Dement Neurocogn Disord. 2022 Jul;21(3):83-92
https://doi.org/10.12779/dnd.2022.21.3.83
pISSN 1738-1495·eISSN 2384-0757

DND Dementia and Neurocognitive Disorder

Review Article

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Is Telomere Length Shortening a Risk Factor for Neurodegenerative Disorders?

Hyun-Jung Yu,[1] **Seong-Ho Koh**[2,3]

[1]Department of Neurology, Bundang Jesaeng General Hospital, Seongnam, Korea
[2]Department of Neurology, Hanyang University College of Medicine, Seoul, Korea
[3]Department of Translational Medicine, Hanyang University Graduate School of Biomedical Science & Engineering, Seoul, Korea

OPEN ACCESS

Received: Jun 15, 2022
Accepted: Jun 30, 2022
Published online: Jul 21, 2022

Correspondence to
Seong-Ho Koh
Department of Neurology, Hanyang University College of Medicine, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea.
Email: ksh213@hanyang.ac.kr

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ORCID iDs
Hyun-Jung Yu
https://orcid.org/0000-0002-9081-4846
Seong-Ho Koh
https://orcid.org/0000-0001-5419-5761

Funding
This work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute funded by the Ministry of Health & Welfare, Republic of Korea (grant numbers: HI20C0253, HU21C0113, and HU21C0007) and the Medical Research Center (2017R1A5A2015395).

Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Telomeres are located at the end of chromosomes. They are known to protect chromosomes and prevent cellular senescence. Telomere length shortening has been considered an important marker of aging. Many studies have reported this concept in connection with neurodegenerative disorders. Considering the role of telomeres, it seems that longer telomeres are beneficial while shorter telomeres are detrimental in preventing neurodegenerative disorders. However, several studies have shown that people with longer telomeres might also be vulnerable to neurodegenerative disorders. Before these conflicting results can be explained through large-scale longitudinal clinical studies on the role of telomere length in neurodegenerative disorders, it would be beneficial to simultaneously review these opposing results. Understanding these conflicting results might help us plan future studies to reveal the role of telomere length in neurodegenerative disorders. In this review, these contradictory findings are thoroughly discussed, with the aim to better understand the role of telomere length in neurodegenerative disorders.

Keywords: Telomere; Neurodegenerative Disorders; Shortening; Alzheimer's Disease; Parkinson's Disease; Frontotemporal Dementia

INTRTODUCTION

The prevalence of age-related neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease (PD), and frontotemporal dementia (FTD) continue to increase worldwide. Although many studies have attempted to reveal the exact etiologies and mechanisms of each disease, they remain unclear. Understanding the role of aging in neurodegenerative disorders could be helpful because aging is a robust nonmodifiable risk factor.[1] Aging of all organisms is eventually associated with progressive physical deterioration and increased vulnerability to death.[2] Aging can result in genomic instability, telomere shortening, epigenetic changes, mitochondrial dysfunction, cellular senescence, altered intercellular communications, and so on.[2] Among these alterations, telomere attribution is considered one of the most remarkable markers for aging and cellular senescence.[3]

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Author Contributions

Conceptualization: Yu HJ, Koh SH; Writing - original draft: Yu HJ; Writing - review & editing: Koh SH.

Telomeres are repetitive nucleotide sequences of TTAGGG at the end of chromosomes. The length of double-stranded telomeric DNA ranges from 5 to 15 bp in humans. Telomeres form special cap structures with t-loop.[4-6] It is well known that telomeres contribute to the maintenance of chromosomal stability by preventing fusion and degradation of chromosomes and regulating the ability of cells to replicate via mitosis.[4-6] However, telomere length decreases during aging and under various stressful conditions. For example, our previous study has shown that approximately 48 bp per year is naturally shortened in healthy Korean males and approximately 56 bp per year in healthy Korean females.[7] Shortening of telomere length can be faster under stressful and pathological conditions. Oxidative stress and other harmful stressors can shorten telomere length. Furthermore, telomere length shortening can also happen in various neurodegenerative disorders.[8] These findings suggest that people with shorter telomere lengths are more vulnerable to neurodegenerative disorders, whereas people with longer telomere lengths might be more resistant to such disorders. Results of many studies support this hypothesis. However, several studies have reported contradictory results, showing that patients with neurodegenerative disorders have longer telomeres.[9,10] These conflicting results should be discussed and explained to better understand the role of telomere length in neurodegenerative disorders.

Thus, the purpose of this review was to summarize papers that have examined the relationship between telomere length and neurodegenerative disorders and to suggest future studies for answering any remaining questions.

AGING AND NEURODEGENERATIVE DISORDERS

Aging is an inevitable event in the lifecycle and an undeniable risk factor for neurodegenerative disorders.[1] Aging leads to many changes such as genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, cellular senescence, deregulated nutrient sensing, stem cell exhaustion, and altered intercellular communication (**Fig. 1**).[1] These hallmarks of aging will be briefly discussed here.

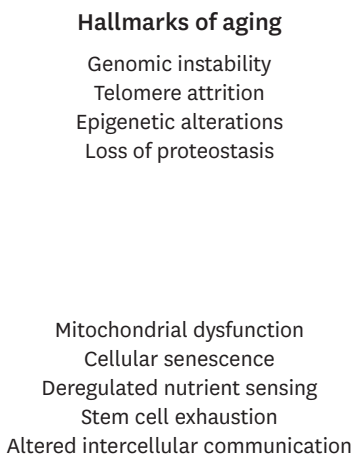

Fig. 1. Hallmarks of aging. Hallmarks of aging include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, cellular senescence, deregulated nutrient sensing, stem cell exhaustion, and altered intercellular communication.

through senescence and induce chronic inflammation and tissue dysfunction.[24] To protect chromosomes from various conditions, telomeres have specific loop structures with telomeric DNA and telomere-binding proteins mediated by TRF2.[25] These loop structures are considered to prime telomeric DNA synthesis by telomerase. Telomerase activity can be observed in most proliferating cells. However, somatic cells have low or undetectable levels of telomerase activity. Therefore, telomeres in somatic cells cannot be repaired when shortened.

Telomere shortening is thought to be able to reflect the pace of aging. Telomeres are inevitably lost with aging in normal diploid cells. For example, human liver cells lose 55 bp of telomeric DNA per year and leukocyte telomere length shortens at an average rate of 30–35 bp per year.[26,27]

Telomere length is inversely correlated with age. Thus, a long telomere length is considered to be associated with aging. Several genetic disorders and stressful conditions can accelerate telomere shortening. It has been reported that people with shorter telomeres have significantly poor survival due to higher mortality rates caused by age-related disorders.[28] In addition, shorter telomere length has been continuously reported to be associated with neurodegenerative disorders, which will be discussed later.

TELOMERE LENGTH IN NEURODEDENERATIVE DISORDERS

AD

AD is the most common neurodegenerative disorder. It is a progressive neurological disorder that causes brain atrophy due to neuronal cell death. As AD is one of the most representative age-related diseases and telomere length is strongly correlated with aging, the relationship between the 2 has been studied.[1] It is impossible to obtain brain tissues of living patients with AD. Most studies have used peripheral blood leukocytes (PBLs) to measure telomere length in patients with AD. To accept these findings, it is important to confirm that telomere length of neurons in the brain is well correlated with that of PBLs. Regarding this, Lukens et al.[29] have shown that telomere length in PBLs is strongly correlated with that in the cerebellum of patients with AD. This finding suggests that the telomere length of PBLs can be used to reveal the relationship between telomere length and AD.

Consistent with the hypothesis that shorter telomere length reflecting more rapid aging is associated with neurodegenerative disorders, many studies have shown that patients with AD have shorter telomeres than healthy people.[29-31] Telomere length of patients with AD has been reported to be even shorter than that of patients with mild cognitive impairment (MCI).[31] In Koreans, telomere shortening has been found to be correlated with cognitive decline and dementia conversion in MCI due to AD.[32] Furthermore, patients with AD have greater telomere shortening every year than healthy individuals and patients with MCI.[7,32] Another study has also confirmed that longer AD duration is associated with shorter telomere length.[33] It has been reported that short telomere length could be useful for predicting the incidence of AD among non-*APOE ε4* carriers.[34]

These results regarding the relationship between telomere length and AD suggest that individuals with shorter telomeres are vulnerable to AD. One *in vitro* study using human hippocampal progenitors has suggested that telomere shortening has a negative influence on human cognitive function, namely, a short telomere length can decrease the proliferative capacity and lead to cognitive function impairment in humans.[35]

https://doi.org/10.12779/dnd.2022.21.3.83

However, results of several papers are inconsistent with these findings. One study has reported no correlation between telomere length and cognitive performance among non-demented and demented people in long-life family study participants.[36] It has also been reported that telomere length is not predictive of dementia or MCI conversion in the oldest old.[37] One study has shown that both longer telomere length and shorter telomere length are associated with an increased risk of AD in the Rotterdam study.[10] An *in vivo* study has shown that telomere shortening can reduce AD amyloid pathology in mice, suggesting that shorter telomere length could be beneficial in AD progression.[38] This is in contrast to findings described above.

It remains unclear whether shorter or longer telomeres are preferable for AD. However, more studies have reported that shorter telomeres have harmful effects, whereas longer telomeres have protective effects on AD. This question should first be answered to understand the effect of telomere length on AD. Considering our finding that the annual rate of telomere length change is more important in sleep quality (including sleep duration, sleep latency, and sleep efficiency) than telomer length at a single time point and that poor sleep quality is strongly correlated with faster longitudinal shortening of telomere length,[38] longitudinal or annual measurement of telomere length in healthy people and patients with MCI or dementia could provide some clues.

PD

PD is a progressive nervous system disorder that affects movement, causing tremors, stiffness, or slowing. It is the second most common neurodegenerative disease affecting approximately 2% of the population aged over 60 years.[39,40] In contrast to AD, there have been few studies about the relationship between telomere length and findings about PD are much more conflicting than ones about AD.

Some studies are consistent with the hypothesis that people with shorter telomeres might be more vulnerable to PD. It has been reported that telomere length is shorter in patients with PD than in age-matched healthy controls.[41] Wu et al.[42] have shown that telomere length is significantly shortened in Chinese patients with PD than in controls and that the shortening of telomere length is independent of LRRK2 variants. Another study has reported that telomere length appears to be associated with the time to the onset of motor complications after levodopa treatment initiation.[43] However, the significance of the association disappeared after adjusting for age at inclusion and disease duration, although relationships between telomere length and other PD-related phenotypes remained the same.[43]

However, some studies have reported conflicting results. For example, long telomere length at diagnosis has been reported to be a risk factor for dementia progression in idiopathic parkinsonism.[44] Another study has reported that shorter telomere length is correlated with reduced PD risk.[45]

Other studies have shown no relationship between telomere length and PD. Wang et al.[46] have reported that shorter telomeres are not related to the risk of PD. Hudson et al.[47] have suggested that telomere shortening is not involved in the pathogenesis of PD by showing that longer telomere length is found in blood from patients with PD. However, a difference in telomere length is not found in the substantia nigra compared to controls. A meta-analysis has also suggested that there is no consistent evidence of shorter telomeres in patients with PD.[48]

FTD and amyotrophic lateral sclerosis (ALS)

In the past, FTD and ALS were thought to be completely different diseases. However, the finding that C9orf72 gene mutation can cause both FTD and ALS suggests that they might be spectrum disorders.[49,50] Unfortunately, only a few studies have reported the relationship between telomere length and FTD or ALS.

Regarding ALS, it has been reported that shorter telomeres are associated with earlier ALS onset in animal models.[51] De Felice et al.[52] have also reported that the telomere length of 50 patients with sporadic ALS is significantly shorter than that of 50 healthy subjects. However, a case-control study including 1,241 European patients with ALS has shown that telomere length is longer in patients with ALS than in healthy controls, suggesting that longer telomere length is not favorable for ALS.[53] In contrast, a Mendelian randomization study has suggested that there is no direct causal association between telomere length and ALS. However, Xia et al.[54] have recently used a 2-sample Mendelian randomization approach and shown that longer telomere length is inversely associated with a lower risk of ALS. Therefore, more longitudinal studies are needed to resolve these discrepancies.

In terms of the association between telomere length and FTD, there have been no reports except our previous study,[9] which shows that patients with FTD have longer telomere lengths. Nevertheless, our study had a small sample size. Thus, we could not conclude whether longer telomere length could be a cause of FTD. Therefore, more studies with a larger number of FTD patients and controls should be performed to determine the effect of telomere length on FTD.[9]

CONCLUSION

This review included a number of studies that focused on the relationship between telomere length and neurodegenerative disorders such as AD, PD, FTD, and ALS. Over 50% of papers reported that shorter telomere length could be a definite risk factor for neurodegenerative disorders. However, other studies reported that there were no relationship between them or that longer telomere length could be a risk factor. These conflicting results might be due to differences in study protocols and no lifestyle regulation before blood sampling as well as the use of different ethnicities and time points. Considering our finding that the amount of telomere length alteration might be more important than telomere length at a single time point, large-scale longitudinal studies are necessary in the future. These studies should help us elucidate the causal relationship between telomere length and various neurodegenerative disorders.

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