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Telomere length in Parkinson's disease: A meta-analysis

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Abstract

Parkinson's disease (PD) is a common and severe movement disorder. Differences in telomere length (TL) have been reported as possible risk factors for several neuropsychiatric disorders, including PD. Results from published studies for TL in PD are inconsistent, highlighting the need for a meta-analysis. In the current work, a meta-analysis of published studies for TL in PD was carried out. PubMed, Web of Science and Google Scholar databases were used to identify relevant articles that reported TL in groups of PD patients and controls. A random-effects model was used for meta-analytical procedures. The meta-analysis included eight primary studies, derived from populations of European and Asian descent, and did not show a significant difference in TL between 956 PD patients and 1284 controls (p value: 0.246). Our results show that there is no consistent evidence of shorter telomeres in PD patients and suggest the importance of future studies on TL and PD that analyze other populations and also include assessment of TL from different brain regions.

Keywords

Movement disorders; Epigenomics; Telomeres; Parkinson's disease; Meta-analysis

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Conflicts of interest:

None reported.

1. Introduction

Parkinson's disease (PD) is a common and severe movement disorder (Lees et al., 2009), which is characterized by clinical signs such as resting tremor, bradykinesia, rigidity and postural instability and by neuropathological alterations such as the loss of dopaminergic neurons in the substantia nigra pars compacta (Lees et al., 2009). Several causal genes for Mendelian forms of PD (such as *SNCA*, *PARK2*, *PARK7* and *LRRK2*) and susceptibility genes for its complex subtypes (such as *STK39* and *MAPT*) have been identified (Verstraeten et al., 2015). Available theories about the etiology and pathophysiology of PD are focused on the possible negative effects of genetic factors and environmental stresses, such as oxidative stress and cytokine-receptor-mediated apoptosis (Lees et al., 2009).

Human telomeres are ribonucleoprotein complexes, which consist on a repetitive DNA sequence and a core of associated proteins. Telomeres are fundamental for the maintenance of genomic stability in cells of different organs, including the brain (Eitan et al., 2014). Differences in telomere length (TL) have been reported as possible risk factors for several neuropsychiatric disorders, such as PD, Alzheimer's disease and vascular dementia, (Eitan et al., 2014). Oxidative stress is known to affect telomere shortening and in PD this could be a mechanism involved in the neurodegeneration processes related to mitochondrial dysfunction; although there are no studies demonstrating the role of telomeres loss in PD (Eitan et al., 2014).

Two methods commonly used to analyze TL in human patients include: the Terminal Restriction Fragment (TRF) assay, which involves Southern blot and is considered the 'gold standard' approach for measuring TL and is widely recommended to validate and optimize new methods (Aviv et al., 2011; Lustig, 2015), and a technique based in quantitative Polymerase Chain Reaction (qPCR) that uses primers binding telomere sequences (Lustig, 2015). A comprehensive description of the advantages and disadvantages of these two methods is beyond the scope of this study and is provided elsewhere (Aviv et al., 2011; Elbers et al., 2014; Lustig, 2015). Results from published studies on TL and PD are inconsistent (Degerman et al., 2014; Wang et al., 2008), highlighting the need for a meta-analysis (Eitan et al., 2014). In the current work, we carried out a meta-analysis of published studies on TL and PD.

2. Methods

Recommendations of the PRISMA statement for reporting of meta-analyses were followed (Moher et al., 2009). PubMed, Web of Science and Google Scholar databases were used for a search of original studies that analyzed telomere length in PD patients and control subjects. Search terms "Parkinson's disease" and "telomere" were combined. In addition, reference lists of relevant review and original papers were manually searched to identify additional reports that were not covered by the electronic search.

Articles published in English in peer-reviewed journals, that described results from case-control studies analyzing the association of TL with PD, were included. Exclusion criteria were: lack of control groups, analysis of other types of neurodegenerative disorders or studies of telomerase activity.

Information about general features of the studies (sample size, age and gender distributions and methodologies used for analysis of TL) was extracted from each publication. Corresponding authors were contacted to ask for TL data that were not available in the main text of the articles or in the supplementary files and when other information needed was missing. Study selection and data extraction and synthesis were performed and checked by two independent investigators.

The Meta-Analyst program was used to carry out the meta-analysis procedures (Wallace et al., 2009), including the implementation of random-effects models, sensitivity analysis and generation of forest plots (Forero et al., 2015). Random-effects models were implemented and the I^2 statistic for heterogeneity was calculated.

3. Results

Eight primary studies were included in the meta-analysis for PD and telomere length (Degerman et al., 2014; Eerola et al., 2010; Guan et al., 2008; Hudson et al., 2011; Schurks et al., 2014; Wang et al., 2008; Wafar et al., 2011). One study was not included in the meta-analysis as TL data were not available and it was not possible to obtain the information from the corresponding author after multiple attempts (Maeda et al., 2012). Details of included studies are provided in Table 1 and data for 956 PD patients and 1284 controls were analyzed. Sample size for PD patients in the different studies ranged from less than 20 to more than 400. An important fraction of the studies used genomic DNA extracted from leukocytes and six studies used qPCR-based methods for analysis of TL.

A random-effects meta-analysis was applied to the available data and no significant differences in TL between PD patients and controls were found, with a standardized mean difference of 0.358 (CI: -0.247 to 0.962; p value: 0.246) (Fig. 1) and there was evidence of heterogeneity (I^2 : 97%).

4. Discussion

Telomere length has been studied in several publications as a possible biomarker for PD, however, no meta-analyses have been carried out so far to evaluate the available cumulative evidence (Eitan et al., 2014). In this work, we performed a meta-analysis for 8 published studies and we found no consistent and significant evidence of shorter telomeres in samples from PD patients (p value: 0.246).

A significant fraction of the studies included in this work used the qPCR-based method developed by Cawthon and coworkers to measure telomere length, which uses two primers binding telomere sequences, normalized to a single copy gene (in a monoplex or multiplex approach) (Cawthon, 2009). Although this method is commonly used by tens of laboratories around the world, several works have reevaluated its consistency (Lustig, 2015). For example, Aviv et al. (Aviv et al., 2011) and Elbers et al. (Elbers et al., 2014) compared TL data for leukocytes, derived by TRF and qPCR. Interassay coefficients of variation (CVs) for TRF and qPCR methods in the two studies were 1.7%/6.5% and 1.2%/ 5.8%, respectively, with linear correlation coefficients (R^2) for the two methods of 0.85 and 0.27. The qPCR-based method has the advantage, in comparison to TRF and other techniques, of

its short processing time, the need for a low amount of DNA and the possibility of running up to 96 samples in parallel. It is important that future studies take into account variables that could enhance the specificity of the qPCR-based method for TL analysis, such as the use of synthetic DNA standards (Lustig, 2015). As our meta-analytical approach was based on an analysis of standardized mean differences, we consider that the inter-study absolute differences in TL, due to variations in experimental methods, were minimized.

The role of TL as a possible biomarker for PD is still unclear. Hudson et al. showed that TL was longer in PBMC from PD patients whereas the samples from the substantia nigra did not show differences (Hudson et al., 2011). In an animal study, knockout mice for the telomerase RNA component TERC (TERC $-/-$) showed telomere shortening but did not exhibit differences in dopamine concentration or in the effects of oxidative stress in a PD model (Oeckl et al., 2014). It has been shown that telomere maintenance mechanisms could play an important role in the response of postmitotic neurons to oxidative and genomic stress (Eitan et al., 2014). However, more experimental studies, using cell and animal models, are needed for a better understanding of the functional role of telomeres in dopaminergic neurons and the risk for PD.

Although there has been a large interest in the analysis of TL in neuropsychiatric disorders, there are few published meta-analyses for some of them, such as schizophrenia, bipolar disorder and major depression. It will be important to carry out future meta-analyses of TL for other neurodegenerative disorders, such as Alzheimer's disease or vascular dementia (Eitan et al., 2014). It is important that journals implement completely the *Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative* (von Elm et al., 2007) and authors describing results for TL in human diseases include the complete details of TL in their articles, which would allow conducting detailed meta-analyses for all published studies.

It will be important to carry out future studies for TL and PD in populations with other ethnic origins and using DNA extracted from different brain regions, given the specific cell variation in telomere length, of PD patients and controls.

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Fig. 1. Forest plot for the meta-analysis of telomere length and Parkinson's disease. p value: 0.284, for a random-effects model.

Table 1

Details of the original studies included in the meta-analysis for telomere length and Parkinson's disease.

Author year	PMID	Country	Sample size	% male	Mean ages	Tissue	Method	TL patients	TL controls	Finding
Degerman, 2014	25501556	Sweden	136/30	59/53	71/70	Leukocytes	qPCR-monoplex	0.77 +/- 0.15	0.82 +/- 0.11	Similar
Schürks, 2014	24010387	USA	408/809	100/100	71/71	Leukocytes	qPCR-monoplex	112.1 +/- 1121	102.0 +/- 1312	Longer
Maeda, 2012	22364520	Japan	17/20	0/0	57/56	Leukocytes	TRF	NR	NR	Shorter
Hudson, 2011-1	21794951	UK	109/99	61/46	71/70	PBMC	qPCR-monoplex	4.769 +/- 0.234	4.087 +/- 0.219	Longer
Hudson, 2011-2	21794951	UK	28/17	57/47	72/77	Substantia nigra	qPCR-monoplex	7.659 +/- 0.366	7.256 +/- 0.644	Similar
Wafar, 2011	21437559	Germany	20/15	55/27	78/79	Leukocytes	TRF	6.06 +/- 0.81	6.45 +/- 0.73	Similar
Eerola, 2010	20639300	Finland	131/115	59/36	67/65	Leukocytes	qPCR-monoplex	0.0062 +/- 1.0019	-0.0071 +/- 0.9934	Similar
Guan, 2008	18511749	Japan	28/27	100/100	60/58	Leukocytes	TRF	7.55 +/- 1.69	7.94 +/- 1.27	Similar
Wang, 2008	18044760	USA	96/172	100/100	68/67	Leukocytes	qPCR-monoplex	0.508 +/- 0.172	0.490 +/- 0.202	Similar

Abbreviations: NR: not reported; PBMC: peripheral blood mononuclear cells; qPCR: quantitative polymerase chain reaction; TRF: terminal restriction fragment method.