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No evidence of substantia nigra telomere shortening in Parkinson's disease

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Abstract

Telomeres are repetitive tracts of DNA which protect chromosomal integrity. Increased oxidative stress leads to shorter telomeres, which have been associated with several late-onset human diseases. Given independent evidence of oxidative stress and Parkinson's disease (PD), and conflicting reports of the role of telomere length in PD, we measured telomere length in both PD peripheral blood monocytes and in *substantia nigra* from affected individuals and controls. We confirmed previous findings of a paradoxically longer telomere length in blood from PD patients, but found no difference in telomere length in *substantia nigra*. Confounding factors provide a likely explanation for the findings in blood, and possibly the reduced frequency of cigarette smoking in PD patients. We conclude that telomere shortening is unlikely to be involved in the pathogenesis of PD.

1. Introduction

Telomeres are regions of repetitive DNA that maintain chromosomal integrity by preventing chromosome ends from being recognised as double strand breaks. Short telomeres have been observed in senescent cells, in response to increased oxidative stress and chronic inflammation, leading to the hypotheses that telomere length may be a useful biomarker for late-onset diseases with increased reactive oxygen species production. It is therefore plausible that Parkinson's disease, an age-related neurodegenerative disorder characterised by selective death of dopaminergic neurons in the *substantia nigra*, is associated with shortened telomere length.

Previous studies of telomere length in PD have reached diametrically opposed conclusions, with one reporting the expected shorter telomere length in PD, and the other significantly longer telomere lengths in PD (Guan et al., 2008, 28 cases and 27 controls; Wang et al., 2008, 96 cases and 172 controls). This study was designed to resolve this controversy, and

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to determine the pathological relevance of these findings by studying *substantia nigra* from affected and unaffected individuals. In addition, we compared telomere length to genetic variants of mitochondrial DNA (mtDNA haplogroups) which have been also associated with increased ROS production and PD.

2. Experimental Procedure

Telomere lengths were compared in DNA from both whole blood (109 PD cases and 99 matched controls) and *substantia nigra* from 45 brains (28 PD cases and 17 matched controls). Full experimental details and a description of the cohort is provided in Supplementary Materials 1.

3. Results

A comparison of PBMCs identified significantly longer telomeres in PD patients compared to controls (mean telomere length; PD = 4769 ± 234.0; Control = 4087 ± 219.0, 2-sample t-test P = 0.0367, Supplementary Fig. 1). However, subsequent analysis of *substantia nigra* failed to show a significant difference in telomere length between PD cases and controls (Supplementary Fig. 2, mean telomeres were; PD = 7659 ± 366.7; Control = 7256 ± 644.4; 2-sample t-test P = 0.5601). Details of statistical power are provided in Supplementary Materials 2.

Previous studies have identified a link between gender and telomere length in PD patients (Wang et al., 2008). However, we found no significant difference between male PD cases and controls (PD = 4935 ± 332.8, Control = 4114 ± 384.5, 2-sample t-test P = 0.13) or between female PD cases and controls (PD = 4498 ± 331.5, Control = 4071 ± 267.2, 2-sample t-test P = 0.31) (Supplementary Fig. 3). There was no correlation between telomere length and age; either in the PD cases (Spearman correlation r = 0.011, P = 0.914), controls (Spearman correlation r = −0.197, P = 0.057) or the combined cohort (Spearman correlation r = 0.01, P = 0.887). There was also no correlation between telomere length and the age of onset of PD (Spearman correlation, r = −0.055, P = 0.584), or disease duration (Spearman correlation, r = 0.103, P = 0.301). Finally, given the putative role of mitochondrial DNA (mtDNA) haplogroups on reactive oxygen species production (Moreno-Loshuertos et al., 2006), we compared the telomere length differences between cases and controls on the nine European mtDNA backgrounds. Again we found no significant differences in telomere length distributions in PD patients (ANOVA P = 0.332) or controls (ANOVA P = 0.895) stratified by mtDNA haplogroup. *Post-hoc* power calculations are presented in the Supplementary Information.

4. Discussion

In this study, the mean telomere length in PBMC was greater in PD patients than in age-matched controls. This finding, whilst contrary to common hypotheses (Honig et al., 2006), is strikingly similar to a recent study linking longer telomeres to an increased risk of PD in males (Wang et al., 2008). On the other hand, there was no difference in mean telomere length between PD patients and controls when we studied the *substantia nigra*, which is the

pathological substrate of PD. This observation suggests that telomere length is not directly involved in the pathogenesis of PD.

How do we reconcile these findings with the previous studies? The increased telomere length in blood in PD may be due to other factors, including treatments for the disease itself, or exposure to cigarette smoking. Patients with PD are less likely to have smoked cigarettes than age-matched individuals without PD (De Palma et al., 2010), and smoking is known to be associated with reduced telomere length (Mirabello et al., 2009). It is therefore plausible that the longer telomeres in PD patients reflect lower smoking rates in this group. These observations have broader ramifications for studies measuring blood telomere length, which may be influenced by many factors not directly related to the disease of interest. Blood telomere measurements may yield potentially misleading results if all relevant factors are not taken into account.

Interestingly, we found significantly longer telomeres in *substantia nigra* than in PBMC, both in patients (mean SN = 7659 ± 366.7 and mean PBMC = 4769 ± 234.0, T-test P = <0.0001) and controls (mean SN = 7256 ± 644.4 and mean PBMC = 4087 ± 219.0, T-test P = 0.0003). This finding is consistent with a recent study of hippocampal telomere length in Alzheimer's disease (Thomas et al., 2008), and is supportive of previous studies which have shown that the maintenance of telomeric length is not ubiquitously controlled in all tissues (Prowse and Greider, 1995; Wang et al., 2005).

Contrary to other studies, we found no significant association between age and telomere shortening, both in the combined cohort, or when separated into PD cases and controls (Supplementary Figure 1a). This may be a manifestation of the considerable intra-individual variability in telomere length, as has been previously shown (Martin-Ruiz et al., 2006), with statistically significant trends only emerging when subjects are studied over a much greater age range. The age-matching carried out in this study, which is an essential step in case-control studies, limited the age range of our subjects, and is thus likely to have obscured the known age-dependence of telomere length.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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