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

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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

O'Callaghan & Fenech (2011) *Biological Procedures online. 13*(1)

Background: DNAmTL

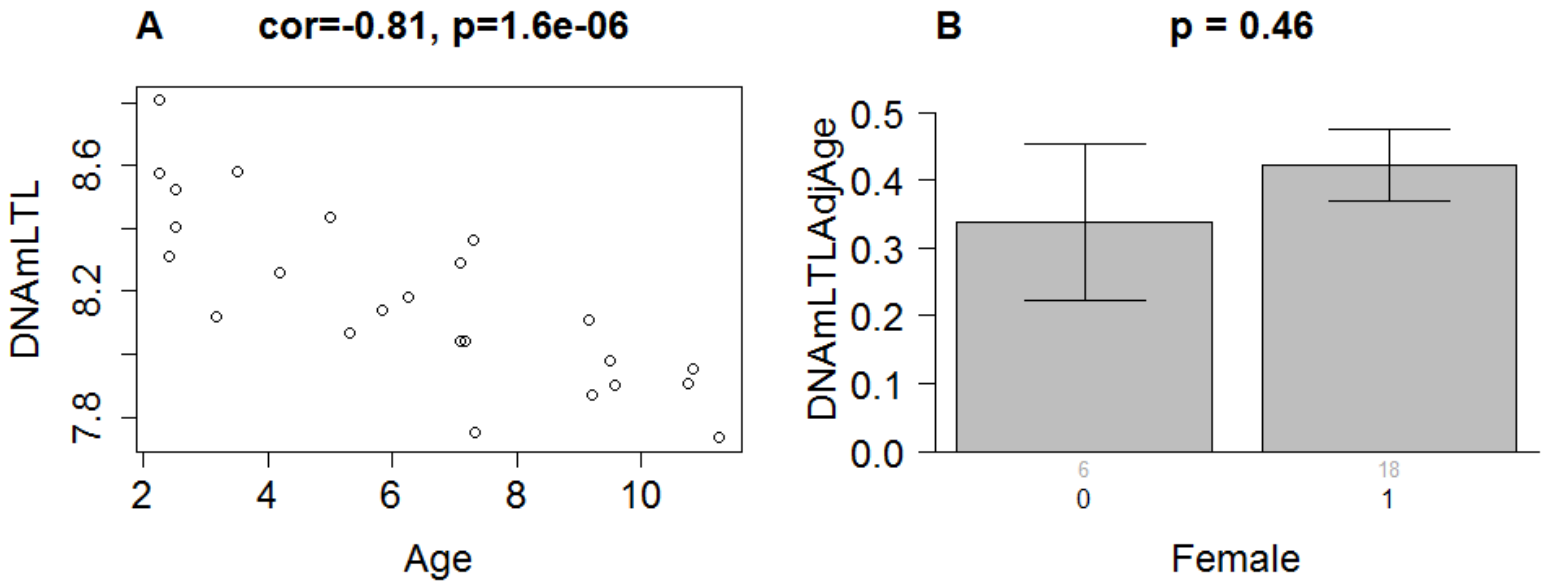
- Estimate TL (in bp) based on methylation status of 140 CpGs
- Trained to approximate TL measurement by Southern blot
  - Trained on 2,256 individuals aged 22-93 years from Framingham Heart Study, Women's Health Initiative, and Jackson Heart Study
- Validity Metrics
  - r= 0.38 to 0.50 with Southern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

Lu, A.T., et al. (2019) *Aging. 11*(16): 5895-5923.

DNAmTL in Children

- r= -0.81 with age (n=24)

- Shorter age-adjusted DNAmTL in males relative to females



Lu, A.T., et al. (2019) *Aging. 11*(16): 5895-5923.

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

doi: 10.17605/OSF.IO/A6TFY

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 Indican or Alaskan Native	0.7%	
Multiracial	12.0%	
Other	4.0%	
Maltreatment Status		
Risk	82.5%	
Control	17.5%	

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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

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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

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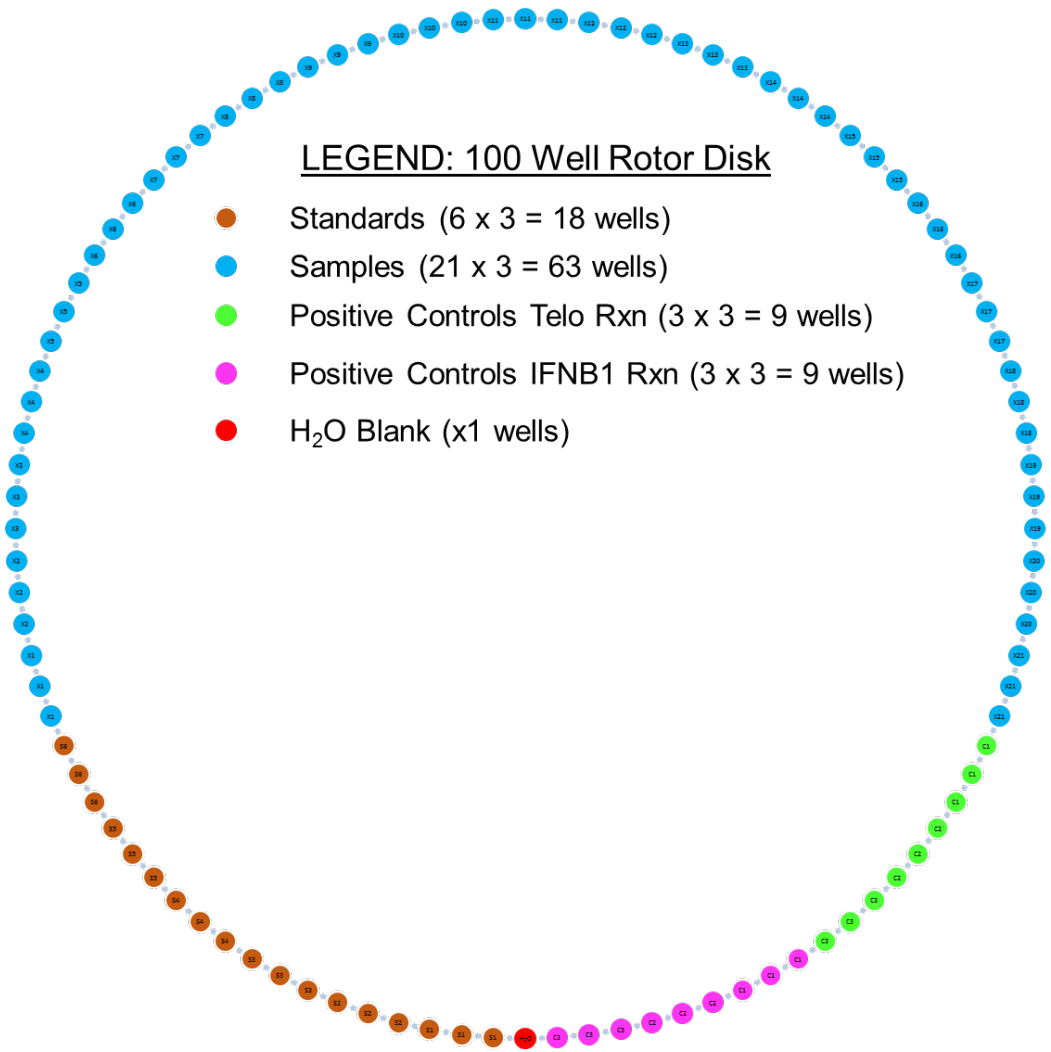
aTL Assays

- 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)



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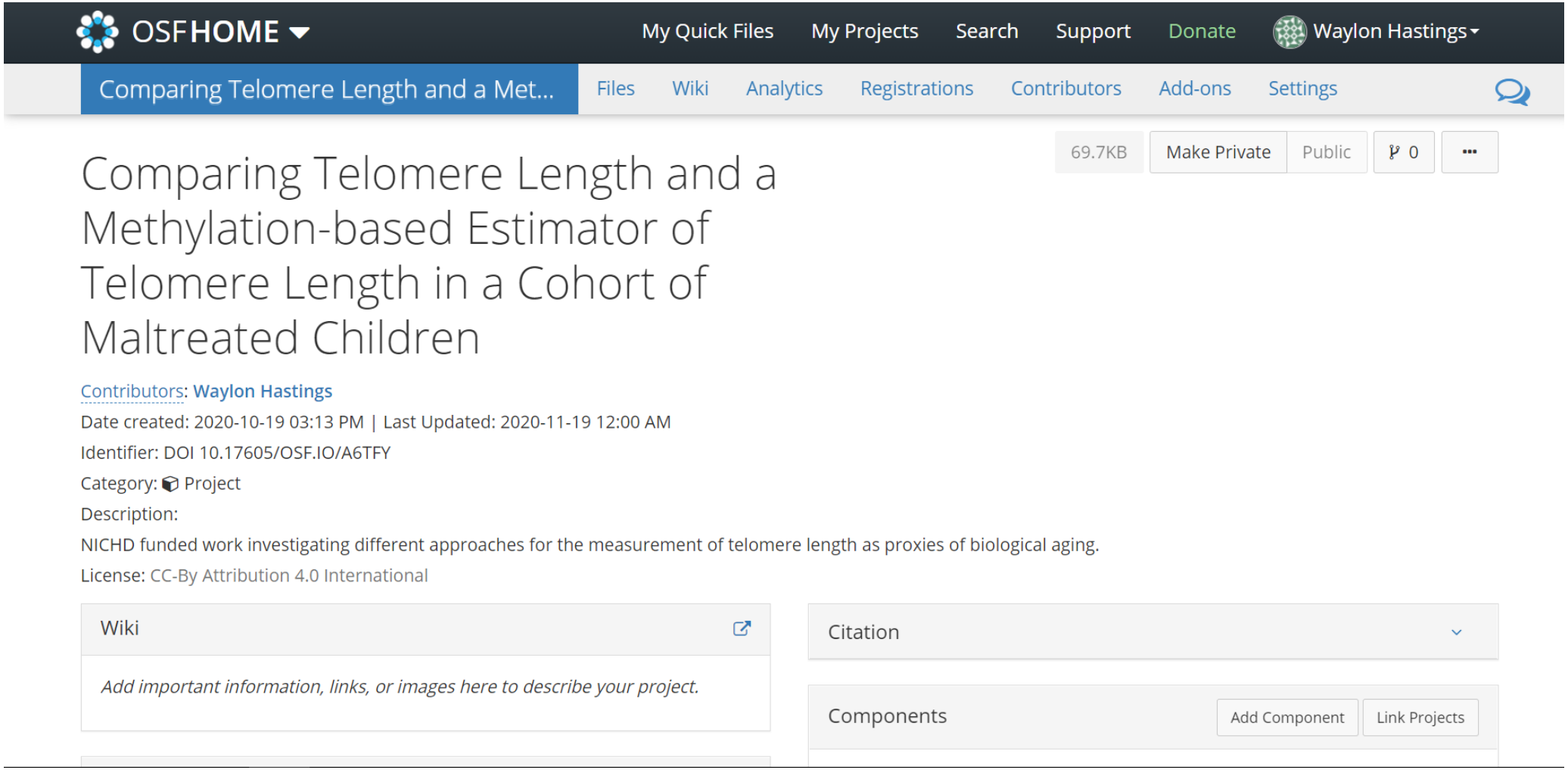
For More Details…



Questions/Comments?

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