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What genetics teaches us about living a long and healthy life

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Studying the genetic information of exceptionally long-lived people may allow us to uncover the secret of their healthy ageing. Combining data from large genetic studies across different longevity-related features, we discover new genomic regions that may play a key role in a long and healthy life.

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Why do some people live a long and healthy life, while others suffer from age-related diseases? We know that this difference is usually explained by chance or environmental factors, such as diet and living conditions. But that's not all! We should also consider another important asset — our genes, popularly thought of as the "recipes for life". The genome — the entire set of all genes — shapes who you are because it is unique to each of us.

Finding out how genetic variation influences the ageing process is not straightforward. We and others have previously studied various features related to ageing, such as the number of years someone's parent(s) lived (parental lifespan), the number of years someone has lived without any disease (healthspan), and whether someone reached an exceptional old age (longevity). Longevity is perhaps the most attractive to study, as we all want to understand the secret of living to an exceptional old age. However, genetic studies of longevity are limited by the low availability of samples from exceptionally long-lived people. Consistently, only a handful of genetic variants have been discovered to influence longevity. On the other hand, genetic studies on parental lifespan and healthspan can be performed in many more individuals and have identified dozens of genetic variants. However, most of these variants — which likely influence behavioural risk factors such as smoking and drinking — do not show a strong relationship with longevity.

To develop a more comprehensive way to link genetic variation with ageing, we wondered if we could combine data from the largest genetic study of longevity with data from genetic studies on parental lifespan and healthspan. We found a strong correlation between these three ageing features at the genetic level, indicating that genes that increase healthspan — especially genes associated with cardiovascular disease and type 2 diabetes — are likely also helping people to live longer and reach an exceptional old age. Pooling data from the three ageing features could therefore reveal new, shared genes affecting ageing and diseases of old age. But, not all identified genes were equally associated with the three ageing features. For example, healthspan genes correlated more strongly with skin cancer, and longevity genes showed a stronger link with Alzheimer's disease. In other words, the three ageing features capture distinct and overlapping aspects of the ageing process.

After combining all these data, we estimated that the resulting dataset could be equivalent to studying more than 60,000 long-lived individuals, more than five times bigger than the largest genetic study on longevity to date.

With these comprehensive datasets, we set out to find regions in the genome, which can affect both how long and healthy we live. We identified ten genomic regions linked to all three ageing features, where people carrying the beneficial genetic variants appeared to live longer and healthier, reaching an exceptional old age. These genomic regions influence the function of many genes, including genes that decline as we age and those that likely affect lifespan.

Each individual genetic variant only has a small effect — altering at most a couple of months of healthy life. However, when looking at all the ageing-related genes, we were able to see whether certain biological processes are especially important to living a long and healthy life. We discovered one biological pathway previously unknown to influence ageing: haem metabolism. Haem is an iron-containing biomolecule that forms part of haemoglobin, the oxygen transporter that makes blood red. Whilst it is known that a deficit in iron can cause anaemia and consequential tiredness and poor health, we found that, for most people in our data, a modest reduction in iron from their present levels was beneficial to health. Moreover, we found additional processes likely influencing healthy ageing, such as control of hypoxia (inadequate circulation of oxygen to organs).

Based on our results, combining genetic data from studies of distinct ageing features can help us find genetic variants influencing healthy ageing. We showed that the identified variants influence the vulnerability to ageing (e.g. haem metabolism), disease (e.g. cardiovascular disease) and lifestyle choices (e.g. smoking), all in turn affecting how long we live. Future work should consider findings from studies of both humans and other animals to identify mechanisms leading to healthy ageing, which will allow developing new drugs and guidelines for a healthier lifestyle. Perhaps one day soon, we will get answers to one of life's most crucial questions — what decides the length of our life.