Journal of the Neurological Sciences 428 (2021) 117565

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Clinical short communication

Increased telomere length in patients with frontotemporal dementia syndrome

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ARTICLE INFO

Keywords:
Frontotemporal dementia
Telomere

ABSTRACT

Background: Telomeres are repetitive DNA sequences of TTAGGG at the ends of chromosomes. Many studies have shown that telomere shortening is associated with aging-related diseases, such as cardiovascular diseases, hypertension, diabetes, cancer, and various neurodegenerative diseases, including Alzheimer's disease, vascular dementia, Parkinson's disease, and dementia with Lewy bodies. However, changes in telomere length (TL) in patients with frontotemporal dementia (FTD) syndrome are unclear. Accordingly, in this study, we assessed TL in blood samples from patients with FTD syndrome.

Methods: Absolute TL was measured in peripheral blood leukocytes from 53 patients with FTD syndromes (25 with behavioral variant FTD, 19 with semantic variant primary progressive aphasia [PPA], six with nonfluent/agrammatic variant PPA, and three with amyotrophic lateral sclerosis [ALS] plus) and 28 cognitively unimpaired (CU) controls using terminal restriction fragment analysis.

Results: TL was significantly longer in the FTD group than in the CU group. All FTD subtypes had significantly longer TL than controls. There were no significant differences in TL among FTD syndromes. No significant correlations were found between TL and demographic factors in the FTD group.

Conclusions: Longer telomeres were associated with FTD syndrome, consistent with a recent report demonstrating that longer telomeres are related to ALS. Therefore, our results may support a shared biology between FTD and ALS. More studies with larger sample sizes are needed.

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https://doi.org/10.1016/j.jns.2021.117565
Received 4 April 2021; Received in revised form 22 June 2021; Accepted 1 July 2021
Available online 3 July 2021

1. Introduction

Frontotemporal dementia (FTD) is the second most common early-onset dementia syndrome characterized by progressive deterioration of behavior or language associated with frontal or temporal degeneration. FTD comprises three clinical phenotypes, namely, behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent/agrammatic variant PPA (nfvPPA). Approximately 10% of FTD can develop amyotrophic lateral sclerosis (FTD-ALS) which arises frequently in bvFTD and less often in svPPA or nfvPPA [1,2]. Additionally, FTD occasionally overlaps with atypical parkinsonian syndromes, such as progressive supranuclear palsy syndrome and corticobasal syndrome [2].

Telomeres are repetitive DNA sequences of TTAGGG located at the ends of chromosomes; these sequences play fundamental roles in DNA replication and repair [3,4]. Telomeres become shorter with aging owing to end-replication. Accordingly, telomere shortening has been reported in various age-related neurodegenerative diseases, including Alzheimer's disease (AD), Huntington's disease, Parkinson's disease, vascular disease, or dementia with Lewy bodies via high oxidative stress, neuroinflammation, or immune senescence [5–9]. There is growing evidence of increased levels of lipid aldehydes which are toxic lipid peroxidation products-conjugated proteins, cortical inflammation, in the form of astrogliosis or microglial activation, in the serum or brain of patients with FTD, and inflammation-associated FTD genes. Further, a substantial level of overlap exists between FTD and immune-mediated disorders. Hence, it is speculated that FTD may share oxidative stress, neuroinflammation, and immune senescence as key pathophysiological elements with other neurodegenerative diseases [10–12], suggesting that telomere shortening may be involved in FTD. However, no studies have investigated the relationships between telomere length (TL) and FTD syndrome.

Therefore, in this study, we explored whether there was an association between FTD syndrome and TL.

2. Materials and methods

2.1. Patients

Patients were prospectively recruited from 14 neurology clinics across Korea between March 2012 and February 2018. All patients enrolled in this study met the FTD criteria proposed by Knopman et al. [13] or the new consensus diagnostic criteria for bvFTD [14], svPPA, and nfvPPA [15]. Patients who had clinical and electrophysiological evidence of ALS were enrolled as having FTD-ALS, regardless of the clinical subtype of FTD. This study was conducted as part of the Clinical Research Center for Dementia of South Korea-FTD (CREDOS-FTD) registry study, which was performed between 2010 and 2018 [16]. Thus, all participants were registered in the CREDOS-FTD registry. Twenty-eight cognitively unimpaired (CU) participants (mean age: 67.9 ± 9.1 years; male: female = 8:20) from one center (Pusan National University Hospital, PNUH) with no previous history of neurological or psychiatric illness, abnormalities in neurological examination, or structural lesions in brain magnetic resonance imaging were included as controls.

Institutional review boards at all participating centers approved this study, and informed consent was obtained from each patient and caregiver.

2.2. TL assay

DNA extracted from whole blood was used in TL assays to examine leukocyte TL. TL analysis was carried out using a nonradioactive TeloTAGGG TL Assay (Roche Boehringer-Mannheim, Grenzach-Wyhlen, Germany). The reason why we used southern blot for TL assay was that it was highly reproducible and commonly used in many comparative research studies [17]. Genomic DNA (2–4 μg) was digested with the restriction enzymes *Rsa*I and *Hin*fI (Roche Diagnostics GmBH, Mannheim, Germany) for 16 h at 37 °C. The resulting DNA fragments were separated on 1% agarose gels using electrophoresis and then denatured, neutralized, transferred to a hybridization nitrocellulose filter (Millipore, Bedford, MA, USA) via capillary transfer using a 20× saline-sodium citrate transfer buffer (Roche Diagnostics GmBH, Mannheim, Germany) and cross-linked with an ultraviolet light (VILBER, France). Blotted DNA fragments were then incubated with a telomeric probe (digoxigenin [DIG] 3′-end labeled 5′-CCCTAA-3; Roche Diagnostics GmBH) at 42 °C for 3 h, followed by incubation with a DIG-specific polyclonal anti-sheep antibody (Roche Diagnostics GmBH) covalently coupled to alkaline phosphatase. Binding sites for the telomere probe were visualized using a highly sensitive chemiluminescence substrate that metabolizes alkaline phosphatase. TL analysis was performed using an image analyzer (ImageQuant LAS 4000; GE Healthcare, Little Chalfont, UK). Mean telomeric repeat-binding factor lengths were determined by comparison with molecular weight standards. In each experiment, we used a positive control and DIG molecular weight markers added to each side of the gel to confirm the reproducibility of TL analysis.

2.3. Genetic analysis

A parallel study of genetic screening using whole exome sequencing (WES) in Korean patients with FTD syndrome was performed by our group. Therefore, two single nucleotide polymorphisms (SNP, rs10936599-*TERC* and rs755017-*RTEL1*) which are known to be involved in mean TL [18,19], and *APOE* genotyping were analyzed by WES. Several SNPs affecting the mean TL other than those two have been identified in genome-wide association studies [18,20]. However, these are located in deep introns or intergenic regions that cannot be evaluated using WES. The method used for WES was previously described [21].

2.4. Statistical analyses

Both FTD patients and controls showed normal distribution of TL. Student's *t*-tests and one-way analysis of variance with Bonferroni's correction were performed to determine significant differences in TL between the FTD and control groups. Because the sample sizes of nfvPPA and FTD-ALS were too small, Kruskal-Wallis and Mann-Whitney *U* tests were used for comparison of TL among each FTD subtype and between nfvPPA or FTD-ALS and control groups. Linear regressions were fitted to determine associations of demographic factors (age, education, sex, disease duration, onset age, frequency of APOE ε4, Korean version of Mini-Mental Status examination [K-MMSE], FTD-Clinical dementia rating [CDR], and family history of dementia) with TL in the FTD group.

3. Results

3.1. Demographic and clinical findings

Among the 200 patients with FTD who participated in the CREDOS-FTD genetic study, fifty-three patients (25 with FTD, 19 with svPPA, six with nfvPPA, and three with FTD-ALS) who had sufficient DNA available for Southern blotting for telomere analysis after WES were included in this study. Of the 53 patients, 13 had been enrolled in our previous genetic study [21]. The mean age was 65.5 ± 10.8 years, and the mean age at disease onset was 60.9 ± 11.3 years. The mean duration of follow-up was 3.5 ± 2.5 years. Seventeen patients (32.1%) had a history of dementia in first-degree relatives. Detailed demographic data of patients with FTD syndrome and controls are summarized in Table 1.

3.2. TL in patients with FTD

The mean TL in the FTD group was 11.4 ± 2.8 kb, whereas that in the

Table 1
Demographics of patients and controls.

	Total	bvFTD	svPPA	nfvPPA	FTD-ALS	Controls	*p*-value**
Number	53	25	19	6	3	28	
Age (y)	65.5 ± 10.8	62.5 ± 13.5	67.9 ± 8.1	65.9 ± 8.0	71.7 ± 6.1	67.9 ± 9.1	0.174
Onset Age (y)	61.1 ± 11.2	58.7 ± 13.1	63.6 ± 8.2	62.7 ± 8.6	62.5 ± 15.9	NA	
Sex (M:F)	22:31	11:14	8:11	2:4	1:2	8:20	0.615
Education (y)	10.1 ± 4.6	11.0 ± 3.8	8.3 ± 4.7	9.6 ± 5.7	15.3 ± 3.1	14.2 ± 3.0	<0.001
Disease duration (y)	3.5 ± 2.5	3.4 ± 2.1	4.1 ± 3.0	3.4 ± 1.9	0.7 ± 0.4	NA	
FTD-CDR (SB)	7.9 ± 5.3	7.9 ± 5.1	8.3 ± 5.6	8.2 ± 6.7	5.3 ± 2.9	NA	
K-MMSE	15.8 ± 8.9	17.8 ± 8.6	13.1 ± 9.2	13.5 ± 8.3	20.3 ± 9.6	27.5 ± 2.0	<0.001
Frequency of APOE ε4 (none:1:2)	38:13:2	19:6:0	13:4:2	5:1:0	1:2:0	22:4:0*	0.900
Family history of dementia	32.1% (17/53)	40% (10/25)	36.8% (7/19)	0% (0/6)	0% (0/3)	NA	
Telomere Length (kb)	11.4 ± 2.8	11.2 ± 2.7	11.5 ± 3.0	11.1 ± 3.2	12.7 ± 2.3	7.2 ± 0.7	<0.001

Abbreviation: ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; CDR, Clinical Dementia Rating; F, female; K-MMSE, Korean version of Mini-Mental State Examination; M, male; NA, not applicable; nfvPPA, non-fluent variant primary progressive aphasia; SB, sum of boxes; svPPA, semantic variant primary progressive aphasia, * Twenty-six out of 28 controls performed APOE genotyping. **comparison between FTD vs controls.

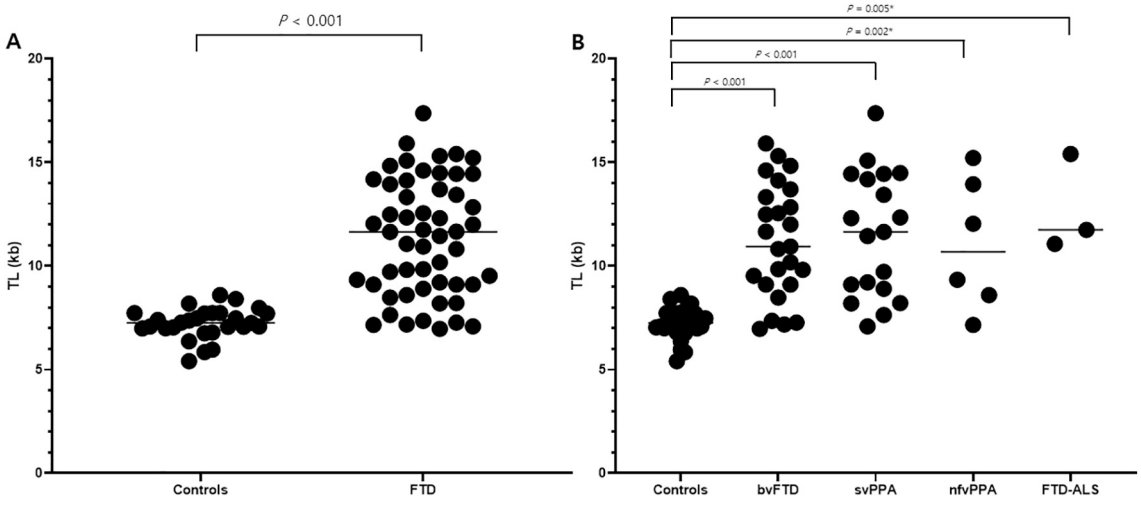

Fig. 1. Telomere length in FTD and control groups.
(A) Telomere length is significantly longer in the FTD group than in the cognitively healthy control group after controlling for age and years of education as covariates.
(B) Telomere length is significantly longer in each FTD subtype than in the cognitively healthy control group. After adjusting for both age and years of education, significant differences are maintained between patients with bvFTD ($p < 0.001$) or svPPA ($p < 0.001$) and controls. * *p*-values were obtained from the Mann-Whitney-U test.

Table 2
Association of clinical characteristics with telomere lengths in patients with FTD.

	B	*t*	*p*-value
Age	−0.040	−1.110	0.272
Sex	−0.360	−0.456	0.650
Onset age	−0.028	−0.796	0.430
Education	−0.100	−1.181	0.243
Duration	−0.016	−1.249	0.217
FTD-CDR	−0.063	−0.846	0.402
K-MMSE	0.004	0.088	0.931
APOE ε4	0.764	0.890	0.378
Family history	0.121	0.144	0.886

Abbreviation: FTD, frontotemporal dementia; CDR, Clinical Dementia Rating; K-MMSE, Korean version of Mini-Mental State Examination; *APOE*, apolipoprotein E.

controls was 7.2 ± 0.7 kb. TL was significantly longer in the FTD group than in controls ($p < 0.001$), even after controlling for age and years of education. There were no significant differences of TL among each FTD subtype ($p = 0.813$). However, all FTD subtypes (bvFTD: 11.2 ± 2.7 kb, svPPA: 11.5 ± 3.0 kb, nfvPPA: 11.1 ± 3.2 kb, FTD-ALS: 12.7 ± 2.3 kb) had significantly longer TL than controls (Fig. 1).

Univariate regression analysis revealed no significant effects of clinical characteristics, such as age, sex, education, onset age, disease duration, APOE ε4 frequency, K-MMSE scores, FTD-CDR, and family history of dementia on TL in patients with FTD syndrome (Table 2).

No significant differences in TL were observed among each genotype of rs10936599-*TERC* ($p = 0.346$) and rs755017-*RTEL1* ($p = 0.784$), (Fig. 2).

4. Discussion

In this study, we observed that TL was longer in patients with FTD syndrome than in CU controls. Each subtype of FTD also showed a longer TL compared with CU controls.

Telomeres play important roles in maintenance of genome stability [22]. Because telomeres become shorter with each somatic cell division, aging and numerous aging-related diseases are associated with TL shortening. Oxidative stress and neuroinflammation, which are essential causes of aging-associated diseases, accelerate the attrition of telomeres [6]. Although many studies have reported that TL shortening is closely related to the pathogenesis of neurodegenerative diseases, results among these studies are quite inconsistent. Under these background conditions, recent meta-analyses have identified consistent evidence of shorter telomeres in AD but not in Parkinson's disease [23,24].

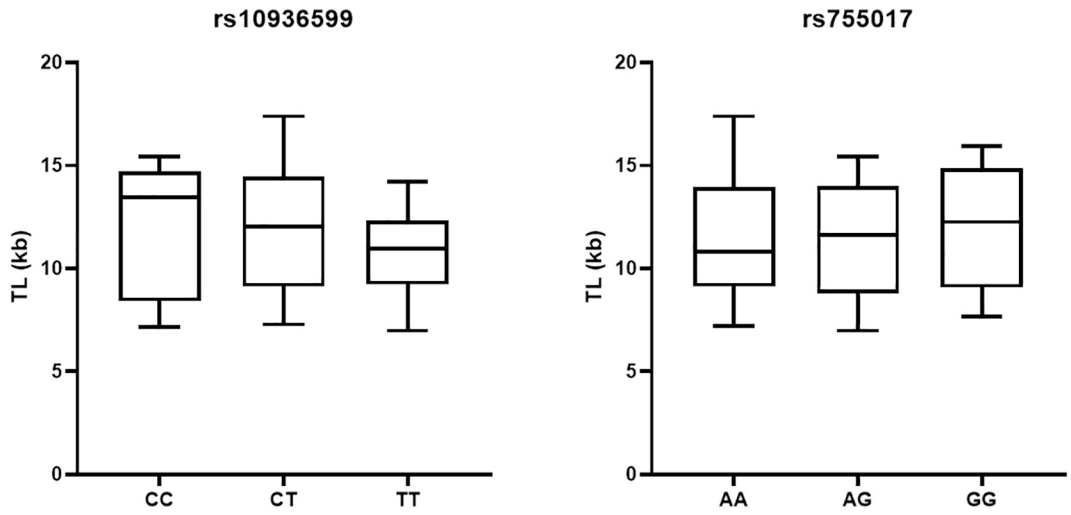

Fig. 2. Telomere lengths according to *TERC* rs10936593 and *RTEL1* rs75017 genotypes in FTD syndrome.
Kruskal-Wallis test showed no significant differences in TLs among each genotypes of rs10936599-*TERC* (p = 0.346) and rs755017-*RTEL1* ($p = 0.784$).

To date, no studies have examined TL in FTD. However, a few studies investigated TL in ALS, but the results were inconsistent. A recent study estimated TL in ALS using a bioinformatics tool on whole genome sequence data and found that longer telomeres were associated with ALS [20]. Another study on TL in human postmortem brain tissue from patients with ALS showed a trend toward longer telomeres in microglial cells; but, the authors also found that shortened telomeres accelerated the disease course in a mouse model of ALS [25]. The other previous study observed shorter telomeres in ALS patients than in controls [26]. FTD shares clinical, genetic, and neuropathological characteristics with ALS; hence, both are considered to be two ends of the same disease spectrum, e.g., the FTD-ALS spectrum [27]. Therefore, the most recent findings on longer telomeres in ALS may be consistent with our results [21]. As described earlier, telomere shortening is associated with aging and aging-related diseases. However, telomere elongation and telomere lengthening are also observed in approximately 15% of human cancers [28,29]. Most human cancers (~85%) with short TL become immortal by reactivating or upregulating telomerase, which is responsible for the de novo synthesis and maintenance of telomere ends [30]. The remaining 15% of tumors use the telomerase-independent pathway referred to as alternative lengthening of telomeres (ALT), which results in elongated telomeres [28,29]. Telomere elongation via ALT in neurodegenerative disease is poorly understood.

Our study has a few limitations. First, the sample sizes of FTD patients, controls, and different FTD subgroups were small, and the samples were relative heterogeneous. Second, in this study, blood samples of patients were collected from 14 different sites and controls' from one center (PNUH). Although genomic DNA of both patients and controls was extracted from peripheral blood leukocytes using a standard procedure, TL assays were performed in three different runs. Therefore, the difference in TL between patients and controls might be due to batch effects. However, to minimize the possible batch effects, two different researchers performed two separate experiments using the same samples, and high levels of consistency between the test values were confirmed, as shown in Supplementary Fig. 2. In addition, the mean TL of four patients with FTD from PNUH (12.8 ± 3.2 kb) was higher than that of controls (7.2 ± 0.7 kb) (Supplementary Fig. 3). Thus, we believe that the difference in TL between patients and controls might not be attributable to batch effects. Third, several demographic factors affect TL, such as age, years of education, and smoking status. Although the result of significantly longer telomeres in FTD patients than in controls was maintained after adjusting for age and years of education as covariates, data on some of these demographic factors (e.g., smoking status) were not available in this study. Despite these limitations, to the best of our knowledge, this is the first study to address and identify the association between TL and FTD syndrome. Further studies replicating our findings and examining genetic and epigenetic factors influencing TL in FTD syndrome are necessary.

Declaration of Competing Interest

The authors have no actual or potential conflicts of interest.

Acknowledgement

This research was supported by the grants 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 (HI20C0253) and the Medical Research Center (2017R1A5A2015395), and a fund (2021-ER1004-00) by Research of Korea Disease Control and Prevention Agency..

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2021.117565.

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