Correlation Analyses Between Telomere Length and DNA Methylation Clocks

Emily Pearce[1], Steve Horvath[2], Shilpa Katta[1,3], Casey Dagnall[1,3,4], Geraldine Aubert[5], Stephen Spellman[6], Rotana Alsaggaf[1], Shahinaz Gadalla[1]

[1] Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, NCI, NIH, Bethesda, MD, [2] Department of Biostatistics, UCLA, CA, [3] Cancer Genomics Research Laboratory, Division of Cancer Epidemiology and Genetics, NCI, NIH, Rockville, MD, [4] Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD, [5] Terry Fox Laboratory, British Columbia Cancer Agency, Vancouver, BC, Canada, [6] Center for International Blood and Marrow Transplant Research, Minneapolis, MN

Introduction

- Biological age is a predictor for many health outcomes, but the relationship between biological markers of aging is still being defined.
- DNA methylation-based clocks (epigenetic clocks) and telomere length (TL) are both biological markers of aging, but their relationship is not fully understood.
- We examined the associations between five epigenetic clocks and two TL assays to investigate the relationship between measures of biological aging.

Methods

- 635 healthy individuals (67% Male, 75% White)
- Chronological age 19-61 yrs (Median=35 yrs)

TELOMERE LENGTH ASSAYS

- **qPCR**: Average TL (T/S ratio z-score, n=635)
- **flow FISH**: Total lymphocyte TL (kb, n=144)

EPIGENETIC CLOCKS

- Based on Chronological Aging
  - **Hannum**: Whole blood (71 CpGs)
  - **DNAmAge**: Pan tissue (353 CpGs)
  - **SkinBlood**: Buccal/blood/skin (391 CpGs)
- Based on Phenotypic Aging
  - **PhenoAge**: Aging phenotypes (513 CpGs)
  - **GrimAge**: All cause mortality (1030 CpGs)

AGE ACCELERATION

- **Age Acceleration Residual (AAR)**
  - Deviation from expected biological age (using DNAmAge) for chronological age
- **Intrinsic Epigenetic Age Acceleration (IEAA)**
  - Controls for immune cell counts
- **Extrinsic Epigenetic Age Acceleration (EEAA)**
  - Upweights immune cell counts

Figure 1. Correlation between: (a) flow FISH TL and epigenetic clocks; (b) qPCR TL and epigenetic clocks; (c) age-adjusted flow FISH TL and age acceleration; (d) age-adjusted qPCR TL and age acceleration.

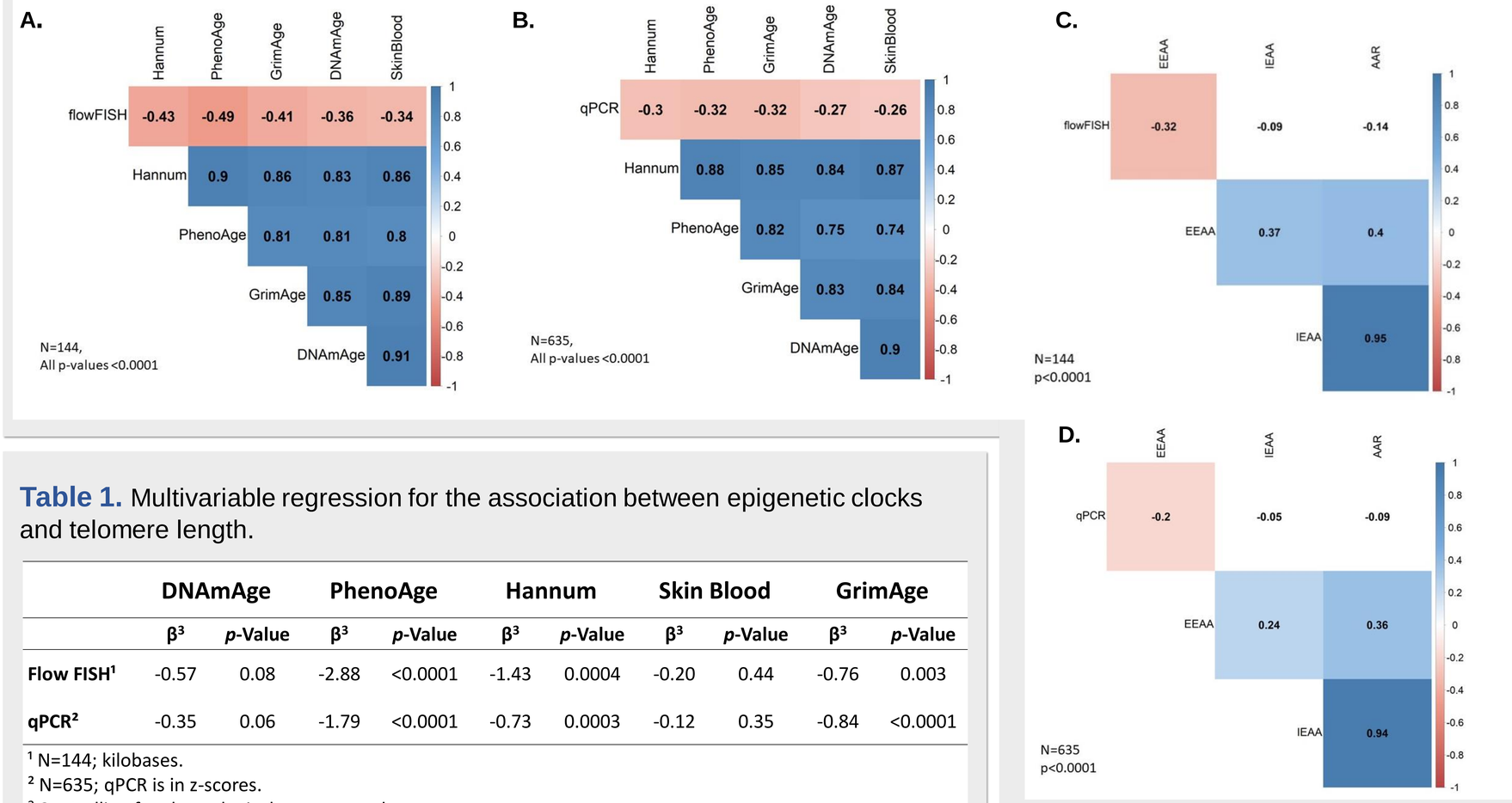

Table 1. Multivariable regression for the association between epigenetic clocks and telomere length.

	DNAmAge		PhenoAge		Hannum		Skin Blood		GrimAge	
	β[3]	*p*-Value	β[3]	*p*-Value	β[3]	*p*-Value	β[3]	*p*-Value	β[3]	*p*-Value
Flow FISH[1]	-0.57	0.08	-2.88	<0.0001	-1.43	0.0004	-0.20	0.44	-0.76	0.003
qPCR[2]	-0.35	0.06	-1.79	<0.0001	-0.73	0.0003	-0.12	0.35	-0.84	<0.0001

[1] N=144; kilobases.
[2] N=635; qPCR is in z-scores.
[3] Controlling for chronological age, sex, and race.

Table 2. Multivariable regression for the association between epigenetic age acceleration (using DNAmAge) and age-adjusted telomere length.

	AAR		IEAA		EEAA	
	β[3]	*p*-Value	β[3]	*p*-Value	β[3]	*p*-Value
Age-Adjusted flow FISH[1]	-0.57	0.08	-0.38	0.25	-2.54	<0.0001
Age-Adjusted qPCR[2]	-0.35	0.06	-0.16	0.35	-1.56	<0.0001

[1] N=144; kilobases.
[2] N=635; qPCR is in z-scores.
[3] Controlling for sex and race.

Conclusion

- The relationship between TL and epigenetic clocks was mainly observed in clocks that reflect phenotypic age.
- TL association with the EEAA, but not other age acceleration, indicates the ability of both measures to identify immunosenescence.
- More research is warranted to understand the interplay between markers of biological aging.

The study is funded by the NCI Intramural Program