The Role of Telomeres in Human Longevity and Aging

Richard M. Cawthon, MD, PhD

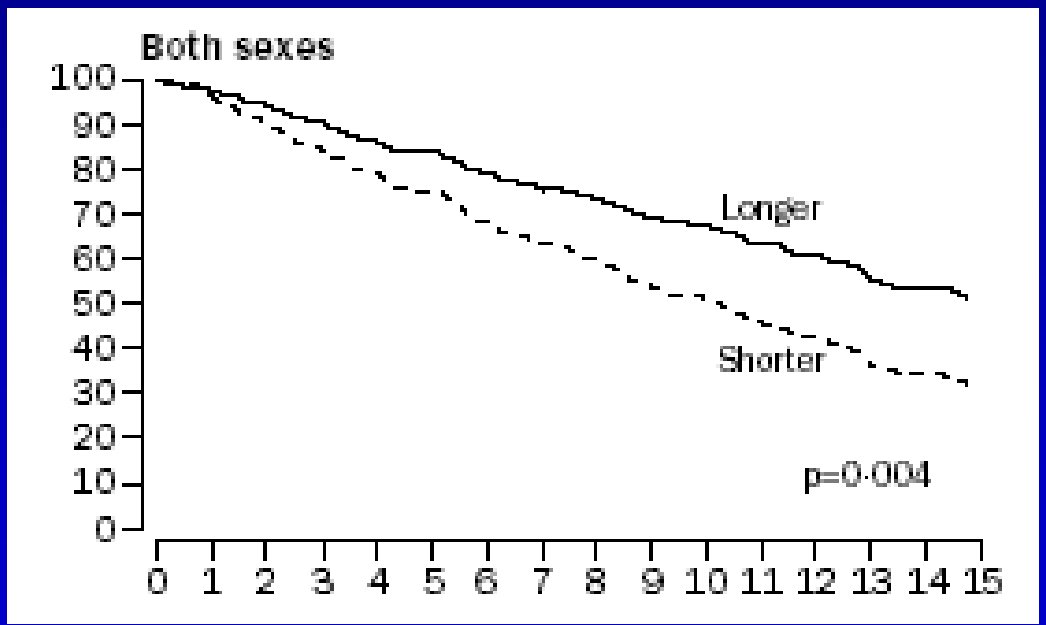
University of Utah

Wen-Chi Hsueh, MPH, PhD

University of California, San Francisco

TL vs. Survival in Humans

- Mendelian disorders exhibiting features of premature aging and accelerated telomere loss
- Shorter telomere length (TL) associated with poorer survival



TL vs. Aging in Humans

- Shorter TL associated with age-related diseases and intermediate traits
- Most studies done in Caucasian populations, many with small sample sizes

++	CVD (e.g. MI, heart failure, BP)
+	diabetes, insulin resistance, BMI
+/-	cognitive function, dementia
	rheumatoid arthritis
	BMD, osteoarthritis

Project Hypotheses

- Individuals with short telomeres have poorer survival, a higher mortality rate and fewer years of healthy life (YHL) vs. those with longer telomeres
- shorter telomeres are associated with certain aspects of aging
- Genetic variants in the TERC (telomerase RNA component) gene are associated with TL, mortality, and YHL

Health Aging, and Body Composition (Health ABC) Study

- population-based prospective cohort study
- Functional Caucasian and African Americans aged 70 – 80 yr at baseline
- Recruited in Pittsburgh or Memphis
- Semi-annual f/u for vital status (latest: Oct 07, Y10)
- Annual f/u for YHL (latest: Y9)
- Extensively phenotyped for age-related traits

Characteristics of Study Subjects

	African Am.	Caucasian Am.
N (% male)	1,115 (42%)	1,606 (46%)
Age (yr)	73.5 ± 2.9 70 - 80	73.8 ± 2.9 70 - 80
TL (bp)†		
Male	4,623 ± 1,133	4,586 ± 1,226
Female	5,046 ± 1,196*	4,973 ± 1,252*

† Measured based on a Q-PCR method
Converted to base-pairs using Southern blot results of reference samples
* Male vs. Female, $p < 0.05$

Potential Risk Factors for TL

- Race
- **Age at baseline** **--**
- Recruitment site
- **Sex (F vs. M)** **+++**
- **Circulating oxLDL levels** **---**
- Smoking and alcohol consumption
- Physical activity
- **SES (education** and family income**)** **++**

+: protective factor, **-** : risk factor

1˚ Outcomes of Interest: Survival and YHL

	African Am.	Caucasian Am.
Duration of f/u (yr)	7.9 ± 2.5	8.4 ± 2.1
Lifespan (yr)†		
Male	80.4 ± 3.7	79.2 ± 4.1**
Female	80.4 ± 3.7	79.5 ± 3.9*
YHL (yr)	4.7 ± 2.9	6.2 ± 2.9**

†: based on 399 African Am. and 433 Caucasian Am. (31% of 2,721 subjects)
*: $p < 0.05$; ** $p < 0.001$

TL vs. Survival
Hazard Ratio (95% CI)

Covariate	Combined	Af. Am	Cau. Am.
Age (yr)	1.08 (1.05 - 1.11)	1.05 (1.02 - 1.09)	1.11 (1.07 - 1.15)
Sex (F vs. M)	0.57 (0.50 - 0.66)	0.57 (0.47 - 0.70)	0.59 (0.48 - 0.72)
TL* (1sd, 1228 bp)	0.97 (0.90 - 1.04)	0.96 (0.87 - 1.07)	0.97 (0.88 - 1.07)

* Adjusted for age, sex, site, and assay batch

Mean f/u time: 8.2 ± 2.3 yr (0.02 – 10.4 yr)

Power < 0.3

TL vs. YHL, ICOD

Outcome	n	β ± s.e.	HR (95%CI)	P
YHL		0.11 ± 0.05	----	**0.03**
ICOD*				
CHD	130	---	0.97 (0.81 - 1.16)	0.7
CVD	35	---	0.83 (0.59 - 1.18)	0.3
Cancers	4	---	0.72 (0.25 - 1.31)	0.5
Respiratory Dz	72	---	0.79 (0.60 - 1.02)	**0.07**
Sepsis	49	---	0.72 (0.53 - 0.98)	**0.04**

Adjusted for age, sex, site, race, and assay batch
Effect size for 1s.d. unit of TL (1228 bp)
* Status determined as of Aug 05. To be updated

2˚ Quantitative Outcomes of Interest

- CVD
- Inflammation
- Diabetes / obesity
- Cognitive function
- Pulmonary function
- Physical function
- Osteoporosis
- Vision
- Hearing

Association (β / p): TL vs. CVD-Related Traits

Outcome	Association w/ survival	Combined	Af. Am.	Cau. Am.
Heart rate	**+++**	**-0.65 / +**	-0.61 / -	**-0.67 / +**
PWV	++	9.5 / -	4.4 / -	12.3 / -
SBP	-	0.23 / -	0.16 / -	0.29 / -
DBP	-	0.04 / -	0.22 / -	-0.18 / -
Ankle-Arm I	+++	0.00 / -	0.00 / -	0.00 / -
Total Chol.	+	0.00 / -	0.31 / -	-0.18 / -
LDL-C	-	-1.19 / -	-0.69 / -	-1.50 / -
HDL-C	**-**	**0.81 / ++**	0.54 / -	**0.99 / ++**
TG	-	0.65 / -	2.12 / -	-0.21 / -

Strength of association +: p = 0.01-0.05; ++: p = 0.001-0.01; +++: p < 0.001

Association (β / p): TL vs. Inflammation Markers

Outcome	Association w/ survival	Combined	Af. Am.	Cau. Am.
WBC	++	-0.02 / -	-0.04 / -	0.05 / -
CRP	**+++**	**-0.17 / +**	**-0.30 / +**	-0.09 / -
IL-6	+++	-0.03 / -	-0.05 / -	-0.01 / -
PAI-1	**+++**	-0.60 / -	0.75 / -	**-1.54 / +**
TNF- α	**+++**	**-0.13 / +++**	-0.08 / -	**-0.16 / +++**

Strength of association +: p = 0.01-0.05; ++: p = 0.001-0.01; +++: p < 0.001

Association (β / p): TL vs. Diabetes / Obesity

Outcome	Assoc. w/ survival	Af. Am.	Cau. Am.	Combined
Glucose	++	-0.72 / -	0.86 / -	-0.79 / -
HbA1c	**+++**	-0.02 / -	**-0.05 / +**	-0.04 / -
Insulin	**-**	-0.04 / -	**-0.50 / +++**	**-0.33 / ++**
BMI	**-**	0.04 / -	**-0.30 / ++**	-0.16 / -
% fat	**+++**	-0.21 / -	**-0.51 / +++**	**-0.39 / +++**
Visceral fat	**-**	1.06 / -	**-5.38 / ++**	**-2.81 / +**
Subcu. fat	**++**	-2.60 / -	**-9.26 / +++**	**-6.60 / ++**
Leptin	**+**	**0.78 / +**	0.11 / -	0.38 / -

Strength of association +: p = 0.01-0.05; ++: p = 0.001-0.01; +++: p < 0.001

Association (β / p): TL vs. Other Age-Related Traits

Outcome	Assoc. w/ survival	Combined	Af. Am.	Cau. Am.
MMSE	+++	0.13 / -	0.22 / -	0.07 / -
% FEV1	**+++**	**1.00 / +**	**2.04 / ++**	0.32 / -
%FVC	**+++**	0.44 / -	**1.38 / +**	-0.20 / -
Grip strength	**+++**	0.26 / -	**0.48 / +**	0.11 / -
Walking speed 400m	**+++**	**0.01 / ++**	**0.01 / +**	**0.01 / +**

TL not associated with BMD, hearing and vision (contrast sensitivity)

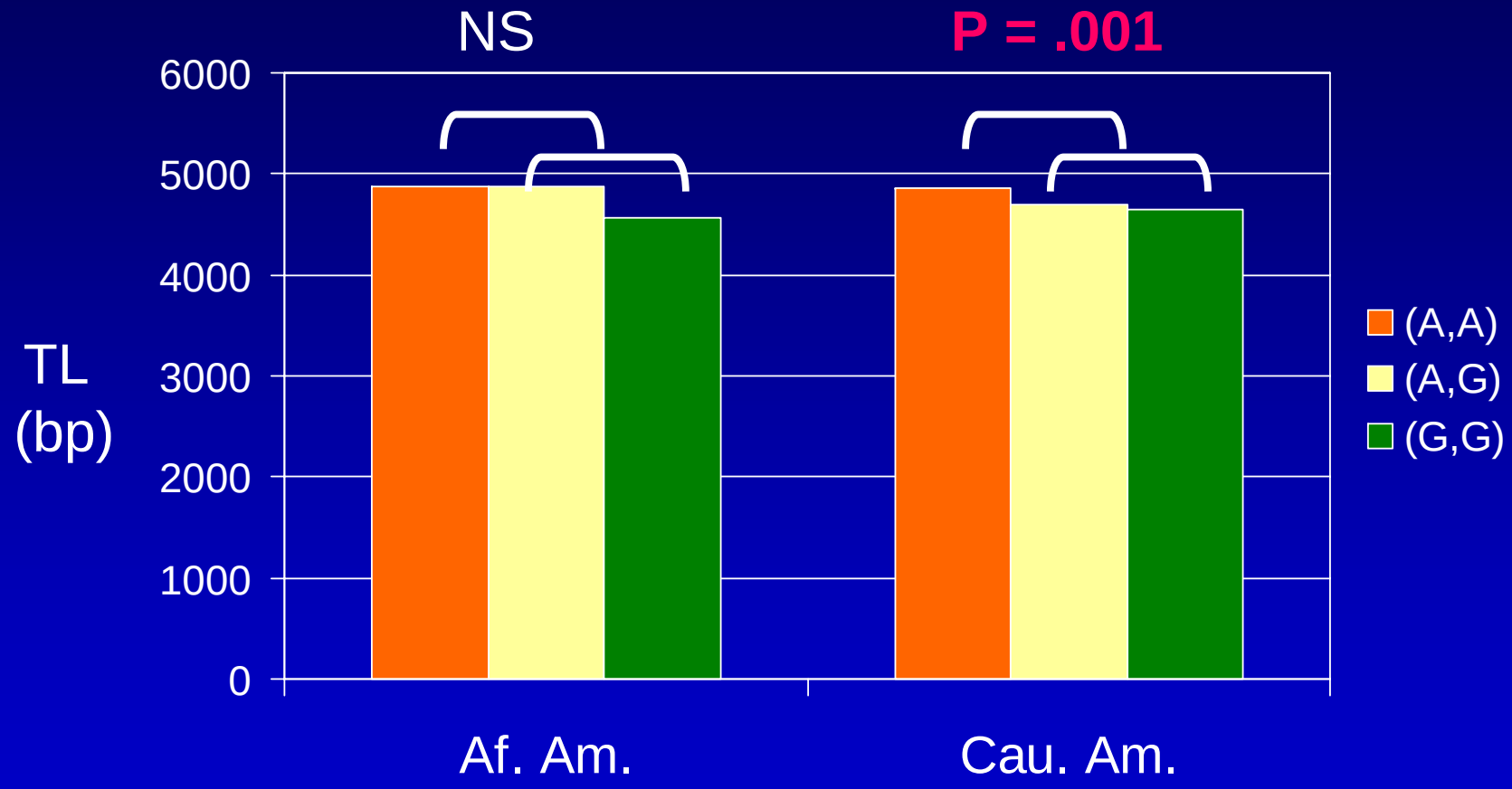
Strength of association +: p = 0.01-0.05; ++: p = 0.001-0.01; +++: p < 0.001

Variants Identified in the TERC Gene Through Sequencing Studies

- CVD Sequenced regions: 451 bp coding region, 385 bp 5’ end and 265 bp 3’ end
- N = 40 Caucasians and 40 African Am.

Base #	Location	MAF in Af. Am.	MAF in Cau. Am.
800	5’ upstream	0	0
1102	RNA coding region	5%	0
1272	RNA coding region	2%	0
1558 (rs2293607)	**3’ end**	**7%**	**24%**
1677	3’ end	0	0

Association Between rs2293607 and TL



P = 0.001 after adjustment of age, sex, site, race, and assay batch

Association Between rs2293607 and Survival, YHL

- **Survival (AA vs. G+, a dominant model)**
  - Combined: HR = 0.87 (95% CI = 0.75 – 1.02, p = 0.1)
  - Af. Am.: HR = 0.80 (95% CI = 0.61 – 1.06, p = 0.1)
  - Cau Am.: HR = 0.91 (95% CI = 0.75 – 1.10, p = 0.3)
- **YHL**
  - Combined: $\beta = 0.15 \pm 0.11$ (p = 0.2)
  - Af Am.: $\beta = 0.28 \pm 0.23$ (p = 0.2)
  - Cau Am.: $\beta = 0.11 \pm 0.12$ (p = 0.4)
- **Association not affected by adjustment of TL**

Summary

- TL-affecting traits mostly associated with survival
- Effect of TL measured in older people on survival may be small
- New findings:
  - oxLDL as a significant risk factor for TL
  - Shorter TL associated with poorer heart rate, lung function, and TNF- α
- TL may be more associated with certain aspects of aging (e.g. CVD, DM, physical function)
- TERC variants affect variation in TL
- TL as a promising biomarker of aging
- Some associations may be influenced by genetic background

Limitations

- No information on WBC subtypes, so not possible to control for the distribution of them in the analysis
- Small sample sizes for COD analysis
- Survival analysis may require longer time of f/u
- Can not differentiate the effect of TL vs. rate of telomere attrition on the outcomes
- Role of telomerase requires to be studied