

Comparing Telomere Length and a Methylation-Based Estimator of Telomere Length in a Cohort of Maltreated Children

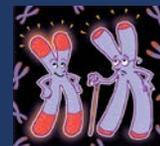
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The Pennsylvania State University

TRN Annual Meeting – December 4, 2020



PennState



Shalev Lab – Department of Biobehavioral Health

Background: aTL

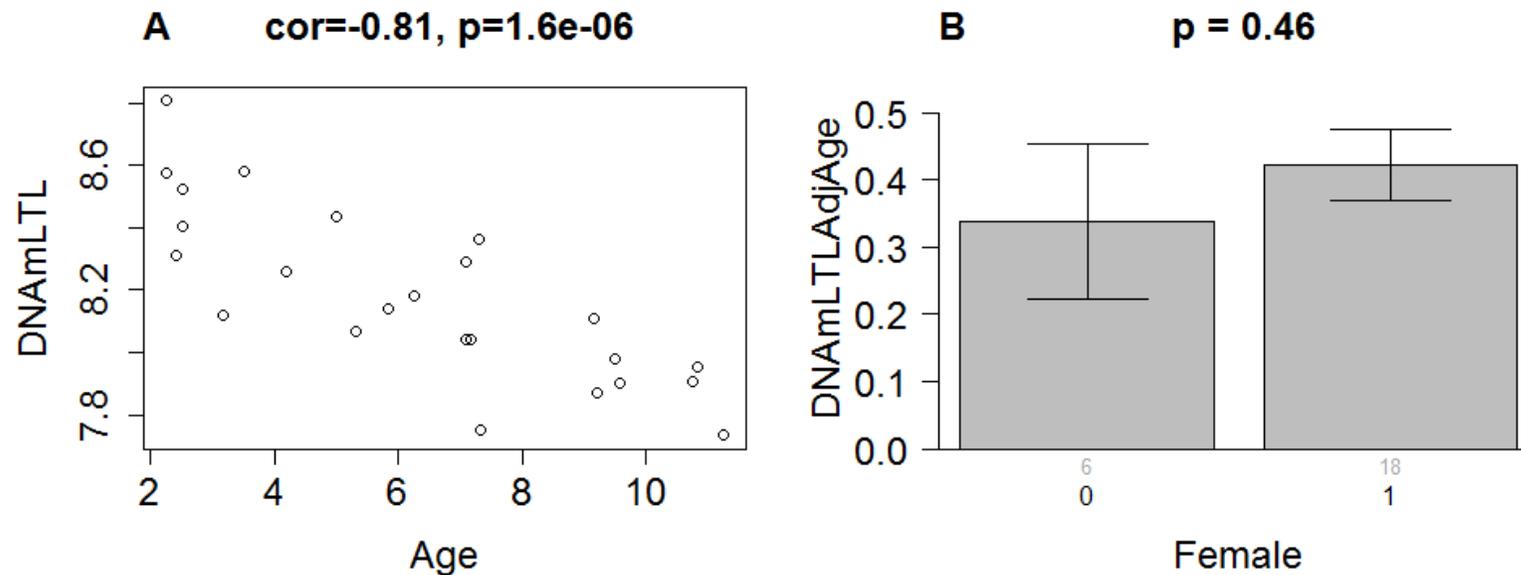
- Estimates TL (in bp) using qPCR
- Strengths
 - High throughput
 - Objective measure in kilobase pairs directly comparable to assessments by other methods (e.g, Southern blot, Flow-FISH, etc.)
 - Simultaneous assessment of T/S ratio
- Limitations
 - Oligomer standards have very low DNA concentration
 - Difficult to accurately construct/quantify

Background: DNAmTL

- Estimate TL (in bp) based on methylation status of 140 CpGs
- Trained to approximate TL measurement by Southern blot
 - Trained on 2,256 individuals aged 22-93 years from Framingham Heart Study, Women's Health Initiative, and Jackson Heart Study
- Validity Metrics
 - $r = 0.38$ to 0.50 with Southern blot
 - $r = 0.40$ with qPCR (aTL)
 - $r = -0.80$ to -0.62 with age
 - Predictive of mortality, heart disease, heart failure, smoking history

DNAmTL in Children

- $r = -0.81$ with age ($n=24$)
- Shorter age-adjusted DNAmTL in males relative to females



Proposed Study

- Assess aTL and DNAmTL in a cohort (n=275) of children from an ongoing NICHD study (*Child Health Study; P50HD089922*)
- Aim 1: Compare associations between aTL/DNAmTL/T:S with metrics of external validity
 - Age
 - Sex
 - Pubertal development (Tanner Stage)
 - Paternal Age
- Aim 2: Examine moderating effect of child maltreatment on associations in Aim 1

Sample Demographics

	Mean/%	(SD)
Age (years)	11.42	(1.52)
DNAmTL (kb)	8.04	(0.18)
Paternal Age (years)	41.01	(8.27)
BMI	21.83	(5.99)
Tanner Stage	2.45	(1.05)
Sex		
Male	49.8%	
Female	50.2%	
Race		
White	65.5%	
African American	17.8%	
American Indian or Alaskan Native	0.7%	
Multiracial	12.0%	
Other	4.0%	
Maltreatment Status		
Risk	82.5%	
Control	17.5%	

Data Structure

Wide Format

ID	DNAmTL	aTL	T/S
1	X_1	Y_1	Z_1
2	X_2	Y_2	Z_2
3	X_3	Y_3	Z_3
...
275	X_{275}	Y_{275}	Z_{275}

Long Format

ID	TL	Approach
1	X_1	DNAmTL
1	X_2	aTL
1	X_3	T/S
2	X_4	DNAmTL
2	X_5	aTL
2	X_6	T/S
3	X_7	DNAmTL
3	X_8	aTL
3	X_9	T/S
...
275	X_{823}	DNAmTL
275	X_{824}	aTL
275	X_{825}	T/S

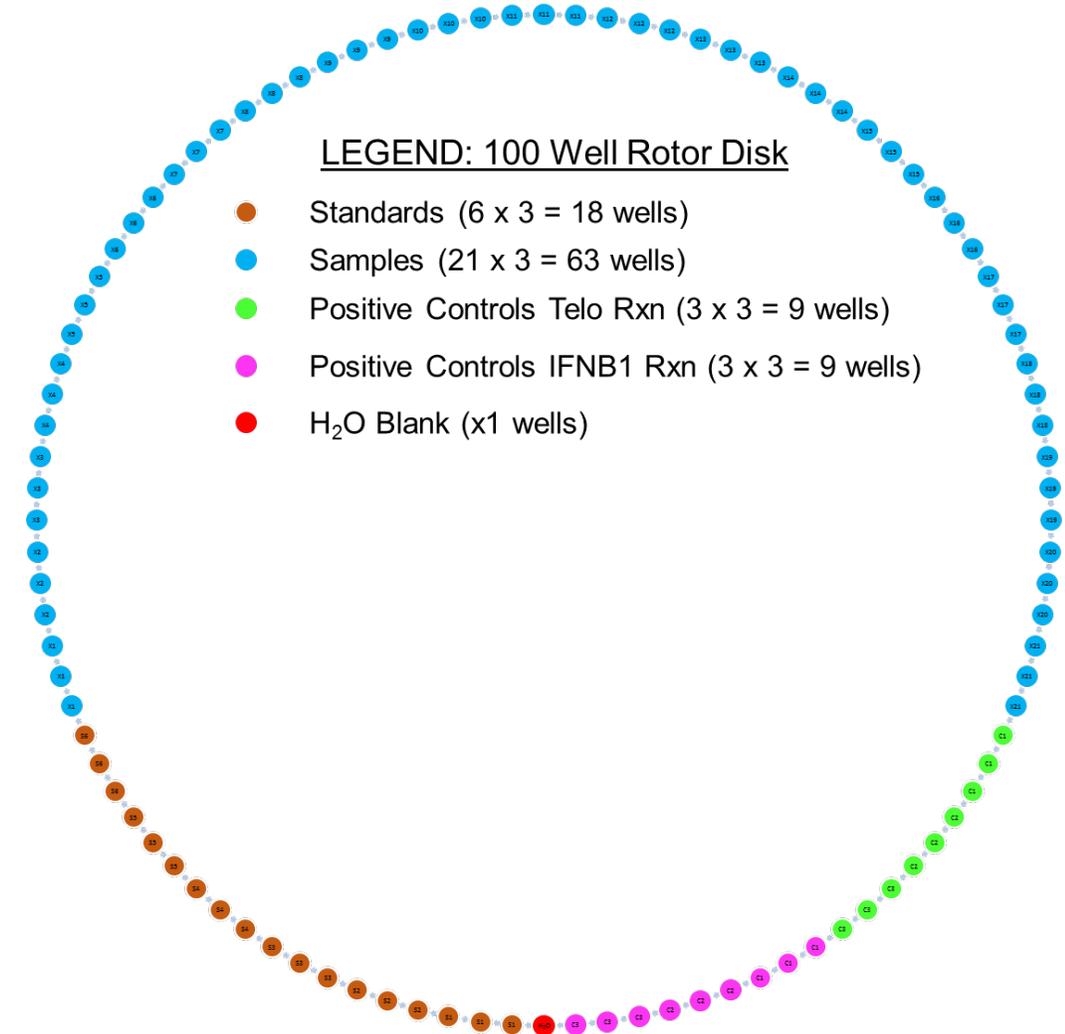
Analytical Plan*

- Comparing distribution of DNAmTL vs. aTL vs. T:S (normalized)
 - Paired samples t-tests (wide data format)
 - Nested ANOVA w/post-hoc comparisons using 'Approach' variable (long data format)
 - Interaction term in ANOVA models (e.g., Approach x Sex)
- Comparing associations between aTL/DNAmTL/T:S with metrics of external validity (age, pubertal development, paternal age)
 - Partial correlations controlling for sex, race/ethnicity, BMI, and age
 - Compare 83.4% confidence intervals; no overlap → significantly different
- Examine moderating effect of child maltreatment
 - Subgroup analysis within each approach (DNAmTL vs. aTL vs. T:S)
 - ANOVA models predicting external validity metrics w/interaction term for maltreatment status (e.g., DNAmTL x Status)

*Age-adjusted measures (residuals) will be used where appropriate

aTL Assays

- Assessment of TL via qPCR
 - Single copy gene: *IFNB1*
- Two PCR runs per assay (1 T run & 1 S run)
 - Each assayed in triplicate using same DNA aliquot
- Account for differences in amplification efficiency between SCG and TELO reactions using LinRegPCR
- Account for inter-run and inter-assay variation using 3 control samples amplifying T and S on each run (18 wells)



For More Details...

The screenshot shows the OSFHOME interface. The top navigation bar includes 'OSFHOME' with a dropdown arrow, 'My Quick Files', 'My Projects', 'Search', 'Support', 'Donate', and a user profile for 'Waylon Hastings'. Below this is a secondary navigation bar with 'Comparing Telomere Length and a Met...' (highlighted), 'Files', 'Wiki', 'Analytics', 'Registrations', 'Contributors', 'Add-ons', and 'Settings'. The main content area features the project title 'Comparing Telomere Length and a Methylation-based Estimator of Telomere Length in a Cohort of Maltreated Children' in large text. To the right of the title are buttons for '69.7KB', 'Make Private', 'Public', '0', and a menu icon. Below the title, it lists 'Contributors: Waylon Hastings', 'Date created: 2020-10-19 03:13 PM | Last Updated: 2020-11-19 12:00 AM', 'Identifier: DOI 10.17605/OSF.IO/A6TFY', and 'Category: Project'. A description follows: 'Description: NICHD funded work investigating different approaches for the measurement of telomere length as proxies of biological aging. License: CC-By Attribution 4.0 International'. At the bottom, there are two panels: 'Wiki' with a text input area containing the placeholder 'Add important information, links, or images here to describe your project.' and a 'Citation' panel with a dropdown arrow. A 'Components' panel at the bottom right contains 'Add Component' and 'Link Projects' buttons.

Questions/Comments?

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