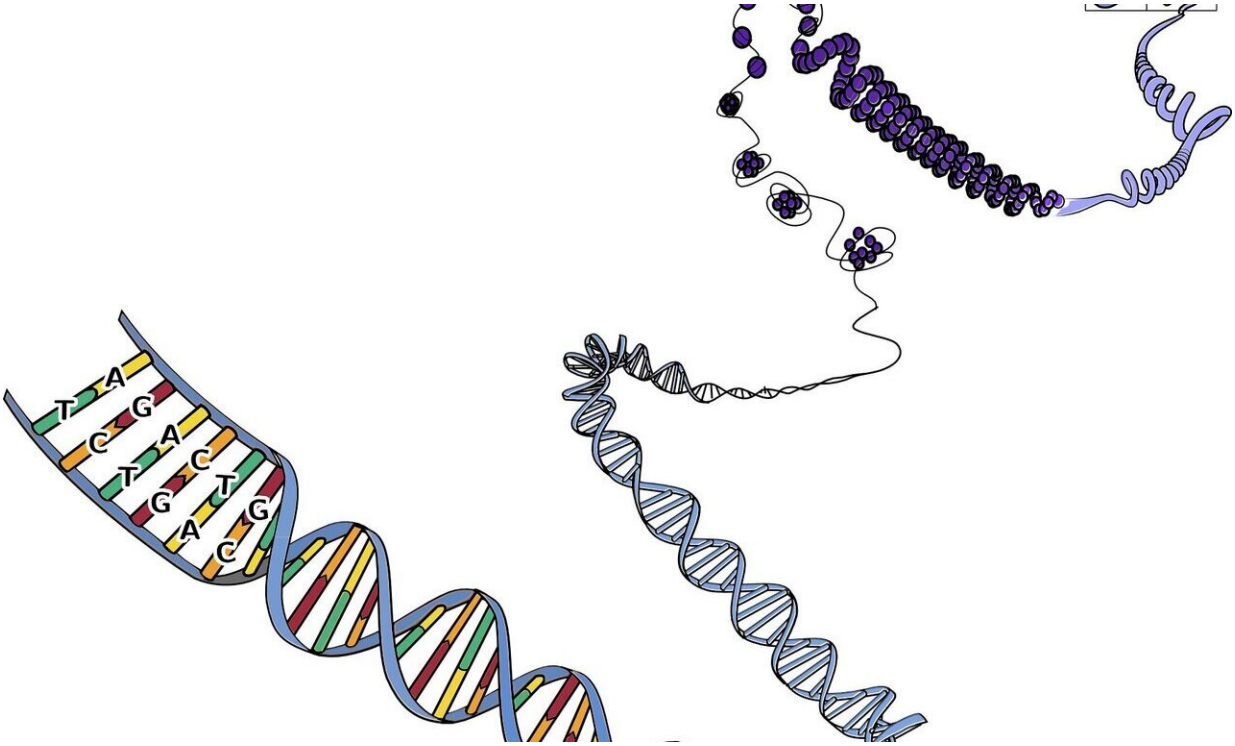
Rare, damaging inherited mutations work together to reduce lifespan

April 9 2020



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Scientists report that the combined effects of rare, damaging mutations present at birth have a negative impact on healthspan and longevity, according to a study published this week in *eLife*.

The findings suggest one additional inherited damaging mutation could

carve off six months of life, and combinations of these rare mutations determine how soon someone will develop diseases such as cancer, heart disease and dementia.

Most of the genetic variants linked to lifespan that researchers currently know about have been found in people who live long, such as centenarians who live to 100 or older. The variants responsible for survival of the rest of the population remain poorly understood.

Now, researchers have proposed that the remaining variance that contributes to lifespan could be attributed to the combination of very rare but highly damaging mutations that are present in every person's genome. "The role of ultra-rare damaging mutations that decrease lifespan and healthspan has been largely overlooked," says co-senior author Vadim Gladyshev, Professor at Brigham and Women's Hospital and Harvard Medical School, Boston, US. "They are different in different people, but in combination, they exhibit an unexpectedly large effect on lifespan."

"Until recently, only common gene variants could be probed in genetic studies due to a small number of participants," explains co-first author Anastasia Shindyapina, a postdoctoral researcher at Brigham and Women's Hospital, Harvard Medical School. "However, large datasets that sequenced tens of thousands of people now allow us to assess the effects of DNA variation that appear in less than one out of 10,000 subjects."

Ultra-rare protein-truncating variants (PTVs) are known to be some of the most damaging genetic variants. These tend to have a larger impact than more common genetic variants, and can dramatically change the amount and function of important proteins in the body. Increased frequency of PTVs has been linked to complex diseases such as schizophrenia, epilepsy and autism. In this study, Shindyapina, along

with co-first author Aleksandr Zenin, researcher at Gero, Singapore, and their colleagues set out to learn how the number of PTVs a person is born with influences their lifespan. They also wanted to see whether accumulating additional PTVs throughout life can affect overall health and length of survival.

The team analysed genomic data from more than 40,000 people registered in the UK Biobank who on average were in their mid-fifties. They compared the individual 'burden' of PTVs (the total number of PTVs per each person's genome) with their lifespan and their 'healthspan': the time taken to develop complex diseases including cancer, heart disease, chronic obstructive pulmonary disease, stroke and dementia.

The team found that people who had a high burden of ultra-rare PTVs had a shorter healthspan and lifespan. Each additional ultra-rare PTV in a person's genome accounted for a reduction in lifespan of six months and a reduction in healthspan of two months.

In addition to the genetic variants we are born with, we accumulate more as we age. The research predicted that the natural accumulation of PTVs increases proportionally with age but their effects are likely to be minor compared with the effects of PTVs we are born with. "This implies that the genetic variation we accumulate throughout life only accounts for a small fraction of the increased risk of disease and death that we all face as we grow older, if our theoretical calculations are correct," explains author Andrei Tarkhov, researcher at Gero and Ph.D. student at Skolkovo Institute of Science and Technology, Moscow, Russia.

"Our finding that accumulated mutations during a lifetime do not accelerate disease or death contradicts previous hypotheses," adds co-senior author Peter Fedichev, Principal Investigator at Gero. "Together our results illustrate the surprising role of rare mutations previously

inaccessible for genetic studies in the aging process. They also demonstrate the power of whole exome and genome sequencing to uncover the genetic architecture of complex diseases in the interest of developing future therapeutics."

More information: Anastasia V Shindyapina et al, Germline burden of rare damaging variants negatively affects human healthspan and lifespan, *eLife* (2020). DOI: 10.7554/eLife.53449

Provided by eLife