GENETICS

Unravelling genetic components of longevity

Many aging-related traits share a common genetic component. How to disentangle it from trait-specific effects has remained largely unexplored. A new study in *Nature Aging* uses an analysis framework for isolating the shared genetic component in GWAS of aging-related traits, and identifies genomic loci that contribute to longevity.

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The commonality of biological processes underlying the development of chronic diseases with age was initially introduced by the 'geoscience hypothesis'[1] and is largely in line with the observed pattern of genetic correlation among age-related traits[2]. Thanks to widespread pleiotropy across the human genome (whereby a single genomic locus affects multiple traits), the genetic architecture of many aging-related traits (ARTs) inevitably overlaps. Indeed, many genome-wide association study (GWAS) signals identified for chronic diseases are also associated with other ARTs, implying a shared genetic architecture. Disentangling the shared genetic component from disease-specific components of aging-related phenotypes should reveal biological mechanisms underlying aging and is important for the development of therapeutic interventions. However, to study the genetics of aging requires very large sample sizes or analysis methods that maximize power. In this issue of *Nature Aging*, Timmers et al.[3] address this problem by using an analysis framework that leverages the genetic covariance structure among six ARTs to uncover genomic loci that contribute to aging.

In a highly correlated aging-related genetic structure, if we presume that the total variance in the system (for example, variance in lifespan) is fully approximated by the shared latent heritable component (that is, commonality of variance), then decomposing the covariance structure to the constituent principal components theoretically offers a suitable solution for the identification of the shared genetic mechanism underlying ARTs. Following this rationale, Timmers et al.[3] combined GWAS of longevity, maternal lifespan, paternal lifespan, healthspan, frailty and self-rated health. They generated six genetically independent phenotypes (GIPs) that capture the genetic covariance between ARTs while being genetically uncorrelated to one another (Fig. 1). Here, the rationale is that each independent GIP captures a distinct element of wellbeing that is exclusively attributable to the shared genetic component approximated by that GIP and is unaccounted for by other GIPs. When ARTs covary substantially with each other, the first component captures the majority of variance, rendering the subsequent components less informative. As expected, the aging GIP1 explains a large portion (about 90%) of variance in the genetics of self-rated health and resilience to frailty, and accounts for over 70% variation in the genetics of healthspan, parental lifespan and longevity. The aging GIP1 also revealed an interesting pattern of genetic correlation with additional traits (Fig. 1). For example,

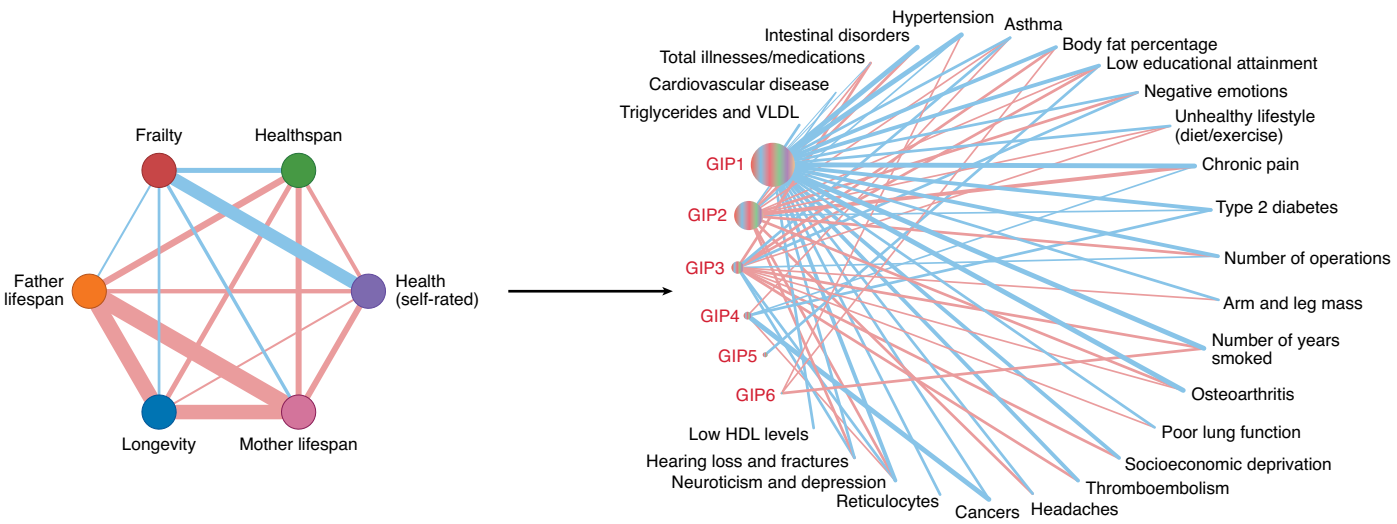

Fig. 1 | Genetically independent phenotypes of aging. The genetic architecture underlying the six aging traits (longevity, maternal lifespan, paternal lifespan, healthspan, frailty and self-rated health) significantly overlaps. The genetic correlation arising from the pleiotropic loci among these traits can be decomposed to construct genetically independent phenotypes (GIPs) that capture the shared genetic component of longevity. Being the most heritable (as indicated by its node size), GIP1 negatively correlates with the 25 groups of phenotypes and traits that are known to be associated with decreased lifespan. Red and blue lines represent positive and negative genetic correlations (r_g), respectively, and line thickness is proportional to the r_g absolute value. HDL, high density lipoprotein; VLDL, very low density lipoprotein.

traits associated with reduced fitness — including late-onset chronic disorders (that is, cardiometabolic disorders, osteoarthritis and cancers), psychological illness and the medication-taking trait — were all negatively correlated with the aging GIP1, while traits such as physical fitness and education were positively correlated with the aging GIP1.

Using the weighted GWAS summary statistic from the aging GIP1, Timmers et al.[3] characterized the shared genetic component underlying lifelong mental and physical health, and collectively identified 27 significant association signals, out of which 24 variants were also associated with other cardiometabolic, immune-related and neuropsychiatric disorders. Intriguingly, variants mapped to loci near *APOE*, *HLA-DRB1*, *HLA-DQA1*, *CDKN2B*, *CDKN2B-AS1*, *ZNF652* and *PHB1* seem to protect against multiple diseases without being pleiotropically associated with socioeconomic factors, including educational attainment and household income. They concluded that these loci largely capture the intrinsic biological source of longevity shared by the six original traits. Finally, using a gene-based scoring method, they aggregated the summary statistics across the genome and carried out a gene-network enrichment analysis. The high-scoring genes were overrepresented in the heme metabolism pathway. In addition, using an approach comparable to a recent cross-population study of genetic associations of multiple human phenotypes[4], their partitioned heritability analysis revealed that a great extent of the aging GIP1 heritability is attributable to the functional part of the genome related to histone imprints in the central nervous system.

If GIP1-derived association signals largely tag the shared genetic component of longevity, then it is important to identify the proteomic signatures of longevity from the GWAS signals for aging GIP1. Timmers et al.[3] used Mendelian randomization to test the causal relationship between the blood serum levels of 857 proteins and the aging GIP1. Among the proteins tested, apolipoprotein a (LPA) and vascular cell adhesion molecule 1 (VCAM1) were identified to be causally linked to the aging GIP1. One unit of increase in the standard deviation of LPA translates to a 3.5% decrease in the scaled aging GIP1 variation or, contextually, seven months of shorter lifespan.

While constructing GIPs is a conceptually interesting development in the analysis of ARTs, the reliance on the aggregate signals from multiple GWAS sources could make the method sensitive to population microstructure. GWAS essentially test for allele-frequency differences between the cases and controls and, in doing so, hold some assumptions, including the normal distribution of the genetic and environmental effects in the population. Therefore, the effect sizes of single-nucleotide polymorphisms are inevitably the sum of the true genetic effect and the environmental contribution arising from the correlation of environmental variables with ancestry[5]. The problem arises when the distribution of the environmental confounder is not normal in the population (for example, when the environmental effect is sharply localized in a specific geographical region or correlated with birth cohort). In that situation, the inflation of the test statistic is primarily due to the association of rare variants with nongenetic risk[6]. This source of systemic bias usually remains uncorrected by common methods for population stratification adjustment[7]. Here, educational attainment and its mediated socioeconomic factors are instances of traits that show strong geographical clustering in the UK Biobank population[8,9]. The six traits used to construct the GIPs are all correlated with measures of social deprivation, and the related effect sizes came from GWAS using the UK Biobank population, either entirely or combined with other populations. While Timmers et al.[3] appreciated the strong and significant correlation between GIPs and household income, and tried to correct for that by removing genetic correlations with the GWAS of household income and socioeconomic deprivation, the extent of this confounding appears to remain appreciable.

Their suggestion of the role of the heme metabolism pathway in longevity is particularly noteworthy in light of recent evidence for the mechanistic interaction of metformin with heme function[10]. Recently, metformin was found to directly target heme-containing proteins (including hemoglobin in erythrocytes and myoglobin in structural muscles) and stabilize the redox state of key electron transport chain proteins in the mitochondria[10]. Metformin also suppresses heme content inside the cells and protects heme from oxidative loss, which in turn helps to maintain glucose consumption in erythrocytes[10]. The implication of heme metabolism pathway in human aging was previously reported by the same group using a different — but closely related — analytical framework for joint-analysis of healthspan, lifespan and longevity[11]. Iron retention has been suggested as an adaptive response to the dietary shift from hunting and gathering to an iron-deficient diet during the Neolithic period in Europe[12]. If the effect of heme metabolism on longevity is mediated through the bioavailability of iron (as previously hypothesized by Timmers et al.[11]), then it is likely that its effect is mediated through an antagonistic pleiotropy mechanism in which higher retention of iron is detrimental for longevity. Whether the core component of longevity can be targeted through heme metabolism needs further study.

In summary, Timmers et al.[3] present an exciting methodological approach for analyzing the shared genetic component underlying resilience to aging. Our understanding of pleiotropic effects among ARTs is advancing, and further development in polygenic modelling of ARTs will soon transform our understanding of the shared biological mechanisms underlying senescence and longevity. ❐

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References

1. Kennedy, B. K. et al. *Cell* **159**, 709–713 (2014).
2. Melzer, D., Pilling, L. C. & Ferrucci, L. *Nat. Rev. Genet.* **21**, 88–101 (2020).
3. Timmers, P. R. H. J. et al. *Nat. Aging* https://doi.org/10.1038/s43587-021-00159-8 (2022).
4. Sakaue, S. et al. *Nat. Genet.* **53**, 1415–1424 (2021).
5. Sella, G. & Barton, N. H. *Annu. Rev. Genomics Hum. Genet.* **20**, 461–493 (2019).
6. Mathieson, I. & McVean, G. *Nat. Genet.* **44**, 243–246 (2012).
7. Zaidi, A. A. & Mathieson, I. *eLife* **9**, e61548 (2020).
8. Abdellaoui, A. et al. *Nat. Hum. Behav.* **3**, 1332–1342 (2019).
9. Haworth, S. et al. *Nat. Commun.* **10**, 333 (2019).
10. Li, X., Wang, X. & Snyder, M. P. *G3* **9**, 513–522 (2019).
11. Timmers, P. R. H. J., Wilson, J. F., Joshi, P. K. & Deelen, J. *Nat. Commun.* **11**, 3570 (2020).
12. Heath, K. M., Axton, J. H., McCullough, J. M. & Harris, N. *Am. J. Phys. Anthropol.* **160**, 86–101 (2016).

Competing interests

The authors declare no competing interests.