

RESEARCH ARTICLE SUMMARY

HUMAN GENOMICS

Determinants of telomere length across human tissues

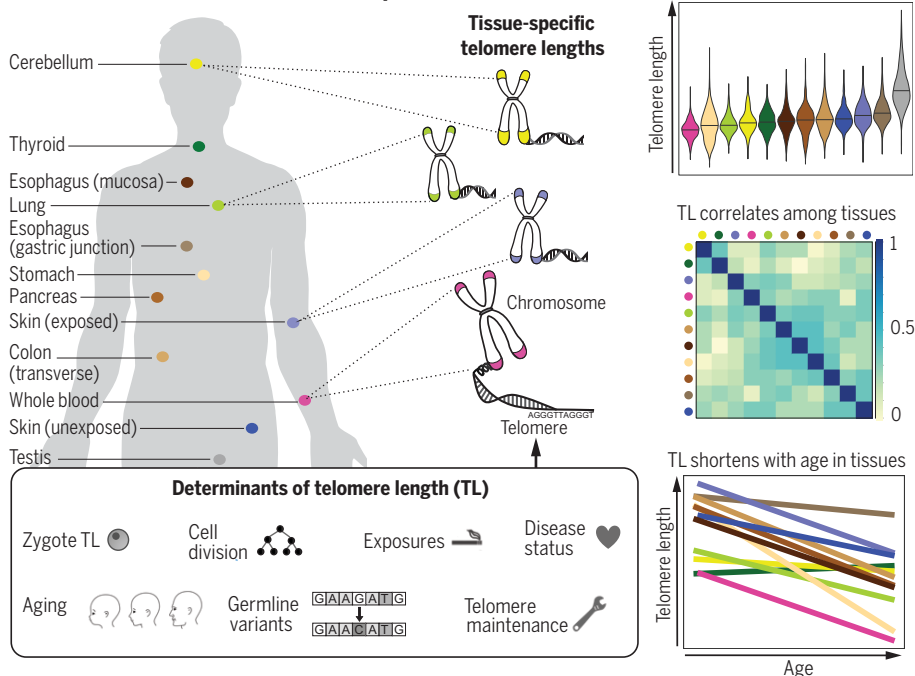
Kathryn Demanelis, Farzana Jasmine, Lin S. Chen, Meytal Chernoff, Lin Tong, Dayana Delgado, Chenan Zhang, Justin Shinkle, Mekala Sabarinathan, Hannah Lin, Eduardo Ramirez, Meritxell Oliva, Sarah Kim-Hellmuth, Barbara E. Stranger, Tsung-Po Lai, Abraham Aviv, Kristin G. Ardlie, François Aguet, Habibul Ahsan, GTEx Consortium, Jennifer A. Doherty, Muhammad G. Kibriya, Brandon L. Pierce*

INTRODUCTION: Telomeres are DNA-protein complexes located at the end of chromosomes that protect chromosome ends from degradation and fusion. The DNA component of telomeres shortens with each cell division, eventually triggering cellular senescence. Telomere length (TL) in blood cells has been studied extensively as a biomarker of human aging and risk factor for age-related diseases. The extent to which TL in whole blood reflects TL in disease-relevant tissue types is unknown, and the variability in TL across human tissues has not been well characterized. The postmortem tissue samples collected by the Genotype-Tissue Expression (GTEx) project provide an opportunity to study TL in many human tissue types, and accompanying data on inherited

genetic variation, gene expression, and donor characteristics enable us to examine demographic, genetic, and biologic determinants and correlates of TL within and across tissue types.

RATIONALE: To better understand variation in and determinants of TL, we measured relative TL (RTL, telomere repeat abundance in a DNA sample relative to a standard sample) in more than 25 tissue types from 952 GTEx donors (deceased, aged 20 to 70 years old). RTL was measured for 6391 unique tissue samples using a Luminex assay, generating the largest publicly available multitissue TL dataset. We integrated our RTL measurements with data on GTEx donor characteristics, inherited genetic variation, and tissue-specific expression

952 GTEx donors → 6391 tissue samples



TL in human tissues. Using a Luminex-based assay, TL was measured in DNA samples from >25 different human tissue types from 952 deceased donors in the GTEx project. TL within tissue types is determined by numerous factors, including zygotic TL, age, and exposures. TL differs across tissues and correlates among tissue types. TL in most tissues declines with age.

and analyzed relationships between RTL and covariates using linear mixed models (across all tissues and within tissues). Through this analysis, we sought to accomplish four goals: (i) characterize sources of variation in TL, (ii) evaluate whole-blood TL as a proxy for TL in other tissue types, (iii) examine the relationship between age and TL across tissue types, and (iv) describe biological determinants and correlates of TL.

RESULTS: Variation in RTL was attributable to tissue type, donor, and age and, to a lesser extent, race or ethnicity, smoking, and inherited variants known to affect leukocyte TL. RTLs were generally positively correlated among tissues, and whole-blood RTL was a proxy for RTL in most tissues. RTL varied across tissue types and was shortest in whole blood and longest in testis. RTL was inversely associated with age in most tissues, and this association was strongest for tissues with shorter average RTL. African ancestry was associated with longer RTL across all tissues and within specific tissue types, suggesting that ancestry-based differences in TL exist in germ cells and are transmitted to the zygote. A polygenic score consisting of inherited variants known to affect leukocyte TL was associated with RTL across all tissues, and several of these TL-associated variants affected expression of nearby genes in multiple tissue types. Carriers of rare, loss-of-function variants in TL-maintenance genes had shorter RTL (based on analysis of multiple tissue types), suggesting that these variants may contribute to shorter TL in individuals from the general population. Components of telomerase, a TL maintenance enzyme, were more highly expressed in testis than in any other tissue. We found evidence that RTL may mediate the effect of age on gene expression in human tissues.

CONCLUSION: We have characterized the variability in TL across many human tissue types and the contributions of aging, ancestry, genetic variation, and other biologic processes to this variability. The correlation observed among TL measures from different tissues highlights the existence of host factors with effects on TL that are shared across tissue types (e.g., TL in the zygote). These results have important implications for the interpretation of epidemiologic studies of leukocyte TL and disease. ■

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Determinants of telomere length across human tissues

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Telomere shortening is a hallmark of aging. Telomere length (TL) in blood cells has been studied extensively as a biomarker of human aging and disease; however, little is known regarding variability in TL in nonblood, disease-relevant tissue types. Here, we characterize variability in TLs from 6391 tissue samples, representing >20 tissue types and 952 individuals from the Genotype-Tissue Expression (GTEx) project. We describe differences across tissue types, positive correlation among tissue types, and associations with age and ancestry. We show that genetic variation affects TL in multiple tissue types and that TL may mediate the effect of age on gene expression. Our results provide the foundational knowledge regarding TL in healthy tissues that is needed to interpret epidemiological studies of TL and human health.

Telomeres are DNA-protein complexes located at the end of chromosomes that protect chromosome ends from degradation and fusion (1). The length of the DNA component of telomeres, a six-nucleotide repeat sequence, shortens as cells divide (2), with short telomeres eventually triggering cellular senescence (3, 4). In most human tissues, telomere length (TL) gradually shortens over time, and TL shortening is considered a hallmark (and a potential underlying cause) of human aging (5). In human studies, short TL measured in leukocytes is associated with increased risk of aging-related diseases, including cardiovascular disease (6) and type 2 diabetes (7), as well as overall mortality and human life span (8). However, long TL may increase the risks for some types of cancer (9–11). Leukocyte TL is influenced by inherited genetic variation [single-nucleotide polymorphisms (SNPs)], some of which reside

near genes with known roles in telomere maintenance (12–15). Leukocyte TL is also associated with lifestyle factors (e.g., physical activity), health factors (e.g., obesity, cholesterol), and environmental exposures (e.g., cigarette smoking) (16, 17).

Epidemiologic studies of TL predominantly use blood (occasionally saliva) as a DNA source. Thus, our understanding of variation in TL, its determinants (e.g., demographic, lifestyle, and genetic factors), and its associations with disease phenotypes almost entirely rely on TL measured in leukocytes from whole blood (WB). Few studies have compared TL in leukocytes with TL in other human tissue types; those that have are relatively small (<100 participants; <5 tissue types) but provide evidence that TL differs across tissue types and that TL measurements from different tissue types are correlated (18, 19). Thus, larger studies of many additional tissue types are needed to gain a comprehensive understanding of variation in TL and its determinants within and across a wide range of human tissues and cell types.

To address these gaps in our understanding of TL and its role in disease risk and its relationship with age, we measured TL in >6000 unique tissue samples, representing >20 distinct tissue types and >950 individual donors from the Genotype-Tissue Expression (GTEx) project version 8 (v8) (20). In this work, we (i) characterize sources of variation in TL, (ii) evaluate leukocyte TL as a proxy for TL in other tissues, (iii) examine the relationship between age and TL across tissue types, and (iv) describe biological determinants and correlates of TL. This work presents results from tissue-specific and pan-tissue TL analyses that are

crucial for improving our understanding of the etiologic role of TL in aging and chronic disease.

We attempted measurement of relative TL (RTL, the telomere repeat abundance relative to a standard reference DNA sample) for 7234 tissue samples from 962 GTEx donors using a Luminex-based assay (21). After removing 836 samples with failed RTL measurements and seven RTL measurements that were within-tissue outliers, our analytic dataset included 6391 tissue-specific RTL measurements from 952 donors, with 24 different tissue types having ≥25 RTL measurements (table S1). Each donor provided only one RTL measurement per tissue type, and on average, each donor had RTL measured in seven different tissue types (range: 1 to 26 tissue types) (fig. S1). The median donor age was 55 (range: 20 to 70) years. The majority of donors were male (67%) and of European descent (85%), and there were more postmortem donors (54%) than organ donors (table S1). Extensive validation and characterization of the Luminex-based RTL assay are described in (21).

TL varies across (and correlates among) human tissue types

We estimated the contribution of tissue type to the variation in RTL using linear mixed models (LMMs) adjusted for fixed effect covariates [age, sex, body mass index (BMI), race and ethnicity category, donor ischemic time, and technical factors, represented by plate (e.g., batch effects, DNA quality and concentration)] and with random effects representing tissue type and donor (table S2) (21). On average, RTL was the shortest in WB and longest in testis, with testis being an outlier tissue type [analysis of variance (ANOVA), $p < 2 \times 10^{-16}$ compared with all other tissues] (Fig. 1A). Tissue type explained 24.3% of the variation in RTL across all tissues but only 11.5% when testis was excluded, indicating that tissue type accounts for substantial variability in human TL.

We examined Pearson pairwise correlations in RTL among tissue types with tissue pairs from same donor, restricting to 20 tissue types with TL data for ≥75 samples (Fig. 1B). Forty-one tissue-pair correlations passed a Bonferroni p value threshold (t tests, $p < 3 \times 10^{-4}$), and all 41 correlations were positive (table S3). Tissue pairs from the same organ were among the strongest correlations observed: sun-exposed and nonexposed skin [Pearson correlation coefficient (r) = 0.24, t test, $p = 9 \times 10^{-3}$, $n = 112$], transverse and sigmoid colon (Pearson $r = 0.40$, t test, $p = 8 \times 10^{-7}$, $n = 139$), and esophagus mucosa (EM) and gastric junction (EGJ) (Pearson $r = 0.22$, t test, $p = 3 \times 10^{-3}$, $n = 188$). After applying hierarchical clustering to these pairwise correlations with average linkage, tissue RTLs separated into three clusters (Fig. 1B and fig. S2). Two clusters were characterized

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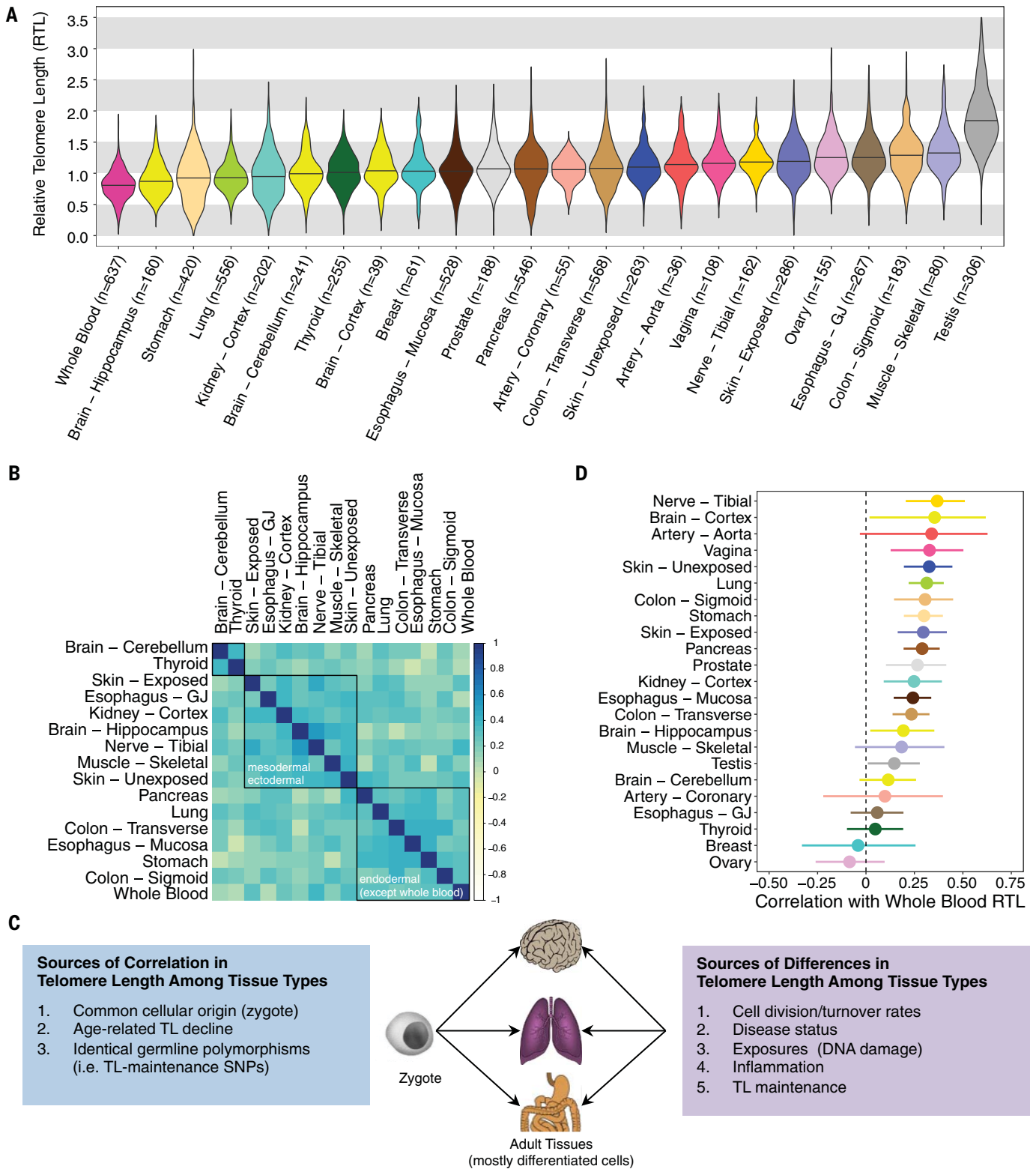


Fig. 1. TLs differ across human tissue types but are correlated among tissues types. (A) Distribution of RTL across 24 GTEx tissue types (ordered by median RTL) (see table S1). Nine-hundred fifty-two donors contributed one or more tissue samples to the analysis, and the sample size for each tissue type corresponds to unique donors (i.e., no donors are represented twice for a given tissue type). (B) Pearson (r) correlations between RTL measures from

different tissue types. Tissues included have ≥ 75 samples and were not sex specific. Red, yellow, and blue correspond to $r = 1, 0,$ and $-1,$ respectively. Black boxes are results from hierarchical clustering (three clusters). (Exact correlations are in table S3.) (C) Theoretical framework describing determinants of TL across human tissue types. (D) Pearson correlations between WB RTL and tissue-specific RTL measurements (with 95% confidence intervals).

by common developmental origin: (i) mesodermal and ectodermal (e.g., muscle and skin) and (ii) endodermal origin tissues (e.g., stomach and lung). Thyroid and brain cerebellum formed the third cluster. Similar clustering patterns among tissue types were observed for females (fig. S3) and males (fig. S4), where testis was also an outlying tissue type and clustered with thyroid. The positive correlations observed among most tissue types are likely due to the fact that the initial TL in the zygote affects TL in all adult tissues through mitotic inheritance. Differences in tissue-type TL and the extent of correlation among tissue-type TLs are likely attributable to variability in both intrinsic (e.g., cell division rate and history, telomere maintenance) and extrinsic (e.g., response to environmental exposures) factors across tissues (Fig. 1C). To assess the possibility that extrinsic factors could modify the correlation between TL in different tissues, we assessed the overall difference in the correlation matrix by smoking history and obesity (as an indicator of disease status and health). In this exploratory analysis, the observed pairwise correlations among tissue types did not substantially differ between obese and normal or overweight donors. However, among individuals with a history of smoking, the correlation among tissue types was somewhat stronger compared with never-smokers (Jennrich's chi-square test, $p = 0.003$), but the underlying reason for this observation is unknown.

WB TL is a proxy for TL in other tissues

WB RTL was positively correlated (Pearson correlation, t test, $p < 0.05$) with tissue-specific RTL measurements from 15 out of 23 tissue types ($n \geq 25$ for each test), with Pearson correlations ranging from 0.15 to 0.37 (Fig. 1D). These results demonstrate that WB TL is a proxy for TL in many tissue types. WB RTL captured between 2% (testis) and 14% (tibial nerve) of the variation in RTL measured in other tissue types. Adjustment for age, sex, BMI, and donor ischemic time did not have a major impact on the associations observed between WB RTL and tissue-type RTL in the 23 tissue types (fig. S5). Notably, tibial nerve RTL had the strongest correlation with WB RTL. The GTEx tibial nerve samples largely contain connective tissue, Schwann cells, and the axons of neuron cells (which do not contain the DNA from neuron cells), and the strong correlation between tibial nerve RTL and WB RTL is likely due to the fact that the tibial nerve tissue and WB have connective tissue origins. Breast and ovary RTL had negative point estimates for their correlations with WB RTL, but the 95% confidence intervals overlapped zero. The relationships between the RTL from these tissue types and WB RTL require further investigation.

RTL measurements have inherent measurement error (22), including our Luminex assay (23), and this error can attenuate the strength of the correlation observed between RTL measurements taken from two different tissue types. To better understand this error, we conducted extensive validation and characterization of our Luminex-based assay, including comparisons to TL measured by Southern blot of terminal restriction fragments (TRFs) reported previously by Pierce *et al.* (23) and conducted within GTEx (21). Based on this validation work (23), we conclude that the percentage of variation in our Luminex RTL measures that is due to (nondifferential) measurement error is $<50\%$. The true percentage cannot be estimated because the extent of measurement error in our gold standard TL measure, Southern blot analysis of TRFs, is unknown. Therefore, we used simulated data to estimate the impact of measurement error (ranging from 0 to 50% of the variation in RTL) on the correlations between RTL measurements from different tissues (21). Our results show that the correlations observed in this study will be attenuated, and this attenuation will increase with increasing error in the RTL measurements (fig. S6).

In addition to validating our Luminex RTL measurements against TL measured using Southern blot, we have also validated these measurements against RTL measured using quantitative polymerase chain reaction (qPCR) (24), both in previous work (25) and using GTEx samples (21). Within GTEx, RTL measurements from qPCR (24) and TL measured from Southern blot (26) showed strong correlation with our Luminex RTL measurements and similar differences among tissue types as observed for the Luminex RTL measurements (Fig. 1A) (21).

TL varies among individuals and by participant characteristics

TL varied across individuals (donors) (Fig. 2A, top), with 8.7% of the variation in RTL attributable to variability among individuals (estimates obtained from an adjusted LMM) (table S2). This percentage increased to 11.2% when testis was excluded. After adjusting for tissue type and donor (as random effects), age explained 3.3% (among all tissues) and 4.4% (excluding testis) of variation in RTL, whereas BMI, TL-associated SNPs, smoking status, and race and ethnicity category each explained $<1\%$ of the variation across all tissues [marginal coefficient of determination (R^2), likelihood-ratio test (LRT), $p < 0.05$] (Fig. 2B, top), demonstrating that these factors contribute to pan-tissue TL dynamics. We observed no clear association between sex and RTL across all tissues (table S2), and sex showed weak evidence of association with RTL in tissue-specific analyses (table S4). Multiple prior studies have reported an association between longer leuko-

cyte TL and female sex (27). However, we may be underpowered to detect this association for WB RTL, considering some larger studies have failed to detect it (28) and the association may be less evident at younger ages (29). The lack of association across all tissue types points to the possibility that this sex difference for leukocyte TL may not be consistent across all tissue types. RTL was shorter among (ever) smokers compared with never-smokers in lung and in WB (LRT, $p < 0.05$) (fig. S7), consistent with prior studies of leukocyte TL (30).

We conducted a principal component (PC) analysis of RTL from 11 nonreproductive tissue types (each with $n \geq 200$ samples) from 750 participants (21) and generated a composite measure of TL for each donor on the basis of the first PC that explains 51% of the variation in TL among these tissue types (Fig. 2A, bottom). We observed that age, BMI, and smoking status were associated with shorter composite RTL and explained 13.7, 1.3, and 0.6%, respectively, of the variation in this composite TL measure (Fig. 2B, bottom). Race and ethnicity category was associated with longer composite TL in African Americans compared with European Americans and explained 1.6% of the variation in composite TL. This composite TL likely reflects variation in TL present in the zygote (and in tissues during early development) that is mitotically inherited by cells in adult tissues.

TL is longer in genomes of African ancestry

To further explore differences in TL by race and ethnicity category, we first confirmed that PCs derived from genome-wide SNP data ($n = 838$ donors), representing genetic ancestry, showed clear clustering by reported race and ethnicity category among donors (Fig. 2C, inset). Genetic ancestry (European versus African) explained 0.6% of the variation in RTL across all tissues (marginal R^2 , LRT, $p = 1 \times 10^{-5}$) after adjusting for tissue type and donor as random effects and 2.3% of the variation in composite RTL (F test, $p = 7 \times 10^{-5}$). After including adjustments for age, sex, donor ischemic time, technical factors, and random effects of tissue type and donor, RTL was longer among individuals of African ancestry compared with individuals of European ancestry across all tissue types (LRT, $p = 0.007$), demonstrating that the effect of ancestry on TL, reported previously for leukocyte TL (31–34), extends to TL in other tissue types. The adjusted association between African ancestry and RTL was positive for 16 out of 19 tissues tested, with LRT p values <0.05 for brain cerebellum ($p = 0.03$), thyroid ($p = 0.02$), prostate ($p = 0.03$), lung ($p = 0.02$), and WB ($p = 0.005$) (Fig. 2C and table S5). The observation that individuals of African ancestry have longer TL in many tissue types is consistent with the hypothesis that ancestry-based differences in TL are present early in development (35) and potentially in

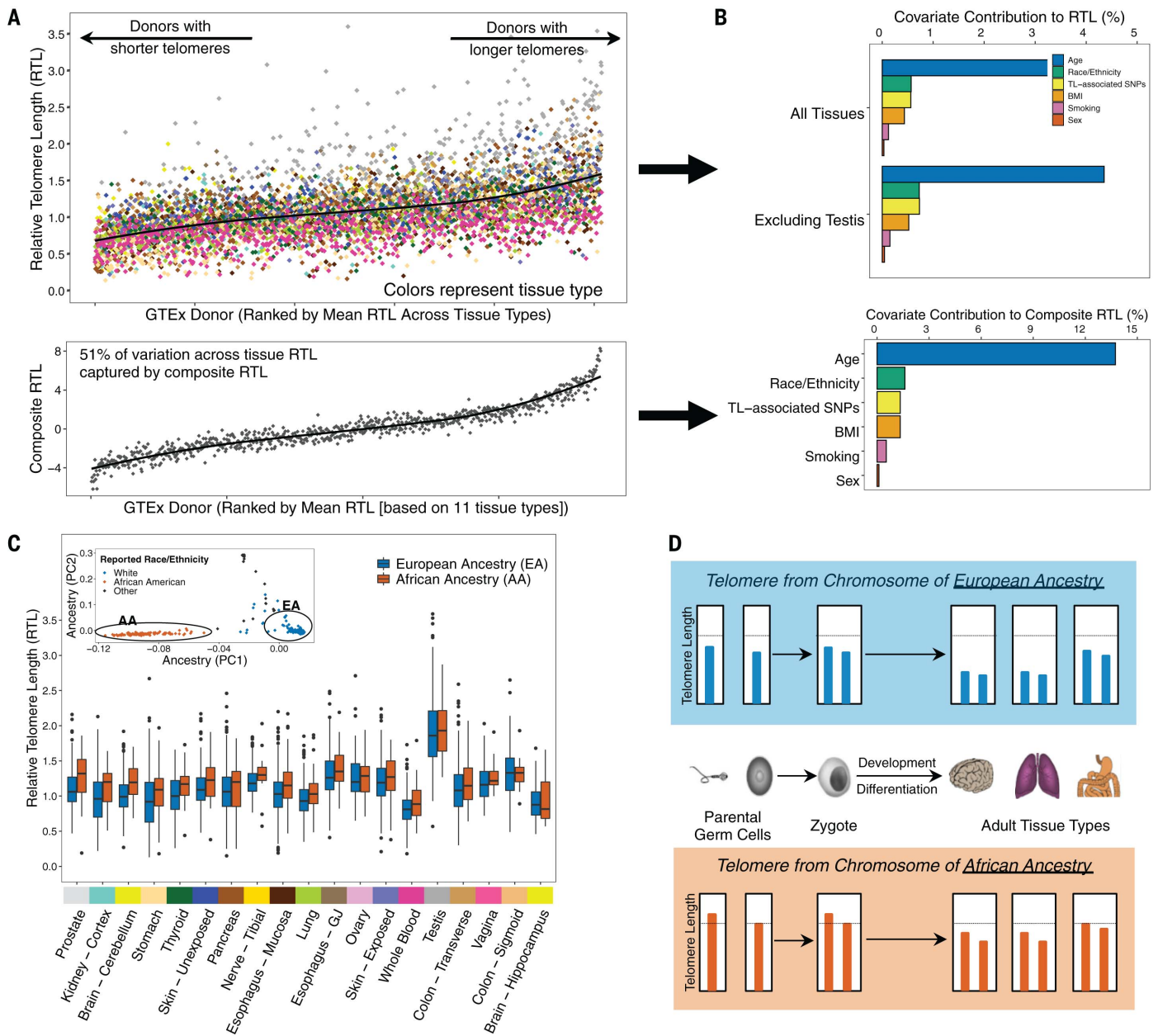


Fig. 2. TL varies among individuals and by ancestry. (A) Distribution of RTL across GTEx donors ranked by donors' mean RTL across all measured tissue types (top) and distribution of a "composite RTL" measure (bottom), estimated as the first PC from a PC analysis (PCA) of 11 tissue types (21). Colors correspond to GTEx tissue type. (B) Contribution of selected covariates to variability in RTL across all tissues (top) and composite RTL (bottom). For the analysis across all tissues, estimates were extracted as marginal R^2 values from LMMs adjusted for tissue type and donor as random effects. (C) Distribution of RTL measures for individuals of European ancestry (EA) and African ancestry (AA). Tissue types are ranked by the largest difference between median RTL of the two ancestry groups. The inset shows genotyping PCs, demonstrating consistent clustering of individuals by genetically predicted ancestry. Sample-size information and associations between African ancestry and RTL are reported in table S5. (D) Schematic describing the direct inheritance of TL from parental germ cells and expected relationship to TL across adult tissue types for individuals of African and European ancestry. Genetic (and reported race and ethnicity category) ancestry was color coded for African (red) and European (blue) in (C) and (D).

germ cells (preconception). In other words, our results suggest that offspring (zygotes) inherit telomeres from germ cells that vary in TL because of ancestry, and these ancestry-based differences in TL are mitotically transmitted to daughter cells, and eventually to cells in many adult tissue types. This "direct trans-

mission" of TL from parent to offspring (36) would result in the observed ancestry-based differences across many tissue types (summarized in Fig. 2D). One likely cause of this ancestry-based difference is natural selection on SNPs known to affect TL (37), although selection on TL itself could also contribute.

TL is correlated with age in most tissues

Of 24 tissues with ≥ 25 samples, RTL was negatively correlated (Pearson $r < 0$) with age in 21 tissue types ($p < 0.05$ in 14 tissue types from t test) (Fig. 3A and fig. S8), providing new evidence to support the hypothesis that age-related TL shortening occurs in most

tissue types. The strongest correlations with age were observed for WB (Pearson $r = -0.35$, t test, $p = 2 \times 10^{-19}$, $n = 637$) and stomach ($r = 0.37$, t test, $p = 7 \times 10^{-15}$, $n = 420$) (table S6). Age explained more of the variation in RTL for tissues with shorter mean RTL [coefficient of determination (r^2) = 0.23, F test, $p = 0.02$] (Fig. 3B). The association between age and RTL differed by sex for hippocampus (t test, $p_{\text{interaction}} = 0.04$), transverse colon (t test, $p_{\text{interaction}} = 0.01$), and lung (t test, $p_{\text{interaction}} = 0.04$), suggesting that TL shortening with age is greater in men compared with women in some tissues. Among tissue types for which RTLs did not have a clear correlation with age (t test, $p > 0.05$), we examined whether RTL differed among 5-year age groups, but we observed no age-related differences in RTL for testis, ovary, cerebellum, vagina, skeletal muscle, thyroid, and EGJ (ANOVA, $p > 0.05$). Although prior studies have observed longer TL in sperm from older men (38), we did not observe a clear increasing (or decreasing) trend for testis RTL with increasing age (fig. S9).

Among tissue types for which RTL was correlated with age (t test, $p < 0.05$), the strength of association varied across tissue types (Fig. 3C and table S6). To further explore the hypothesis that TL shortens at different rates in different tissue types, we calculated the difference in RTL (Δ RTL) between all pairs of tissue types available for each donor. We constructed 155 Δ RTL variables, restricting to tissue pairs with complete data for ≥ 50 donors. The Pearson correlation between Δ RTL and age was estimated for each tissue-type pair

to determine if the Δ RTL varies with age (fig. S10). Forty-two of the 155 Δ RTL variables were correlated with age (Pearson correlation, t test, $p < 0.05$), and the absolute values of these correlations ranged from 0.12 to 0.38 (table S7). Four of the Δ RTLs surpassed a Bonferroni p value of 3×10^{-4} : EGJ and stomach ($r = 0.32$, t test, $p = 1 \times 10^{-5}$, $n = 176$), WB and thyroid ($r = 0.30$, t test, $p = 3 \times 10^{-5}$, $n = 182$), EM and stomach ($r = 0.25$, t test, $p = 3 \times 10^{-5}$, and $n = 276$), and WB and ovary ($r = 0.33$, t test, $p = 2 \times 10^{-4}$, $n = 120$). Our results indicate that age explains up to 14% of the variation in the difference in RTL between pairs of tissue types. A prior study of 87 adults reported that the rate of age-related TL shortening was similar for muscle, leukocytes, fat, and skin (i.e., no association between age and Δ RTLs), concluding that age-related TL loss within stem cells is consistent across adult tissue types (18). When we examined these tissue types among our Δ RTL pairs ($n \geq 50$), age was correlated with Δ RTL for skeletal muscle and blood ($r = 0.36$, t test, $p = 2 \times 10^{-3}$, $n = 68$) but less for skin (unexposed) and blood ($r = 0.09$, t test, $p = 0.20$, $n = 197$) and skin (exposed) and blood ($r = 0.08$, t test, $p = 0.24$, $n = 200$).

Leukocyte TL-associated genetic variants and TL in other tissues

Prior genome-wide association studies (GWASs) have identified SNPs associated with leukocyte TL (12–15). We constructed a weighted polygenic SNP score for each donor using nine leukocyte TL-associated SNPs (21), with higher score reflecting longer TL (table S8) (39). We examined the association between this poly-

genic SNP score and RTL for tissue types with ≥ 100 samples. After adjustment for age, sex, genotyping PCs, donor ischemic time, and technical factors as a random effect, an association with the SNP score (LRT, $p < 0.05$) was observed for WB RTL ($p = 0.007$) (fig. S11), cerebellum RTL ($p = 0.03$), pancreas RTL ($p = 0.04$), and transverse colon RTL ($p = 0.02$) (Fig. 4A, fig. S12, and table S9). Among these 18 tissue types, 16 had positive association estimates [binomial test ($p_0 = 0.5$), $p = 0.001$]. In analyses of all tissue types, RTL was positively associated with the SNP score (LRT, $p = 0.01$) after adjustments. These results indicate that at least some of the genetic variants (or regions) that affect leukocyte TL also affect TL in other tissue types.

TL-associated variants influence local gene expression

Among the nine regions known to harbor SNPs associated with leukocyte TL, we examined whether these SNPs also affect local gene expression in GTEx tissue types and cell lines (21). Colocalization analysis can be used to determine if a common causal variant affects a trait (e.g., TL) and expression of a nearby gene (40). If there is a common causal variant underlying both association signals, then we may infer that SNPs may influence TL via effects on gene expression. We used colocalization analysis to estimate the probability that a common causal variant underlies association signals for leukocyte TL (from GWASs) (12–15) and cis-eQTL (expression quantitative trait loci) association signals from GTEx (v8) analyses (20). Colocalization results indicated that at least

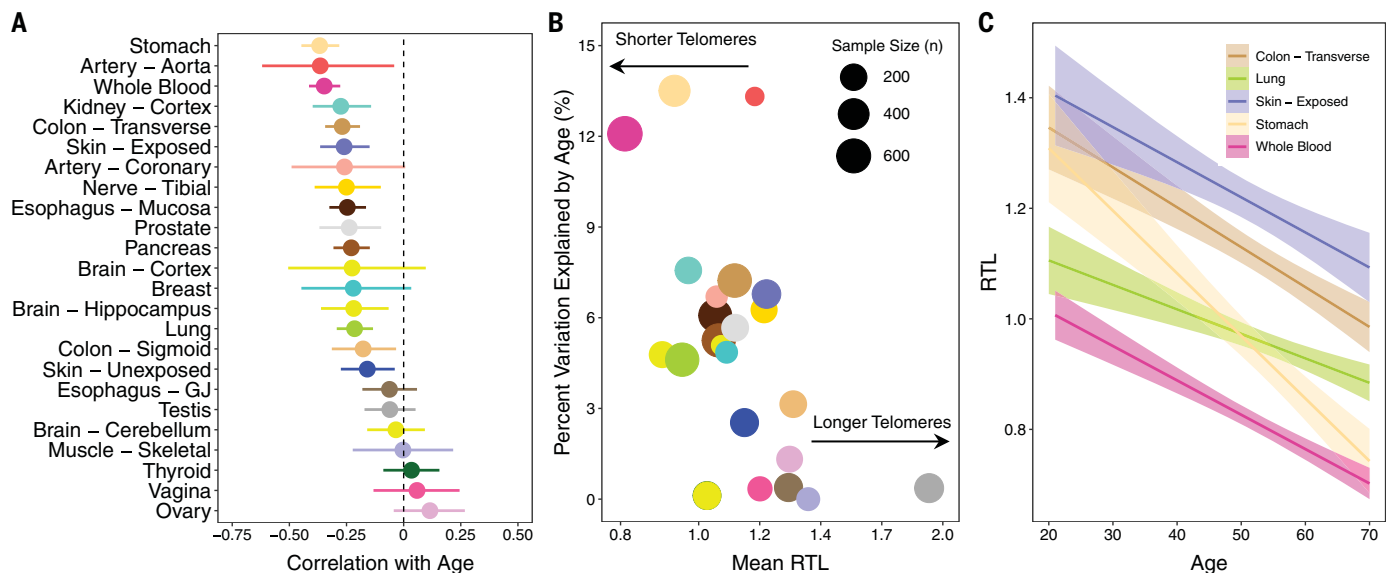


Fig. 3. Age is negatively correlated with TL in most tissues, and correlation is strongest in tissues with shorter telomeres. (A) Pearson correlations between age and tissue-specific RTL measures. (B) Scatterplot of mean RTL for each tissue versus the percent variation explained by age (r^2) for each

tissue. The size of each point is proportional to sample size for that tissue type. (C) Relationship between RTL and age for five selected tissue types [WB, lung, stomach, transverse colon, and skin (exposed)]. For all plots, colors correspond to tissue type.

six of the nine TL-associated regions shared a common causal variant with a cis-eQTL in at least one tissue type, on the basis of a posterior probability of colocalization of $\geq 80\%$ across all three sets of priors tested (Fig. 4, B and C; fig. S13; and table S10).

The association signal for TL on chromosome 19 (represented by rs8105767) showed strong evidence of colocalization with an eQTL affecting expression of gene *ZNF257* in eight tissue types, including skin (sun exposed), transverse colon, and stomach (Fig. 4B). *ZNF257* encodes a zinc-finger protein that may be involved in transcriptional regulation. The association signal for TL on chromosome 10 (represented by rs9420907) colocalized with an eQTL affecting expression of *STN1* in seven tissue types,

including skin (sun exposed), transverse colon, and EM (Fig. 4C). Additional TL-associated loci showed colocalization with GTEx eQTLs for *NAF1*, *MYNN*, *RP11-109N23.6*, and *TSPYL6* (fig. S13 and table S10). Although these colocalizations were observed for eQTLs in tissue types with largely differentiated cells, eQTLs observed in induced pluripotent stem cells have been shown to be largely shared with eQTLs in GTEx tissue types (41). This finding suggests that the observed evidence of colocalization may be pertinent to TL maintenance within stem and progenitor cells, which have active telomerase activity. Notably, *NAF1* encodes a protein involved in telomere assembly, and loss-of-function (LOF) mutations in this gene are associated with shorter telomere length in

pulmonary fibrosis (PF) patients (42). These results suggest that TL-associated loci influence TL within human tissues through regulation of the expression of genes known to be involved in telomere maintenance (e.g., *STN1*, *NAF1*) (12), as well as genes whose role in telomere maintenance is unclear (e.g., *ZNF257*).

Notably, we observed little evidence of colocalization of the *TERT* or *TERC* TL-associated regions with any cis-eQTLs. *TERT* and *TERC* are important components of telomerase. The telomerase enzyme can extend the telomere repeat sequence, typically in stem and/or progenitor cells, to compensate for TL shortening; however, *TERT* and *TERC* have low or undetectable expression in a majority of adult GTEx tissue samples. This suggests that eQTL studies

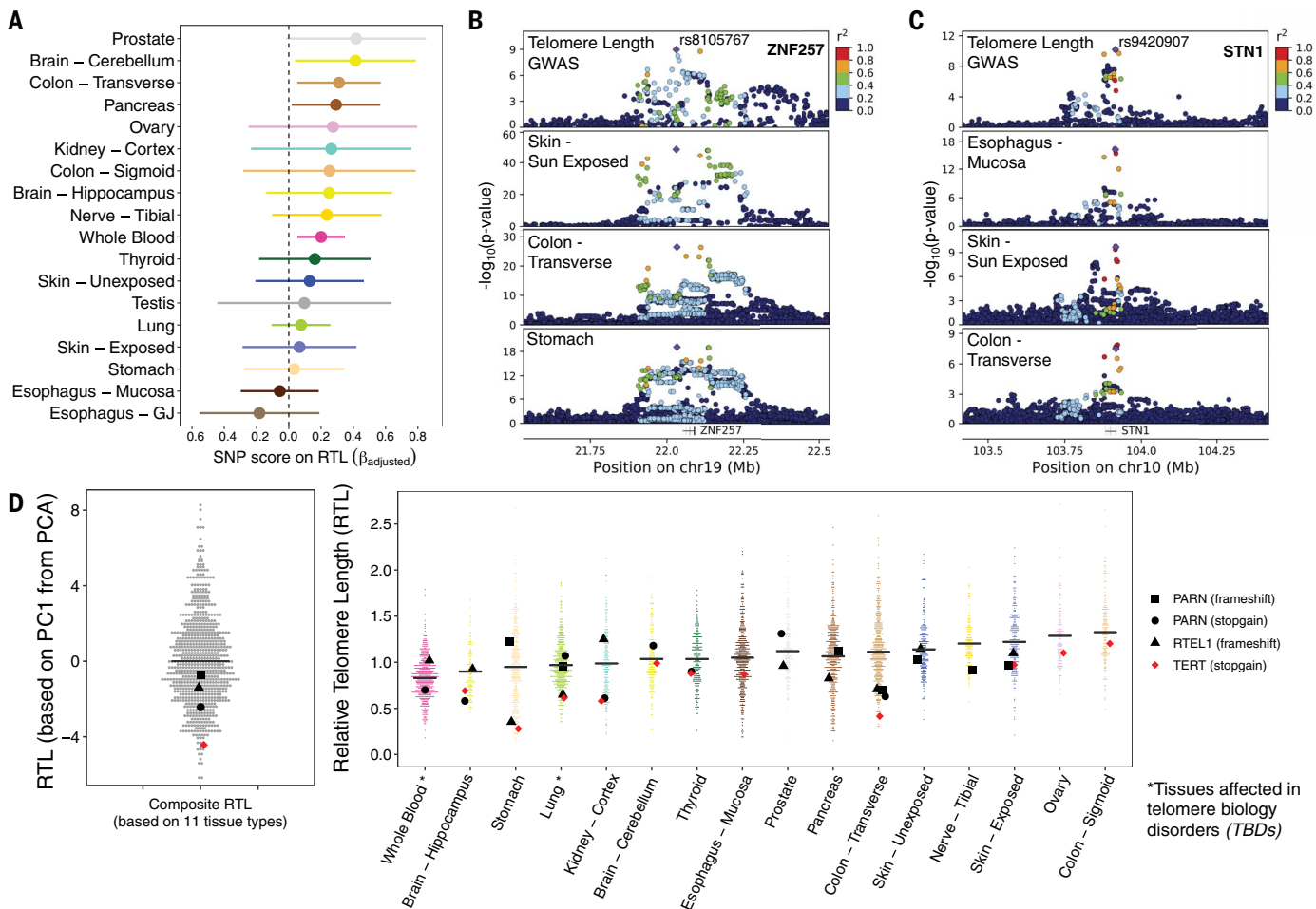


Fig. 4. Inherited genetic variation affects telomere length in multiple tissue types and expression of nearby genes. (A) Associations between a polygenic SNP score for leukocyte TL and tissue-specific RTL measures. Colors correspond to tissue type. (B) Leukocyte TL association signal from GWASs colocalizes with a cis-eQTL for *ZNF257* (~40 kb upstream of *ZNF208*). The top plot shows results from the ENGAGE Consortium GWAS of leukocyte TL, and the bottom three plots correspond to cis-eQTL results from GTEx tissues: skin–sun exposed, colon–transverse, and stomach. chr19, chromosome 19. (C) Leukocyte TL association signal colocalizes with a cis-eQTL for *STN1* (also known as *OBFC1* in human genome

reference hg19). The top plot corresponds to results from the ENGAGE Consortium GWAS of leukocyte TL, and the bottom three plots correspond to cis-eQTL results from GTEx tissues: skin–sun exposed, EM, and colon–transverse. (D) Distribution of composite RTL (based on PC1 from PCA of 11 tissue types) (left) and tissue type RTL (right), with highlighted dots representing GTEx donors carrying a rare LOF variant in a telomere maintenance gene previously implicated in TBDs. LOF variants are noted in the legend. The black horizontal line corresponds to median composite RTL and tissue type RTL. The tissue types presented contain one or more LOF carriers, and colors correspond to tissue type.

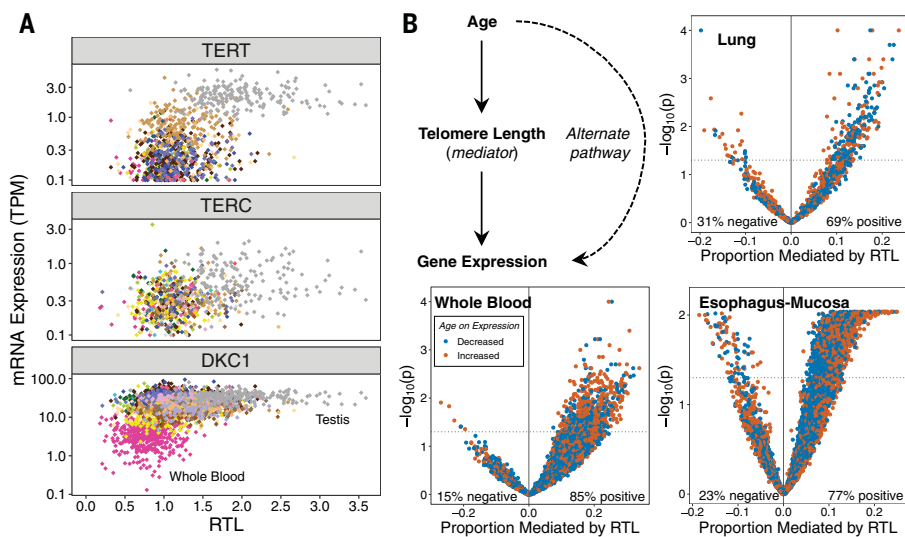


Fig. 5. TL is associated with telomerase subunit gene expression and may mediate the effect of age on gene expression. (A) RTL plotted against *TERC*, *TERT*, or *DKC1* expression across tissue types. Colors correspond to GTEx tissue types. (B) Analyses addressing the hypothesis that TL mediates the effect of age on expression of specific genes. Scatterplots show estimates of the proportion of the effect of age on gene expression mediated by RTL (for each gene) and the $-\log_{10}(p)$ value corresponding to the average causal mediation effect of RTL (for each gene). Results are presented for all age-associated genes in each of the three selected tissue types (WB, lung, and EM). The mediation p value was obtained using a nonparametric bootstrapping approach ($n = 10,000$ bootstraps).

of cells from stem and/or developmental tissues may be needed to understand the mechanisms underlying genetic regulation of *TERT* and *TERC* expression.

Carriers of rare LOF variants may have shorter TL

Telomere biology disorders (TBDs, e.g., PF, dyskeratosis congenita, aplastic anemia) are characterized by short TL in affected individuals owing to inherited LOF mutations in telomere maintenance genes (1, 43–45). Individuals with TBDs often present with early-onset aging-related phenotypes—such as immune dysfunction, bone failure, liver disease, and lung function decline—and these effects can inform our understanding of how TL contributes to aging in the general population. Using whole-genome sequencing data from GTEx donors, we searched for LOF rare variants in seven genes that have evidence of autosomal dominant (or partial dominant) inheritance in relation to TBDs (e.g., *TERC*, *TERT*, *TINF2*, *RTEL1*, *PARN*, *ACD*, and *NAF1*). We identified four donors carrying a rare exonic variant (minor allele frequency <1%) resulting in a predicted LOF frameshift insertion or deletion or a stop-gain mutation (Fig. 4D). These LOF carriers had shorter TL across all tissues (LRT, $p = 0.04$) and shorter composite TL (t test, $p = 0.03$). One donor carried a stop-gain variant in *TERT*, and their composite TL was among the lowest observed (~first percentile), consistent with prior studies of *TERT* mutations among individuals with PF (46, 47).

Our results suggest that rare variants in TL-maintenance genes may contribute to shorter TL in multiple tissues in the general population (i.e., primarily individuals without TBDs). However, the *PARN* and *RTEL1* mutation carriers among the GTEx donors did not have RTL values in the (lower) extreme of the composite TL and tissue-specific RTL distribution(s). Although mutations in TL maintenance genes and very short TL are often found in individuals with TBDs (43–45), prior studies of individuals with TBDs have shown that TL can vary substantially among carriers (of mutations in *PARN*, *RTEL1*, and *TERT*), and some carriers have TL values similar to noncarriers (46, 48, 49). Prior studies of PF patients suggest that LOF *TERT* mutations may have a larger impact on TL than LOF mutations in *PARN* or *RTEL1* (46, 47, 49).

TL is associated with telomerase subunit expression across tissues

The protein products of *TERT*, *TERC*, and *DKC1* comprise the telomerase catalytic subunit. We examined the association between RTL and expression of these genes using 3885 GTEx tissue samples with both RTL and RNA sequencing (RNA-seq) gene expression data (v8). *TERT* and *TERC* expression was detectable [i.e., transcripts per million (TPM) >0.1] in 28% ($n = 1089$) and 20% ($n = 783$) of these samples, respectively, but *DKC1* was ubiquitously expressed ($n = 3885$) in all samples (table S11). Whereas *DKC1* showed correlation with both *TERT* (Pearson $r = 0.30$, t test, $p < 2 \times 10^{-16}$, $n = 1089$) and *TERC* ($r = 0.23$, t test, $p = 3 \times 10^{-11}$,

$n = 783$) across all samples, the correlation between *TERT* and *TERC* expression across samples was stronger ($r = 0.49$, t test, $p < 2 \times 10^{-16}$, $n = 364$) (fig. S14). Testis had substantially higher mean expression of *TERT* and *TERC* compared with all other tissues (ANOVA, $p < 2 \times 10^{-16}$) (table S11), but there was no association between testis RTL and *TERT* or *TERC* expression. Across all tissues, RTL was positively correlated with *TERT* ($r = 0.58$, t test, $p < 2 \times 10^{-16}$, $n = 1089$), *TERC* ($r = 0.33$, t test, $p < 2 \times 10^{-16}$, $n = 783$), and *DKC1* ($r = 0.29$, t test, $p < 2 \times 10^{-16}$, $n = 3885$) (Fig. 5A). When testis was removed, the correlation decreased substantially for both *TERT* ($r = 0.14$, $p = 4 \times 10^{-5}$, $n = 890$) and *DKC1* ($r = 0.23$, $p < 2 \times 10^{-16}$, $n = 3686$) and disappeared for *TERC* ($r = 0.02$, $p = 0.63$, $n = 617$). After adjustment for covariates and random effect of tissue type, RTL showed a positive association with increasing quartiles of *TERT* expression (LRT, $p = 0.005$ including testis and $p = 0.002$ excluding testis) and of *DKC1* expression (LRT, $p = 0.001$ including testis and $p = 3 \times 10^{-4}$ excluding testis) across all tissues. Overall these results support the following: (i) high telomerase activity in testis (i.e., spermatocytes) likely contributes to longer TL observed in that tissue, and (ii) GTEx tissue samples consist primarily of differentiated cells, which typically have little to no telomerase activity, resulting in minimal detectable association between telomerase activity in those cells and the observed TL (50, 51).

TL may mediate the effect of age on gene expression

Aging affects gene expression, so we examined whether TL mediates the association between age and expression of age-associated genes. We analyzed the association between age and RNA-seq-based gene expression levels among tissues with ≥ 150 samples and selected three tissue types with >1000 age-associated genes [false discovery rate (FDR) of 0.05] (21): WB ($n = 5239$), lung ($n = 1366$), and EM ($n = 6024$) (Fig. 5B). Using mediation analysis (52), we estimated the proportion of the effect of age on expression that was mediated by TL for each age-associated gene. For each tissue type, we observed substantially more positive than negative estimates of the “proportion mediated” (Fig. 5B), as expected under the hypothesis that TL is a mediator. (An equal number of positive and negative estimates are expected under the hypothesis of no mediation.) If TL is a mediator for a specific gene, then adjustment for TL will attenuate the association between age and gene expression. We observed evidence that RTL mediated the effect of age on expression for 607 genes (12%) in WB, 224 genes (16%) in lung, and 1177 genes (20%) in EM ($p_{\text{mediation}} < 0.05$, and proportion mediated > 0) (tables S12 to S14). In these tissue types, RTL mediated between 4 and 34% of the effect

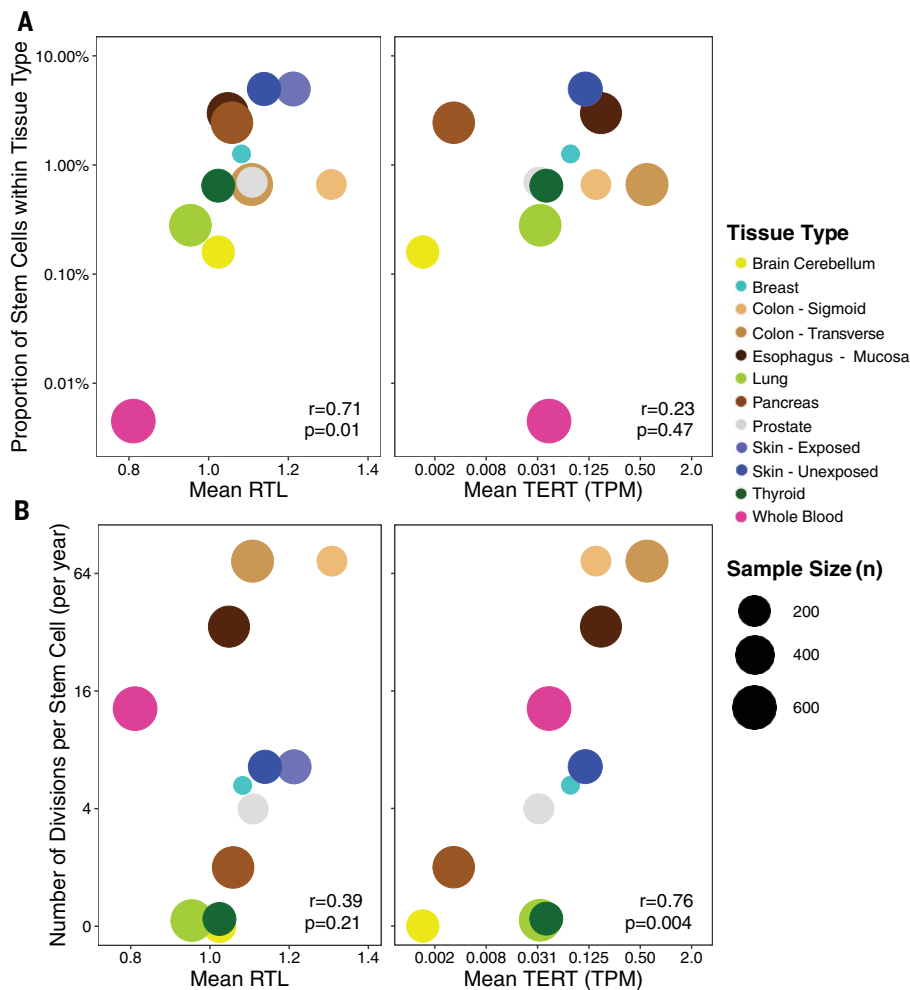


Fig. 6. TL and TERT expression are associated with estimated stem cell features. (A) Estimated proportion of stem cells within tissues and its relationship between mean RTL (left) and mean *TERT* expression (right). (B) Estimated number of divisions per stem cell (per year) within tissues and its relationship between mean RTL (left) and mean *TERT* expression (right). Colors correspond to GTEx tissue types, and the size of each point reflects the sample size of the tissue type. Pearson correlations and corresponding *p* values are reported. Analysis included nonreproductive tissues only.

of age on expression of individual genes; however, full mediation will be detected as partial mediation in the presence of measurement error (for either the mediator or the outcome) (53). We evaluated the enrichment of these RTL-mediated genes in gene ontology (GO) terms among the age-associated genes (Fisher's exact test, FDR < 0.1). Enriched GO terms were identified for lung (5 terms), EM (30 terms), and WB (108 terms) (tables S15 to S17). No GO terms (FDR < 0.1) were common to WB, lung, and EM for any ontology. Among 108 enriched GO terms in WB, several terms related to apoptosis, cell death, and telomere DNA binding were identified. The results from this analysis provide evidence that TL is a potentially relevant biologic factor in the mediation of age on gene expression and may contribute to processes related to biologic aging.

Tissue-level stem cell features are associated with TL and TERT expression

After extracting tissue-specific estimates of the number of divisions per stem cell (per year) and the proportion of stem cells (among all cells) for specific tissue types from Tomasetti and Vogelstein *et al.* (54, 55), we examined their relationship with mean RTL and mean *TERT* expression among nonreproductive GTEx tissue types ($n = 12$; table S18). No associations were identified between mean *TERT* and *DK1C1* expression and these stem cell features. Mean RTL was positively correlated with estimated proportion of stem cells within a tissue type ($r = 0.71$, t test, $p = 0.01$) (Fig. 6A), and this association persisted after adjustment for number of divisions per stem cell (t test, $p = 0.008$) and mean *TERT* expression (t test, $p = 0.02$). We did not observe a clear association

between mean *TERT* expression and the estimated proportion of stem cells within a tissue type. These results suggest that tissue types with a higher proportion of stem cells in their cellular composition may have longer TL measurements in bulk tissues as a consequence.

We observed a positive correlation between mean *TERT* expression and the number of divisions per stem cell ($r = 0.76$, t test, $p = 0.004$) (Fig. 6B). This association persisted after adjustment for the proportion of stem cells within a tissue type (t test, $p = 0.006$) and mean RTL (t test, $p = 0.01$). Mean RTL showed suggestive evidence of correlation with the number of divisions per stem cell ($r = 0.39$, t test, $p = 0.21$), and when we restricted to nonblood tissue types, mean RTL was positively correlated with number of divisions per stem cell ($r = 0.65$, t test, $p = 0.03$). This finding suggests that tissue types that undergo more cellular turnover and replacement, such as colon, may have higher telomerase expression to maintain TL in the stem cell compartments.

Cell-type composition is associated with TL within tissues

To determine whether TL varies among the cell types within a given tissue sample, we examined the association between RTL and estimated cell-type enrichment scores (CTES) [generated using RNA-seq data and the xCell software (56)]. Seven CTES (for adipocytes, epithelial cells, hepatocytes, keratinocytes, myocytes, neurons, and neutrophils) were benchmarked by the GTEx Consortium (57), and we examined the association between these seven CTES and RTL in tissue types with ≥ 100 samples ($n = 16$ tissue types). After removing cell types not detected within a tissue type ($n = 37$ total CTES tested across 16 tissue types) and adjusting for age and sex, we identified eight associations (t test, $p < 0.05$) between CTES and RTL among 37 associations tested (fig. S15). In exploratory analyses, we examined all 64 CTES provided by xCell that had a detection *p* value < 0.05 for >90% samples within a tissue type. Restricting to tissue types with ≥ 300 samples that had both CTES and RTL data (WB, lung, and EM), there were 27, 24, and 17 CTES detected in each tissue, respectively (fig. S16). EM and lung had 13 and 14 CTES that were associated with RTL, after adjustment for age and sex (t test, $p < 0.05$). RTL was positively associated with epithelial cell, smooth muscle cell, keratinocyte, and sebocyte CTES in both lung and EM ($p < 0.05$). Notably, five CTES were inversely associated with RTL ($p < 0.05$) in both lung and EM, including fibroblasts and endothelial cells. In WB, lymphoid and myeloid cell CTES accounted for 70% of the CTES detected, and eight CTES were associated with RTL (t test, $p < 0.05$). Neutrophil CTES were positively associated with RTL. Both CD8⁺ T cell CTES

were inversely associated with RTL, consistent with prior work examining cell types and TL in blood (58). These results provide evidence that TL varies across cell types within a given tissue, and consequently, cell-type composition can affect TL measurement in human tissues.

TL across all tissues is associated with age-related chronic disease status

Using medical history data from GTEx donors, we examined the association between common age-related chronic diseases and RTL within and across tissues. A history of type 2 diabetes (22% of donors) was associated with shorter RTL across all tissues (LRT, $p = 0.02$) as well as shorter pancreas RTL ($p = 0.07$) and coronary artery RTL ($p = 0.01$) (fig. S17). Among all donors, 50% had no history of any chronic disease, and 30, 14, and 6% had a history of one, two, and three (or more) chronic diseases, respectively. Chronic disease burden (sum of chronic diseases from 0 to 5) was associated with shorter RTL across all tissues (LRT, $p = 0.008$) and in testis, coronary artery, kidney cortex, and cerebellum (LRT, $p < 0.05$ for each). When we excluded cancer from the chronic disease burden, these associations persisted across all tissues (LRT, $p = 0.02$) and in all tissues listed above except for kidney cortex (LRT, $p = 0.09$). These observations suggest that TL may capture some aspect of the biologic age-related health decline across tissues.

We did not observe any associations between RTL and history of cancer; however, to test the hypothesis that normal tissues with relatively short (or long) TL are also short (or long) in tumors occurring in that tissue, we compared the mean tissue-to-WB TL ratio for each GTEx tissue with the mean tumor-to-WB TL ratio in corresponding cancer types from The Cancer Genome Atlas (TCGA) (21, 59). The mean cancer TL ratio from TCGA and normal TL ratio from GTEx were positively correlated ($r = 0.44$, t test, $p = 0.04$, $n = 23$) (fig. S18), providing support for this hypothesis.

After reviewing the medical and death report information for diseases and conditions related to TBDs (21), we identified six donors with a reported history of PF and/or interstitial lung disease (ILD). Five of these donors had TL measurements ($n = 35$ tissue-type samples). We observed that three of the donors with a history of PF or ILD had composite RTL below the fifth percentile (fig. S19). A history of PF or ILD was associated with shorter TL across all tissues (LRT, $p = 0.02$) and shorter composite RTL (t test, $p = 0.01$). Notably, we observed that within tissues, the median RTL was substantially shorter for WB (Mann-Whitney U test, $p = 0.02$), pancreas ($p = 0.01$), and EM ($p = 0.05$) among donors with a history of PF or ILD.

Discussion

This study provides a view of the substantial variation in human TL that exists across human tissue types and among individuals. We show that TL is generally positively correlated across human tissue types, and that WB TL is a proxy for tissue-specific TL for many tissues, a finding that may support the use of blood TL as a proxy for TL in some tissues in large epidemiological studies. TL was negatively associated with age in the majority of tissues studied, confirming the hypothesis of pervasive age-related telomere shortening in most human tissues. However, our results suggest that the rate of shortening can vary across tissues, and age explained more variation in TL in tissues with shorter mean TL. *TERT* and *TERC* expression were low or undetectable in most tissues and not associated with TL within any tissue, likely because progenitor cells, which express telomerase, are not present in large numbers in adult tissue samples, which consist primarily of differentiated cells. Notably, testicular TL was ~1.5- to 2.5-fold longer than TL in any other tissue type, and *TERT* was expressed in 100% of these samples and at higher levels than in any other tissue, consistent with the predominance of spermatogenic cells in testis (i.e., cells developing from germ cells into spermatozoa), which have high telomerase activity (51).

RTL measured in a tissue sample is an average of the TLs among all chromosomes within a heterogeneous population of cell types with different cell division rates and history, stem cell composition, and oxidative and inflammatory environments. To characterize variation in TL within specific cell types, cell type-specific and single-cell TL studies are needed, potentially using interphase quantitative fluorescence in situ hybridization approaches (60) and flow cell cytometry to isolate specific cell types, including stem cells.

A large proportion of the variation in RTL was unexplained across all tissue types, potentially attributed to sources such as cell-type composition (e.g., stem and progenitor cells), measurement error, and lifestyle and environmental factors with variable effects across tissues. From our simulation-based analysis of the impact of TL measurement error on our results, we show that random measurement error biases our estimate of the true correlation in TL between two tissues toward zero, suggesting that the correlations presented in this study are attenuated compared with their true associations.

We lack detailed exposure data (e.g., smoking and alcohol use) for GTEx donors; studies that can link human tissue samples to environmental and lifestyle histories are needed to better understand environmental determinants of TL across different tissues and cell types. As of now, all TL-associated SNPs have

been identified in GWASs of leukocyte TL (12–15); our study suggests that some of these effects are also present in other tissue types, but larger studies of tissue-specific TL measurements are needed to characterize how these effects vary across tissues and cell types. Identifying variants that affect TL in all or most cell types (e.g., variants with effects on TL that may be present during development or in stem cells in multiple tissue types) may be ideal for evaluating the causal impact of TL on risk for a wide array of diseases (occurring in diverse tissues or cell types) using Mendelian randomization. TL shortening is an important hallmark of aging in human tissues, but TL should also be studied in conjunction with other hallmarks of aging. Characterizing the relationships among TL and other aging-related processes and biomarkers within and across tissues will improve our understanding of cellular aging and its impact on human health.

Methods summary

We measured RTL in 6391 samples from 952 GTEx donors using a Luminex-based method. These measurements were validated against other TL measurement methods, including TL measured using Southern blot of TRFs (fig. S20) (26), relative TL measured using qPCR (fig. S21) (24), and TL estimated from whole-genome sequencing data (fig. S22) (61). Publicly available GTEx donor covariate, genotyping, and RNA-seq gene expression data (all v8) were integrated into our analyses. We applied LMMs to examine the relationships of RTL with age, genetic ancestry, gene expression of telomerase components, estimates of cell types, and other covariates across and within tissue types. Using GTEx genotyping data, we constructed a weighted polygenic SNP score for each donor using nine leukocyte TL-associated SNPs identified from the ENGAGE GWAS of leukocyte TL (12) and examined colocalization of these GWAS association signals with local gene expression using summary statistics from the ENGAGE study and eQTL results from the GTEx Consortium. Mediation analyses were applied to examine the extent to which TL mediates the effect of age on gene expression. Estimates of stem cell division and proportion of stem cells were extracted from prior studies (54, 55) for corresponding GTEx tissues, and their relationship with average RTL and *TERT* expression was examined.

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Determinants of telomere length across human tissues

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Telomere length within individuals

Telomeres are DNA-protein complexes that protect chromosome ends. Their length is of great interest because short telomeres are associated with specific diseases and with aging. Demanelis *et al.* measured telomere length from 952 Genotype-Tissue Expression (GTEx) project donors across tissues, of which 24 tissue types have measurements for more than 25 samples. This dataset shows that telomere length is not constant but is correlated across tissues. Most tissue telomeres shorten with age, but some, such as those in the testis and cerebellum, do not. In African Americans, telomeres are longer on average than those from individuals of primarily European descent across many tissue types. This observation is consistent with variability being passed from germ cells to zygote to differentiated cells during development.

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