Computational and Structural Biotechnology Journal 20 (2022) 4251–4256

COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL

journal homepage: www.elsevier.com/locate/csbj

Genetically predicted telomere length and its relationship with neurodegenerative diseases and life expectancy

Blanca Rodríguez-Fernández [a], Juan Domingo Gispert [a,b,c,d], Roderic Guigo [e,f], Arcadi Navarro [a,e,f,g,h], Natalia Vilor-Tejedor [a,e,f,i,*,1,2], Marta Crous-Bou [a,j,k,*,1,3]

[a] Barcelonaβeta Brain Research Center – Pasqual Maragall Foundation, Barcelona, Spain
[b] IMIM – Hospital del Mar Medical Research Institute, Barcelona, Spain
[c] Centro de Investigación Biomédica en Red Bioingeniería, Biomateriales y Nanomedicina, Madrid, Spain
[d] Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain
[e] Centre for Genomic Regulation (CRG), The Barcelona Institute for Science and Technology, Barcelona, Spain
[f] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[g] Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Catalonia, Spain
[h] Institute of Evolutionary Biology (CSIC-UPF), Department of Medicine and Life Sciences, Universitat Pompeu Fabra, Spain
[i] Erasmus University Medical Center, Department of Clinical Genetics, Rotterdam, the Netherlands
[j] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[k] Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO)-Bellvitge Biomedical Research Center (IDIBELL), Hospitalet del Llobregat, Spain

ARTICLE INFO

Article history:
Received 8 March 2022
Received in revised form 3 August 2022
Accepted 3 August 2022
Available online 06 August 2022

Keywords:
Alzheimer's disease
Life expectancy
Mendelian randomization
Neurodegenerative diseases
Telomere length

ABSTRACT

Telomere length (TL) is a biomarker of biological aging. Shorter telomeres have been associated with mortality and increased rates of age-related diseases. However, observational studies are unable to conclude whether TL is causally associated with those outcomes. Mendelian randomization (MR) was developed for assessing causality using genetic variants in epidemiological research. The objective of this study was to test the potential causal role of TL in neurodegenerative disorders and life expectancy through MR analysis. Summary level data were extracted from the most recent genome-wide association studies for TL, Alzheimer's disease (AD), Parkinson's disease, Frontotemporal dementia, Amyotrophic Lateral Sclerosis, Progressive Supranuclear Palsy and life expectancy. MR estimates revealed that longer telomeres inferred a protective effect on risk of AD (OR = 0.964; adjusted p-value = 0.039). Moreover, longer telomeres were significantly associated with increased life expectancy (β_{IVW} = 0.011; adjusted p-value = 0.039). Sensitivity analyses suggested evidence for directional pleiotropy in AD analyses. Our results showed that genetically predicted longer TL may increase life expectancy and play a protective causal effect on AD. We did not observe significant causal relationships between longer TL and other neurodegenerative diseases. This suggests that the involvement of TL on specific biological mechanisms might differ between AD and life expectancy, with respect to that in other neurodegenerative diseases. Moreover, the presence of pleiotropy may reflect the complex interplay between TL homeostasis and AD pathophysiology. Further observational studies are needed to confirm these results.

Abbreviations: **AD**, Alzheimer's disease; **ALS**, Amyotrophic lateral sclerosis; **CI**, Confidence Interval; **FTD**, Frontotemporal dementia; **GWAS**, Genome-wide association study; **IV**, Instrumental Variable; **IVW**, Inverse-Variance Weighted; **LRRC34**, Leucine Rich Repeat Containing 34; **MR**, Mendelian Randomization; **MR-PRESSO**, MR-Pleiotropy RESidual Sum and Outlier; **OR**, Odds ratio; **PD**, Parkinson's disease; **PSP**, Progressive Supranuclear Palsy; **SE**, Standard Error; **SNP**, Single Nucleotide Polymorphism; **TL**, Telomere length.

* Corresponding authors at: Catalan Institute of Oncology, Avda. Gran Via de l'Hospitalet 199-203, 08908 l'Hospitalet de Llobregat, Barcelona, Spain (Marta Crous-Bou), BarcelonaBeta Brain Research Center (BBRC), Pasqual Maragall Foundation. C. Wellington 30, 08005 Barcelona, Spain (Natalia Vilor-Tejedor).
E-mail addresses: nvilor@barcelonabeta.org (N. Vilor-Tejedor), marta.crous@iconcologia.net (M. Crous-Bou).
[1] These authors contributed equally to this work.
[2] ORCID: 0000-0003-4935-6721.
[3] ORCID: 0000-0003-1493-4288.

https://doi.org/10.1016/j.csbj.2022.08.006

1. Introduction

Aging is a major risk factor for most neurodegenerative diseases [1]. As life expectancy rises worldwide [2], the prevalence of neurodegenerative diseases also increases [3,4]. Numerous studies speculated that neurodegenerative diseases are expressions of accelerated biological aging [1]. Traditionally, chronological age has been used as a proxy to estimate the gradual physiological deterioration that all living beings experience with time [5,6]. However, chronological age is an imperfect measure of biological aging, which is the true cause of morbidity and disability [7].

Telomere length (TL) is a well-known hallmark of biological aging [8], being telomere shortening associated with age-related diseases [9,10]. For instance, shorter telomeres have been found in Alzheimer's disease (AD) patients [11,12], and it has been proposed as a valuable predictor of the AD incidence [13]. Nevertheless, its association with other neurodegenerative diseases and age-related processes remains unclear. At these crossroads, observational studies fail to discern whether aging-related changes in the brain are harbingers or mere consequences of neurodegeneration [14]. Mendelian Randomization (MR) approaches were developed to assess causality in observational studies. MR approaches use genetic instrumental variables (IVs) (i.e., Single Nucleotide Polymorphisms, SNPs) whose estimation of the exposure of interest (i.e., TL) is not influenced by confounding or reverse causation [15,16]. Previous MR studies have described potential causal effects of genetically predicted TL on the risk of AD [17–20]. However, other MR studies failed to provide evidence of causal associations between TL and the risk of Parkinson's disease (PD) [21] or Amyotrophic lateral sclerosis (ALS) [22].

The aim of this study was to assess the existence of common biological aging mechanisms (through telomere biology) to several neurodegenerative diseases and life expectancy. We perform multiple independent two-sample MR analyses to evaluate whether TL may play a causal role in the risk of neurodegenerative diseases and life expectancy by using instrumental variables from recent genome-wide association studies (GWAS).

2. Methods

2.1. Genetic instrumental variables of telomere length

Summary statistics from a genome-wide *meta*-analysis of leukocyte TL across large-scale European-descent studies including up to 78,592 individuals were obtained from [23]. We selected summary data (i.e., allele frequency, beta value, standard error, and p-values) for 21 SNPs genome-wide associated with leukocyte TL (p-value $< 5 \times 10^{-8}$) (Supplementary Table S1). Further details of the GWAS can be found in Supplementary Table S2.

2.2. Genome-wide association study data for neurodegenerative conditions

We used summary-level data from the most recent large-scale GWAS on five neurodegenerative diseases: AD (N = 455,258) [24], Parkinson's disease (PD) (N = 1,437,688) [25], Frontotemporal dementia (FTD) (N = 6,462) [26], Amyotrophic lateral sclerosis (ALS) (N = 36,052) [27] and Progressive Supranuclear Palsy (PSP) (N = 12,308) [28]. Further details of the GWASs can be found in Supplementary Table S2. To reduce potential bias from population stratification, we only drew on summary-level data from European-descent individuals. Proxies for the genetic instrumental missing variables were included when possible through LDlink [29] (Supplementary Table S3).

2.3. Genome-wide association study data for life expectancy

For life expectancy, we used summary-level data from a GWAS using age at death of parents of middle-aged UK Biobank participants of European descent (N = 45,627 with age at death data for both parents, excluding early deaths) [30]. Further details can be found in Supplementary Table S2.

2.4. Statistical analysis

Alleles were harmonized to take as reference the effect allele associated with longer TL. In this study, we used Inverse-Variance Weighted (IVW) [31], MR-Egger regression [32], weighted median [33] and maximum likelihood [34] methods with summarized data to estimate the causal effect of genetically predicted longer TL on the outcomes of the study. MR-Egger regression intercept-test [32], leave-one-SNP-out and Cochran Q statistic [35] were used as *ad hoc* sensitivity analysis for evaluating the robustness of significant results. MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) was also used to identify horizontal pleiotropic outliers [36]. Effect sizes were reported in Odds Ratio (OR) for all the pathologies and the SD change in life expectancy (β_{IVW}) per copy of the allele associated with longer telomere length. False Discovery Rate corrections for multiple comparisons were performed at significant level 0.05. MR-Egger regression intercept-test was used as *ad hoc* sensitivity analysis for evaluating directional pleiotropy [37]. P-values for intercept terms below 0.05 were indicators of pleiotropy. All analyses were conducted under R software, version 4.1.0 [38]. MR analyses were performed using the MendelianRandomization package in R [39]. Further details about the statistical procedure can be found in Supplementary Methods.

3. Results

IVW estimates revealed that longer TL inferred a protective effect on risk of AD (OR_{IVW} = 0.964; q-value = 0.039) (Table 1; Fig. 1). Maximum likelihood, MR-Egger regression, weighted median and weighted mode methods suggested similar protective effects. MR-Egger intercept test provided evidence for directional pleiotropy in AD analyses (p-value = 0.021). Nevertheless, there was no sign of increased heterogeneity according to both Cochran Q and MR-PRESSO (Table 1). IVW leave-one-out analysis showed MR estimates did not fluctuate after sequentially removing each of the 21 SNPs used as IVs (Supplementary Figure S1). No statistically significant associations were identified between genetically predicted longer TL and other neurodegenerative diseases (Supplementary Table S4; Supplementary Figures S2-S5). Leave-one-out analysis showed similar null effects when sequentially leaving out genetic variants from the analyses (Supplementary Figures S6-S9).

Moreover, longer TL was significantly associated with increased life expectancy (β_{IVW} = 0.011; q-value = 0.039) (Fig. 2). Maximum likelihood, MR-Egger regression weighted median and weighted mode methods suggested analogous patterns of effect on life expectancy. In this case, MR-Egger intercept test did not suggest the presence of unbalanced directional pleiotropy (p-value = 0.462). Cochran Q and MR-PRESSO further supported the absence of heterogeneity in MR estimates (Table 1). Leave-one-out analysis showed IVW estimates lost significance when excluding rs10936600 from life expectancy analysis (Fig. 3).

4. Discussion

In this study, we explored the potential causal role of genetically predicted longer TL on the risk of neurodegenerative diseases

Table 1
Mendelian randomization results for the relationship between genetically predicted longer telomere length, life expectancy and Alzheimer's disease.

	Life expectancy				Alzheimer's disease			
Causal inference methods	***β***	**SE**	**p-value**	**q-value**	**OR**	**95 % CI**	**p-value**	**q-value**
Inverse-variance weighted	0.011	0.004	**0.010**	**0.039**	0.964	(0.936, 0.992)	**0.013**	**0.039**
Maximum likelihood	0.011	0.004	**0.010**	**0.043**	0.964	(0.936, 0.993)	**0.014**	**0.043**
MR-Egger regression	0.020	0.013	0.113	0.339	0.884	(0.818, 0.956)	**0.002**	**0.012**
Weighted median	0.013	0.006	**0.038**	0.165	0.966	(0.932, 1.001)	0.055	0.165
Weighted mode	0.021	0.009	**0.021**	0.126	0.976	(0.934, 1.020)	0.282	0.432
Sensitivity methods	***p-value***				***p-value***			
Cochran Q, heterogeneity test	0.978				0.101			
MR-PRESSO, global test	0.982				0.106			
MR-Egger, intercept test	0.462				**0.021**			

Legend: CI, Confidence Intervals; MR, Mendelian Randomization; OR, Odds Ratio; SE, Standard Error; PRESSO, Pleiotropy RESidual Sum and Outlier.

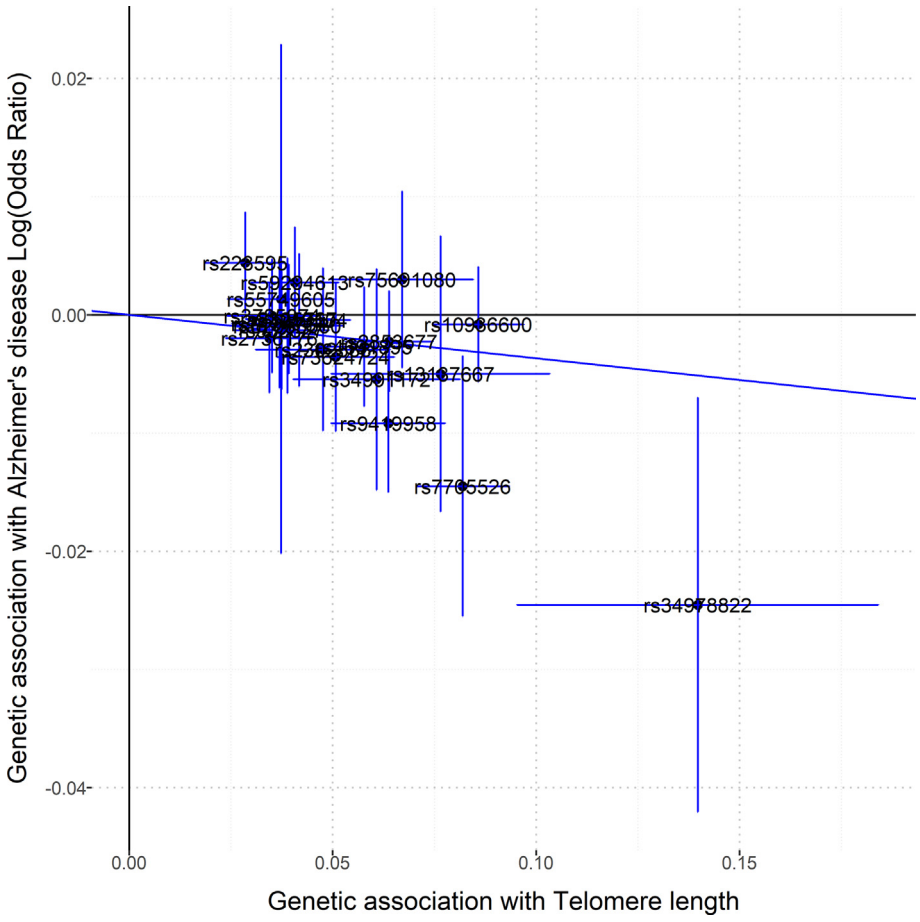

Fig. 1. Scatter plot representing the significant causal effects of genetically predicted longer telomere length on Alzheimer's disease risk. The slope of the line represents the Inverse-Variance Weighted causal estimate.

and life expectancy through a multiple independent two-sample MR approach. We observed that genetically predicted longer TL was associated with increased life expectancy and lower risk of developing AD. No associations were observed in relation to other neurodegenerative diseases.

Our study confirms and extends previous MR studies regarding TL association with AD risk [17–20]. Nevertheless, we observed evidence of directional pleiotropy and AD estimates were relatively inconsistent when using several MR methods. Interestingly, [40] reported a similar pattern of MR estimates when using summary-level data from [24], where AD cases were both clinically diagnosed or AD-by-proxy (i.e., based on parental diagnoses). Despite the heritability of sporadic AD (~80 %) [41], and the proven value of proxy case-control association studies [42], this could partially explain the decreased statistical power to detect consistent causal associations through robust MR methods.

We did not find further significant associations between genetically predicted TL and other neurodegenerative disease, which also confirms results from previous studies. For instance, two previous MR studies did not find significant causal associations between TL and the risk of PD [21], ALS and FTD [22]. Additionally, most observational studies showed contradictory results [43–45]. On the other hand, as far as we know, no previous MR studies have evaluated the causal role of TL on PSP. Although neurodegenerative diseases share common pathological pathways [46], our results might suggest that different hallmarks of aging could distinctly

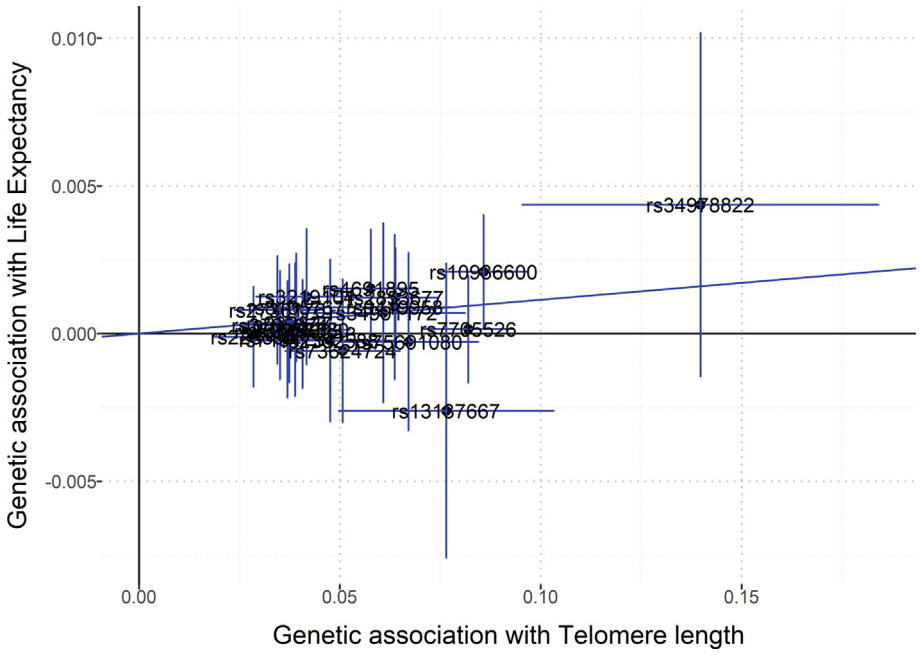

Fig. 2. Scatter plot representing the significant causal effects of genetically predicted longer telomere length on life expectancy. The slope of the line represents the Inverse-Variance Weighted causal estimate.

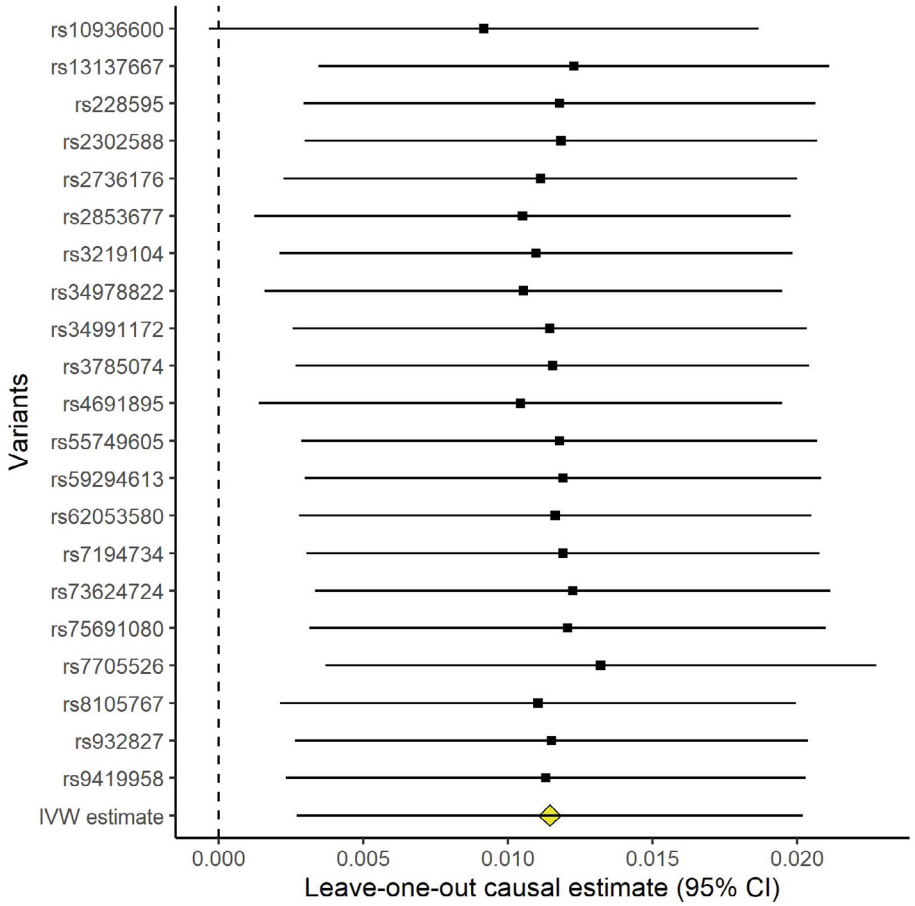

Fig. 3. Leave-one-out permutation analysis plot for life expectancy obtained by leaving out the SNP indicated and repeating the Inverse-Variance Weighted method with the rest of the instrumental variables.

interact with the complex etiology of these diseases [3,47]. Indeed, a composite biomarker panel of aging could increase the predictive power of these studies by pointing to different aspects of the aging process [48].

Additionally, we observed a statistically significant association between genetically predicted longer TL and increased life expectancy. Telomere shortening rate is known to predict species lifespan [49]. Nonetheless, little evidence of association between genetically predicted TL and parental lifespan has been previously described [50]. Importantly, we found that rs10936600, located at the leucine rich repeat (*LRRC34)* gene, was primarily driving the results of the MR analysis. Although the role of *LRRC34* in telomere biology is not fully understood yet, gene-enrichment analysis has identified *LRRC34* as the most significant gene associated with telomere length [51].

Therefore, our results support a potential causal relationship between shorter telomeres, AD risk, and increased life expectancy. Indeed, [30] described that offspring of longer-lived parents had more protective alleles for AD. Interestingly, AD contributes to a shortened life expectancy, although non-Alzheimer's dementia usually show shorter life expectancy than AD [52]. Together with our results, this suggests that telomere biology might play a shared role in life expectancy and the pathophysiology of AD but no other neurodegenerative processes. Nonetheless, the higher prevalence of AD compared to other neurodegenerative diseases could also explain our results [4].

The causal effect of TL cannot be empirically tested in humans; therefore, MR approach provides a unique opportunity to disentangle the effect of TL in human health. Nevertheless, our study is not free of limitations. On the one hand, we found evidence of directional pleiotropy on AD analysis. Although supplementary sensitivity analyses did not support the presence of increased heterogeneity, IVW estimates could be biased in the presence of pleiotropy [33]. In this sense, although robust MR methods produced similar patterns of effects, the lack of significant associations encountered by applying the generally conservative MR methods (i.e. weighted median and weighted mode) could indicate a lack of statistical power or the presence of non-valid instrumental variants in AD analyses [37]. Indeed, we cannot fully ensure other MR assumptions have not been violated. In addition, proxies for some SNPs were used as IVs in MR analyses on PD, FTD and PSP. On the other hand, MR statistical power is dependent on the sample size of each GWAS. In this sense, the GWAS of FTD included a relatively small sample size (N cases = 2,154) and different FTD subtypes [25], which could explain the wide confidence intervals obtained in MR analyses (Supplementary Table S4). Moreover, the GWAS included in the MR analyses were exclusively performed in individuals of European ancestry, thus these results should not be extrapolated to other populations. Finally, telomere length in the GWAS [23] was measured in leukocytes. Although leukocyte TL is a valid proxy of TL in other tissue types including the brain [53], measuring TL among distinct brain cell types could help addressing the molecular mechanisms that connect telomere biology to AD risk.

As future research, MR analysis focused on addressing the role of TL on the pathological mechanisms of neurodegeneration could further help to identify which molecular pathways are involved in this potential causal association. Furthermore, the use of *meta*-GWAS including both larger samples and higher number of cases will increase the statistical power of future MR analysis. Finally, further observational studies could help to elucidate such associations.

Funding

This project has received funding from the Alzheimer's Association (Grant AARG-19-618265). JDG is supported by the Spanish Ministry of Science and Innovation (RYC-2013-13054) Ministry of Science and Innovation– Spanish State Research Agency. NV-T is funded by a postdoctoral grant, Juan de la Cierva Programme (IJC2020-043216-I). All CRG authors acknowledge the support of the Spanish Ministry of Science, Innovation and Universities to the EMBL partnership, the Centro de Excelencia Severo Ochoa and the CERCA Programme / Generalitat de Catalunya.

CRediT authorship contribution statement

Blanca Rodríguez-Fernández: Conceptualization, Data curation, Methodology, Formal analysis, Visualization, Writing – original draft. **Juan Domingo Gispert:** Writing – review & editing. **Roderic Guigo:** Writing – review & editing. **Arcadi Navarro:** Writing – review & editing. **Natalia Vilor-Tejedor:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Marta Crous-Bou:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the International FTD-Genetics Consortium (IFGC) for the summary data. We additionally thank all the Consortium members involved in the analysis and generation of summary statistics used in this project: Leukocyte Telomere Length (https://doi.org/10.1016/j.ajhg.2020.02.006); Alzheimer's Disease (https://ctg.cncr.nl/software/summary_statistics); Frontotemporal Dementia (https://ifgcsite.wordpress.com/data-access/); Parkinson's Disease (https://drive.google.com/file/d/1FZ9UL99LAqyWnyNBxxlx6qOUlfAnublN/view?usp=sharing); Semantic Dementia (https://ifgcsite.wordpress.com/data-access/); Life Expectancy (http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST003001-GCST004000/GCST003395/results.UKBiobank_9millionSNPs.parents_lifespan.Pilling_et_al_2016_top_1_percent.txt). Schematic representations were created with Biorender.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.csbj.2022.08.006.

References

[1] Wyss-Coray T. Ageing, neurodegeneration and brain rejuvenation. Nature 2016;539:180–6. https://doi.org/10.1038/nature20411.
[2] United Nations Department of Economic and Social Affairs, Population Division (2020). World Population Ageing 2020 Highlights: Living arrangements of older persons (ST/ESA/SER.A/451).
[3] Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, et al. Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurol 2019;15:565–81. https://doi.org/10.1038/S41582-019-0244-7.
[4] Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:459–80. https://doi.org/10.1016/S1474-4422(18)30499-X.
[5] Carmona JJ, Michan S. Biology of Healthy Aging and Longevity. Rev Invest Clin n.d.;68:7–16.
[6] Fuellen G, Jansen L, Cohen AA, Luyten W, Gogol M, Simm A, et al. Health and aging: unifying concepts, scores biomarkers and pathways. Aging Dis 2019;10:883. https://doi.org/10.14336/AD.2018.1030.
[7] Higgins-Chen AT, Thrush KL, Levine ME. Aging biomarkers and the brain. Semin Cell Dev Biol 2021;116:180–93. https://doi.org/10.1016/J.SEMCDB.2021.01.003.

[8] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013;153:1194–217. https://doi.org/10.1016/j.cell.2013.05.039.
[9] Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 2014;349. https://doi.org/10.1136/BMJ.G4227.
[10] Blackburn EH, Epel ES, Lin J. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. Science (80-) 2015;350:1193–8. https://doi.org/10.1126/SCIENCE.AAB3389.
[11] Forero DA, González-Giraldo Y, López-Quintero C, Castro-Vega LJ, Barreto GE, Perry G. Meta-analysis of telomere length in Alzheimer's disease. J Gerontol Ser A Biol Sci Med Sci 2016;71:1069–73. https://doi.org/10.1093/gerona/glw053.
[12] Fu J, Ji X, Liu J, Chen X, Shang H. Meta-analysis of the connection between Alzheimer disease and telomeres. Alzheimer Dis Assoc Disord 2022;36:73–9. https://doi.org/10.1097/WAD.0000000000000468.
[13] Hackenhaar FS, Josefsson M, Adolfsson AN, Landfors M, Kauppi K, Hultdin M, et al. Short leukocyte telomeres predict 25-year Alzheimer's disease incidence in non-APOE ε4-carriers. Alzheimer's Res Ther 2021;13. https://doi.org/10.1186/S13195-021-00871-Y.
[14] Azam S, Haque ME, Balakrishnan R, Kim IS, Choi DK. The ageing brain: molecular and cellular basis of neurodegeneration. Front Cell Dev Biol 2021;9. https://doi.org/10.3389/FCELL.2021.683459.
[15] Katan M. Apoupoprotein E isoforms, serum cholesterol, and cancer. Lancet 1986;327:507–8. https://doi.org/10.1016/S0140-6736(86)92972-7.
[16] Smith GD, Ebrahim S. Mendelian randomization: Prospects, potentials, and limitations. Int J Epidemiol 2004;33:30–42. https://doi.org/10.1093/IJE/DYH132.
[17] Zhan Y, Song C, Karlsson R, Tillander A, Reynolds CA, Pedersen NL, et al. Telomere length shortening and Alzheimer disease-A mendelian randomization study. JAMA Neurol 2015;72:1202–3. https://doi.org/10.1001/JAMANEUROL.2015.1513.
[18] Guo Y, Yu H. Leukocyte telomere length shortening and Alzheimer's disease etiology. J Alzheimer's Dis 2019;69:881–5. https://doi.org/10.3233/JAD-190134.
[19] Scheller Madrid A, Rasmussen KL, Rode L, Frikke-Schmidt R, Nordestgaard BG, Bojesen SE. Observational and genetic studies of short telomeres and Alzheimer's disease in 67,000 and 152,000 individuals: a Mendelian randomization study. Eur J Epidemiol 2020;35:147–56. https://doi.org/10.1007/S10654-019-00563-W.
[20] Yu G, Lu L, Ma Z, Wu S. Genetically predicted telomere length and its relationship with Alzheimer's disease. Front Genet 2021;12. https://doi.org/10.3389/FGENE.2021.595864.
[21] Chen R, Zhan Y. Association between telomere length and Parkinson's disease: a Mendelian randomization study. Neurobiol Aging 2021;97:144.e9–144.e11. https://doi.org/10.1016/j.neurobiolaging.2020.07.019.
[22] Gao Y, Wang T, Yu X, Ferrari R, Hernandez DG, Nalls MA, et al. Mendelian randomization implies no direct causal association between leukocyte telomere length and amyotrophic lateral sclerosis. Sci Rep 2020;10. https://doi.org/10.1038/S41598-020-68848-9.
[23] Li C, Stoma S, Lotta LA, Warner S, Albrecht E, Allione A, et al. Genome-wide association analysis in humans links nucleotide metabolism to leukocyte telomere length. Am J Hum Genet 2020;106:389–404. https://doi.org/10.1016/J.AJHG.2020.02.006.
[24] Jansen IE, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat Genet 2019;51:404–13. https://doi.org/10.1038/s41588-018-0311-9.
[25] Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol 2019;18:1091–102. https://doi.org/10.1016/S1474-4422(19)30320-5.
[26] Ferrari R, Hernandez DG, Nalls MA, Rohrer JD, Ramasamy A, Kwok JBJ, et al. Frontotemporal dementia and its subtypes: a genome-wide association study. Lancet Neurol 2014;13:686–99. https://doi.org/10.1016/S1474-4422(14)70065-1.
[27] van Rheenen W, Shatunov A, Dekker AM, McLaughlin RL, Diekstra FP, Pulit SL, et al. Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. Nat Genet 2016;48:1043–8. https://doi.org/10.1038/ng.3622.
[28] Chen JA, Chen Z, Won H, Huang AY, Lowe JK, Wojta K, et al. Joint genome-wide association study of progressive supranuclear palsy identifies novel susceptibility loci and genetic correlation to neurodegenerative diseases. Mol Neurodegener 2018;13. https://doi.org/10.1186/S13024-018-0270-8.
[29] Myers TA, Chanock SJ, Machiela MJ. LDlinkR: an R package for rapidly calculating linkage disequilibrium statistics in diverse populations. Front Genet 2020;11. https://doi.org/10.3389/FGENE.2020.00157.
[30] Pilling LC, Atkins JL, Bowman K, Jones SE, Tyrrell J, Beaumont RN, et al. Human longevity is influenced by many genetic variants: evidence from 75,000 UK Biobank participants. Aging (Albany NY) 2016;8:547–60. https://doi.org/10.18632/aging.100930.
[31] Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 2013;37:658–65. https://doi.org/10.1002/GEPI.21758.
[32] Bowden J, Smith GD, Burgess S. Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. Int J Epidemiol 2015;44:512–25. https://doi.org/10.1093/IJE/DYV080.
[33] Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016;40:304–14. https://doi.org/10.1002/GEPI.21965.
[34] Thompson JR, Minelli C, Abrams KR, Tobin MD, Riley RD. Meta-analysis of genetic studies using Mendelian randomization - A multivariate approach. Stat Med 2005;24:2241–54. https://doi.org/10.1002/SIM.2100.
[35] Bowden J, Del Greco MF, Minelli C, Zhao Q, Lawlor DA, Sheehan NA, et al. Improving the accuracy of two-sample summary-data Mendelian randomization: Moving beyond the NOME assumption. Int J Epidemiol 2019;48:728–42. https://doi.org/10.1093/IJE/DYY258.
[36] Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018;50:693–8. https://doi.org/10.1038/S41588-018-0099-7.
[37] Burgess S, Davey Smith G, Davies NM, Dudbridge F, Gill D, Glymour MM, et al. Guidelines for performing Mendelian randomization investigations. Wellcome Open Res 2020;4. https://doi.org/10.12688/WELLCOMEOPENRES.15555.2.
[38] R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; 2022.
[39] Yavorska OO, Burgess S. MendelianRandomization: An R package for performing Mendelian randomization analyses using summarized data. Int J Epidemiol 2017;46:1734–9. https://doi.org/10.1093/IJE/DYX034.
[40] Gao K, Wei C, Zhu J, Wang X, Chen G, Luo Y, et al. Exploring the causal pathway from telomere length to Alzheimer's disease: an update mendelian randomization study. Front Psychiatry 2019;10. https://doi.org/10.3389/FPSYT.2019.00843.
[41] Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, et al. Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry 2006;63:168. https://doi.org/10.1001/archpsyc.63.2.168.
[42] Liu JZ, Erlich Y, Pickrell JK. Case-control association mapping by proxy using family history of disease. Nat Genet 2017;49:325–31. https://doi.org/10.1038/NG.3766.
[43] De Felice B, Annunziata A, Fiorentino G, Manfellotto F, D'Alessandro R, Marino R, et al. Telomerase expression in amyotrophic lateral sclerosis (ALS) patients. J Hum Genet 2014;59:555–61. https://doi.org/10.1038/jhg.2014.72.
[44] Degerman S, Domellöf M, Landfors M, Linder J, Lundin M, Haraldsson S, et al. Long leukocyte telomere length at diagnosis is a risk factor for dementia progression in idiopathic parkinsonism. PLoS ONE 2014;9:e113387.
[45] Al Khleifat A, Iacoangeli A, Shatunov A, Fang T, Sproviero W, Jones AR, et al. Telomere length is greater in ALS than in controls: a whole genome sequencing study. Amyotroph Lateral Scler Front Degener 2019;20:229–34. https://doi.org/10.1080/21678421.2019.1586951.
[46] Levstek T, Kozjek E, Dolžan V, Trebušak PK. Telomere attrition in neurodegenerative disorders. Front Cell Neurosci 2020;14. https://doi.org/10.3389/FNCEL.2020.00219/FULL.
[47] Gan L, Cookson MR, Petrucelli L, La Spada AR. Converging pathways in neurodegeneration, from genetics to mechanisms. Nat Neurosci 2018;21:1300–9. https://doi.org/10.1038/s41593-018-0237-7.
[48] Eitan E, Hutchison ER, Mattson MP. Telomere shortening in neurological disorders: an abundance of unanswered questions. Trends Neurosci 2014;37:256–63. https://doi.org/10.1016/j.tins.2014.02.010.
[49] Vaiserman A, Krasnienkov D. Telomere length as a marker of biological age: state-of-the-art open issues, and future perspectives. Front Genet 2021;11. https://doi.org/10.3389/FGENE.2020.630186/FULL.
[50] Whittemore K, Vera E, Martínez-Nevado E, Sanpera C, Blasco MA. Telomere shortening rate predicts species life span. Proc Natl Acad Sci USA 2019;116:15122–7. https://doi.org/10.1073/PNAS.1902452116.
[51] Kuo CL, Pilling LC, Kuchel GA, Ferrucci L, Melzer D. Telomere length and aging-related outcomes in humans: A Mendelian randomization study in 261,000 older participants. Aging Cell 2019;18. https://doi.org/10.1111/ACEL.13017.
[52] Coutts F, Palmos AB, Duarte RRR, de Jong S, Lewis CM, Dima D, et al. The polygenic nature of telomere length and the anti-ageing properties of lithium. Neuropsychopharmacology 2019;44:757–65. https://doi.org/10.1038/S41386-018-0289-0.
[53] Liang CS, Li DJ, Yang FC, Tseng PT, Carvalho AF, Stubbs B, et al. Mortality rates in Alzheimer's disease and non-Alzheimer's dementias: a systematic review and meta-analysis. Lancet Heal Longev 2021;2:e479–88. https://doi.org/10.1016/S2666-7568(21)00140-9.

Further Reading

[54] Demanelis K, Jasmine F, Chen LS, Chernoff M, Tong L, Delgado D, et al. Determinants of telomere length across human tissues. Science (80-) 2020;369. https://doi.org/10.1126/SCIENCE.AAZ6876.