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Negative results

Association between telomere length and Parkinson's disease: a Mendelian randomization study

Ruoqing Chen[a], Yiqiang Zhan[b,c,*]

[a] Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
[b] German Center for Neurodegenerative Diseases, Ulm, Germany
[c] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

In this study, we examined the potential association of telomere length with Parkinson's disease (PD) using the publicly available genome-wide association study summary statistics from the International Parkinson's Disease Genomics Consortium involving up to 37,688 patients with PD and 449,056 controls in Mendelian randomization framework. The Mendelian randomization approach has the potential to investigate a causal relationship between a risk factor and a disease, avoiding confounding and reverse causation that often present in conventional epidemiological studies. We did not find that longer telomeres were associated with higher risks of PD (odds ratio: 1.18, 95% confidence interval: 0.94, 1.48, $p = 0.15$). Our study, therefore, did not provide evidence to support a potential causal relationship between telomere length and PD.

1. Introduction

Telomeres are short sequences of nucleotides at the end of the chromosomes. They function as stabilizing the chromosome structure and protecting them from fusion with neighboring chromosomes (Blackburn et al., 2015). Several studies reported longer telomeres in patients with Parkinson's disease (PD) (Hudson et al., 2011; Wang et al., 2008), whereas others found the opposite as shown in the recent meta-analysis (Forero et al., 2016). These studies, however, had small sample sizes and were prone to residual confounding that makes it difficult to draw conclusions on whether the telomere length is causally associated with PD. To alleviate the concerns of residual confounding and maximize the sample size on etiological research, a 2-sample Mendelian randomization (MR) approach was developed by taking advantage of genetic variants as instruments to estimate the magnitude of the association between an exposure and outcome (Smith and Ebrahim, 2004). To this end, we examined the association between telomere length and PD by applying the MR method to the summary statistics of the genome-wide association study (GWAS) for the telomere length (Li et al., 2020) and PD (Nalls et al., 2019).

2. Methods

2.1. Instrument variable selection

In a recent GWAS (Li et al., 2020), 20 genetic variants at 17 genomic loci were independently associated with telomere length at a level of genome-wide significance ($p < 5 \times 10^{-8}$). Of them, 6 single-nucleotide polymorphisms (SNPs) were palindromic and therefore were substituted by respective proxy SNPs as instrumental variables in the MR analysis. These 20 SNPs were harmonized with the estimates from the PD GWAS. We calculated the magnitude of the association between telomere length and PD by using the inverse variance–weighted method as the primary analysis and the MR-Egger regression, weighted median, and weighed mode approaches as complementary analysis. All statistical analyses were performed using the *TwoSampleMR* package (Hemani et al., 2018) in R 3.6 (R Project for statistical computing). We also performed power calculation through an online power calculator for MR analysis (https://shiny.cnsgenomics.com/mRnd/). By assuming an odds ratio of 1.20 per one–standard deviation decrease of the telomere length, the power for the present analysis is 96%. This study only uses GWAS summary statistics and not individual-level data, and ethical permit is not required in accordance with the regulations at Karolinska Institutet.

3. Results

The associations of these SNPs with telomere length and PD are shown in Fig. 1. A longer telomere length was associated with a

* Corresponding author at: German Center for Neurodegenerative Diseases (DZNE), Oberer Eselsberg 45, Ulm 89081, Germany. Tel.: +46 762707985; fax: +46-8 31 11 01.
E-mail address: yiqiang.zhan@dzne.de (Y. Zhan).

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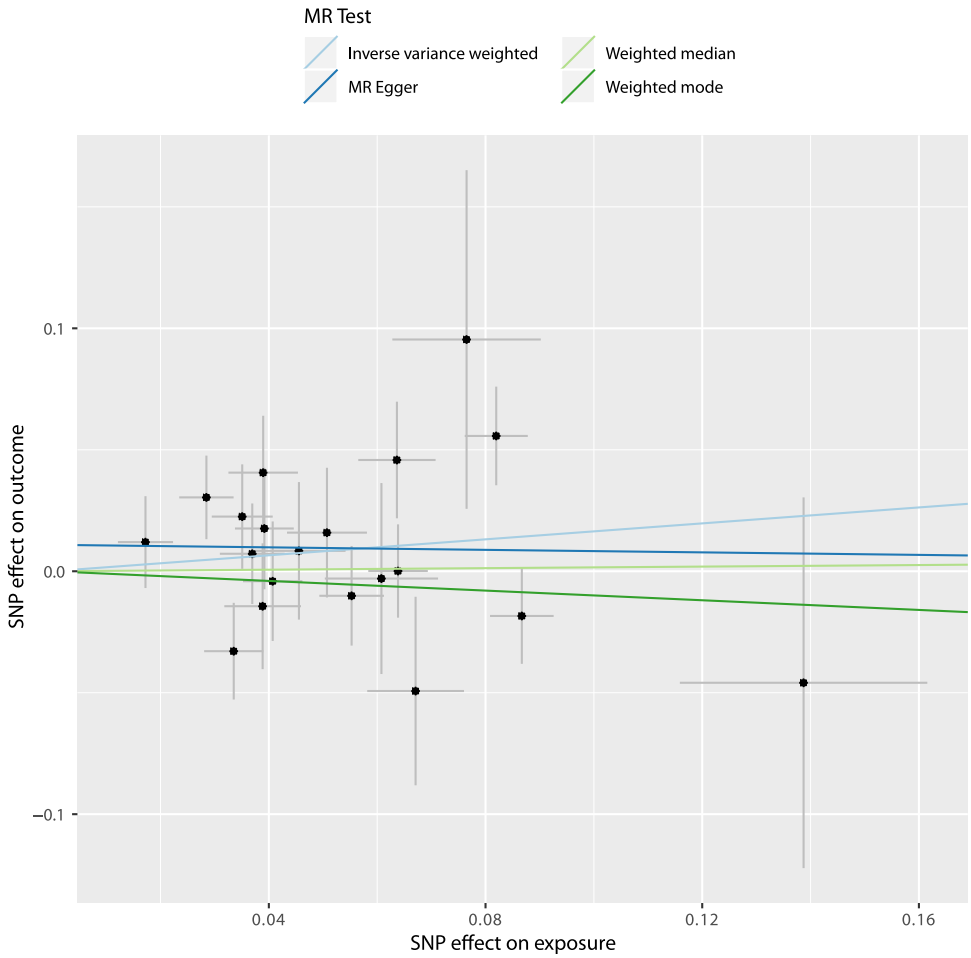

Fig. 1. Scatter plot of the effects of genetic variants on the telomere length and PD. The slopes of the solid lines denote the magnitudes of the associations estimated from the MR analyses. Abbreviations: PD, Parkinson's disease; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

higher risk of PD using the inverse variance–weighted approach; this association was, however, not statistically significant (odds ratio = 1.18 per one–standard deviation increase of the telomere length, 95% confidence interval: 0.94, 1.48, $p = 0.15$). Other methods, including MR-Egger regression, weighted median, and weighted mode approaches, yielded similar results with slightly wider confidence intervals (Table 1). The intercept ($\beta = -0.01$, 95% CI: −0.02, 0.04, $p = 0.50$) of the MR-Egger regression implied that there was no strong evidence for horizontal pleiotropy.

4. Discussion

In the present study, for the first time to our knowledge, the MR approach was used to examine the association between telomere length and PD using GWAS summary statistics involving more than 30,000 individuals with PD and more than 400,000 controls. We did not find that longer telomere length was associated with a higher risk of PD.

A previous meta-analysis summarizing all studies of telomere length and PD reported that patients with PD had longer telomeres ($\beta = 0.358$, 95% CI: −0.247 to 0.962, $p = 0.246$) compared with controls. Part of the reasons for wider confidence intervals might be the relatively small sample size (956 cases and 1284 controls). Our present study, in contrast, alleviates this concern by exploiting the advantage of large sample sizes in GWAS summary statistics. The MR analysis, however, relies on the assumptions that the genetic variants selected as instrumental variables affect the outcome (e.g., PD) only through the exposure of interest (e.g., telomere length). Although the assumption cannot be tested in practice, our results are still meaningful when interpreting them as the genetically determined telomere length affecting the risk of PD.

In summary, our study did not provide further evidence to support a potential causal relationship between telomere length and PD.

Table 1
Association between telomere length and Parkinson's disease using the Mendelian randomization analysis, OR (95% CI)

Methods	OR (95% CI)	*p*-value
Inverse variance weighted	1.18 (0.94, 1.48)	0.15
MR-Egger regression	0.97 (0.54, 1.75)	0.93
Weighted median	1.02 (0.74, 1.40)	0.92
Weighted mode	0.91 (0.55, 1.50)	0.91

Key: OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

Disclosure statement

The authors have no disclosures to report.

CRediT authorship contribution statement

Ruoqing Chen: Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing,

Visualization. **Yiqiang Zhan:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization.

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