DOI 10.18699/SBB-2022-646

Novel multivariate approach identifies LPA and VCAM1 as drug targets for human ageing

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Key words: GWAS, ageing, frailty, healthspan, lifespan, longevity, Mendelian randomisation

Motivation and Aim: The length and quality of life is important to us all, yet identification of promising drug targets for human ageing using genetics has had limited success. Quantifying the aging process is not straightforward. A variety of aging-related phenotypes has been studied as proxies, from chronological measurements such as the length of time from birth until the occurrence of a major disease (healthspan) or death (lifespan), to cellular deterioration measurements and holistic measurements. The benefit of combining GWASs of several aging phenotypes, especially in different populations, is the ability to detect biological mechanisms that influence multiple core components of aging. In the present study we characterize the common genetic aging phenotype, identify robust genomic loci and highlight proteins that may be potential drug targets for improving the length and quality of life. Replication was performed using a study of Finnish and Japanese subject survival.

Methods and Algorithms: We combine six large European-ancestry genome-wide association studies (GWAS) of human ageing traits – healthspan, father and mother lifespan, exceptional longevity, frailty index, and self-rated health – in a principal component framework that maximises their shared genetic architecture.

Results: The first principal component (GIP1) is more heritable than the original studies and shows strong genetic correlations with length of life as well as multiple indices of mental and physical wellbeing. We identify 27 genomic regions associated with GIP1, and provide additional, independent evidence for an effect on human ageing for loci near *HTT* and *MAML3*. Across the genome, GIP1 associations are enriched in genes involved in haem metabolism and pathways related to transcription, neurogenesis, homeostasis, proteolysis, intracellular signalling, immunity, and the muscle system. Finally, using proteome-wide two-sample Mendelian randomisation and colocalisation, we provide robust evidence for a detrimental effect of blood levels of apolipoprotein(a) (LPA) and vascular cell adhesion molecule 1 (VCAM1) on GIP1.

Conclusion: Our results demonstrate that combining multiple ageing traits using genetic principal components enhances power to detect biological targets for human ageing.

Acknowledgements: This study was supported by the Russian Ministry of Education and Science under the 5-100 Excellence Programme and by the budget project No. FWNR-2022-0020.