Genetically predicted telomere length and Alzheimer's Disease endophenotypes: a Mendelian Randomization study

Blanca Rodriguez-Fernandez[1], *Natalia Vilor-Tejedor*[2], *Marta Crous-Bou*[3]

[1]brodriguez@barcelonabeta.org, Barcelonaβeta Brain Research Center, Pasqual Maragall Foundation
[2]nvilor@barcelonabeta.org, Barcelonaβeta Brain Research Center, Pasqual Maragall Foundation
[3]mcrous@barcelonabeta.org, Unit of Nutrition and Cancer, Cancer Epidemiology Research Program. Catalan Institute of Oncology (ICO)-Bellvitge Biomedical Research Center (IDIBELL)

Observational studies are designed for measuring an association between an exposure and the occurrence of a disease. However, results may be biased due to confounding factors and the direction of the association may be wrongly determined. Several observational studies have been designed to evaluate the influence of telomere length (TL) on the risk of age-related diseases such as Alzheimer's disease (AD). These studies were limited to concluding whether TL is causally associated with those outcomes. This study aimed to evaluate the potential causal role of TL in AD endophenotypes through a Mendelian randomization (MR) analysis. Our analysis was conducted in the context of the ALFA study. We created episodic memory, executive function, and global cognitive performance composites. We calculated AD and aging signatures as composite measures reflecting cortical thickness of specific AD and aging vulnerable brain regions, respectively. We measured CSF levels of core AD and neurodegeneration biomarkers, that is, amyloid-β ($A\beta$), p-tau, t-tau, and neurofilament light (NfL). A total of 20 single nucleotide polymorphisms associated with TL were used to determine the effect of TL on AD endophenotypes. Analyses were adjusted by age, sex, and years of education. Stratified analyses by *APOE*-$\epsilon 4$ status and polygenic risk score of AD were conducted. Inverse-variance weighted (IVW), maximum likelihood, weighted median and weighted mode methods were used to estimate the causal effect of genetically predicted longer TL on the outcomes of the study. Cochran Q statistic, MR-PRESSO and MR-Egger intercept-test were used as *ad hoc* sensitivity analysis for evaluating the robustness of significant results. Effect sizes were reported in the SD change (β_{IVW}) per copy of the allele associated with longer TL. MR analysis revealed significant associations between genetically predicted longer TL and lower levels of CSF $A\beta$ and higher levels of CSF NfL only in *APOE*-$\epsilon 4$ non-carriers. Moreover, inheriting longer TL was associated with greater cortical thickness in age and AD-related brain signatures and lower levels of CSF p-tau among individuals at a high genetic predisposition to AD. Further observational analyses are warranted to better understand these associations.

Keywords: Alzheimer's disease, causal inference, genome-wide association study

Reference: [1] Rodriguez-Fernandez B., Vilor-Tejedor N., Arenaza-Urquijo E., et al. (2022). Genetically predicted telomere length and Alzheimer's Disease endophenotypes: a Mendelian Randomization study. *Alzheimer's research & therapy*, 14. 167.