

Telomere Length and Its Association with Progression of Early-onset Dementia: The LEAF cohort study

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- Telomere length was slightly longer in the EOAD group than in the EOFTD group.
- It showed substantial variability across dementia subtypes and genetic variants.
- In cross-sectional analyses, telomere length was not significantly associated with cognitive performance or plasma biomarkers in either EOAD or EOFTD
- Longitudinally, longer telomere length was associated with faster MMSE decline in EOAD

INTRODUCTION

Telomere shortening has been implicated in aging and neurodegenerative processes, but its clinical relevance in young onset dementia subtypes remains unclear.

METHODS

- 388 participants (248 EOAD, 79 FTD, and 62 other dementia)
- Baseline demographics, MMSE, CDR-SB, and blood biomarkers (Aβ40, Aβ42, Aβ40/42 ratio, NFL, GFAP, and p-tau 181, p-tau217 were assessed.
- Telomere length was measured using quantitative PCR.
- Associations between telomere length and longitudinal changes in cognition and biomarkers were analyzed with linear mixed models adjusted for age, sex, APOE ε4 carrier status, and education.

RESULTS

Table1.Comparison of baseline demographic and clinical characteristics of EOAD and EOFTD.

	EOAD (n=194)	EOFTD (n=47)	P value
Age	58.6±4.3	59.6±4.4	0.155
Male (%)	66 (34.0)	19 (40.4)	0.255
Education year	12.4±3.5	11.5±4.2	0.157
Telomere length	7.2±1.1	6.9±1.0	0.044
MMSE	18.3±6.7	19.2±7.5	0.422
FTD-CDR		8.6±6.1	
CDR-SB	6.0±4.5	5.5±4.1	0.493
APOE ε4 carrier	88 (45.4)	34 (72.3)	<0.001

Values are presented as mean ± standard deviation or number (%).

Figure 1. Telomere length according to dementia subtype and genetic variant

A

B

Table2.Association between telomere length and progression of EOAD and EOFTD in the longitudinal study

	β (SE)	P value
EOAD		
MMSE	-0.0293 (0.437)	0.947
CDR-SOB	0.1239 (0.3048)	0.685
Ab40	1.862(1.509)	0.219
Ab42	0.130(0.0861)	0.134
Ab40/42	-0.4034(0.2718)	0.140
GFAP	-4.12(6.19)	0.506
pTau217	-0.174(0.2826)	0.538
NFL	0.135(4.83)	0.987
pTau181	0.904(0.956)	0.345
EOFTD		
MMSE	0.723(1.195)	0.548
FTD CDR-SOB	-1.3446(0.929)	0.156
Ab40	2.892(3.975)	0.471
Ab42	0.00119(0.3451)	0.997
Ab40/42	-0.407(0.608)	0.507
GFAP	-5.063(6.92)	0.469
pTau217	-0.0433(0.3631)	0.906
NFL	8.44(4.318)	0.058
pTau181	4.386(2.196)	0.053

◀Multivariable linear regression models were adjusted for age, sex, education, and telomere length in the FTD and other dementia groups. For the EOAD group, models were additionally adjusted for APOE genotype (MMSE ~ age + sex + education + APOE + telomere length; CDR-SB ~ age + sex + education + APOE + telomere length).

◀Box plots depict telomere length distributions among diagnostic groups, including EOAD, bvFTD, nfvPPA, CBS, svPPA, PSPS, PSEN1, ANXA, and ALSP. Each box represents the interquartile range (IQR, 25th–75th percentile), with the horizontal line indicating the median. Individual black dots correspond to each participant's telomere length, plotted with jitter for visibility. Black circles and error bars denote the mean ± standard deviation (SD) for each group.

Table3.Association between telomere length and progression of EOAD and EOFTD in the longitudinal study

	V1	V2	Coeff(SE)	P for interaction
EOAD				
Cognitive test				
MMSE	18.3±6.74	16.7±7.56	-0.575(0.267)	0.0327
CDR SOB	6.02±4.53	7.07±5.39	0.218(0.167)	0.1936
Blood biomarker				
Ab40	61.04±21.29	55.36±22.26	-2.148(1.649)	0.1954
Ab42	3.64±1.21	3.42±1.33	-0.029(0.095)	0.7596
Ab40/42	17.97±3.85	17.91±4.29	0.121(0.259)	0.6416
GFAP	209.05±87.91	224.2±109.4	1.451(5.337)	0.7863
pTau217	7.96±4.04	9.04±4.58	0.212(0.343)	0.5374
NFL	29.3±71.0	24.4±16.6	-0.540(5.746)	0.925
pTau181	46.0±14.5	48.3±14.6	0.140(1.045)	0.894
EOFTD				
Cognitive test				
MMSE	18.8±7.83	15.7±8.89	-0.985(1.554)	0.5315
FTDCDR-SOB	8.63±6.05	13.8±7.56	-0.245(1.088)	0.8235
Blood biomarker				
Ab40	61.5±23.5	51.6±22.7	3.201(5.544)	0.5690
Ab42	4.36±2.09	3.98±1.50	0.488(0.377)	0.2124
Ab40/42	14.9±3.78	14.2±2.79	0.197(0.584)	0.7390
GFAP	104.0±43.1	121.0±63.2	6.058(9.438)	0.5264
pTau217	4.07±2.11	3.84±2.86	-0.429(0.567)	0.4569
NFL conc	46.4±29.0	41.8±26.0	1.721 (3.377)	0.6147
pTau181	26.9±14.0	25.8±12.8	-5.866 (2.248)	0.0147

Values represent estimated coefficients (SE) derived from linear mixed-effects models adjusted for age, sex, APOE ε4 carrier status, and years of education.

Figure 2. Longitudinal changes in MMSE according to telomere length in the EOAD group.

Time × telomere length interactions on MMSE were analyzed using linear mixed-effects models

CONCLUSION

- TL showed limited associations with cross-sectional disease severity.
- However, longer TL was associated with faster cognitive decline in EOAD but not EOFTD
- TL may reflect heterogeneity in disease progression rather than disease severity.

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