Telomere Length: The Intersection of Sociology, Molecular Biology, and Human Disease

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Telomeres, tandem TTAGGG nucleotide repeats located at the ends of eukaryotic chromosomes, are DNA-protein complexes critical to the maintenance of genomic stability and cellular longevity. They are among the most-studied markers of the aging process, with multiple studies showing that telomeres shorten with age. This, in turn, has led researchers to posit a relationship between telomere shortening and a variety of age-related health conditions, particularly cancer. Many studies have identified associations between cancer risk and both longer and shorter telomeres (Hou et al., 2012), a contradiction that can potentially be explained via a dynamic relationship over time wherein people early in cancer development experience accelerated telomere shortening that is subsequently arrested as cancer cells hijack various telomere-lengthening mechanisms (Hou et al., 2015). This process is believed to be necessary not only for immortalizing cells, but also because it can be used to delay cell senescence and thus provide opportunity for the accumulation of additional mutations (via DNA damage or other processes) necessary to complete the transformation into a cancerous cell (Noy, 2009).

The racial disparity in US rates of cancer (among other diseases) has been well-characterized and continues to persist with African-Americans having generally worse cancer incidence and mortality than Whites (Siegel et al., 2015). While many researchers have identified proximal causes for this disparity current research remains unable to completely explain the frequent and dramatic differences in cancer rates between US racial/ethnic subgroups, prompting researchers in molecular epidemiology to undertake new studies of this problem. Many of the risk factors thought to contribute to racial health disparities in the US (e.g., socioeconomic status/health care access, stress, environmental exposures) have also been associated with shorter telomeres (Needham et al., 2013), however most studies comparing telomere length (TL) across racial/ethnic groups have found that in general African-Americans tend to have longer telomeres than Whites (Hou et al., 2015; Needham et al., 2013). This counterintuitive finding has led researchers to hypothesize that these differences are due to genetic ancestry, specifically polymorphisms related to genes that regulate TL, or possibly unaccounted-for environmental factors such as pollutant exposure (Scinicariello and Buser, 2015).

Previous studies, including genome-wide association studies (GWAS), have identified numerous genes associated with TL through mechanisms including shelterin, DNA repair, helicases, and telomerase (Mirabell et al., 2010) but few have explored variation in the expression of these genes by race/ethnicity. In this issue of EBioMedicine, Hamad et al. (Hamad et al., 2016) attempt to answer the question of genetic vs. environmental interplay in racial TL differences via a cross-sectional exploration of genes associated with TL and various sociodemographic characteristics including race/ethnicity. Using genetic data from 11,141 participants in the Health and Retirement Study (HRS) collected in 2006 and 2008 they construct a polygenic risk score (PRS) of seven single nucleotide polymorphisms following the method developed by Codd et al. (Codd et al., 2013). They then identify racial and ethnic differences in PRS, with African-Americans having a lower PRS (predicting longer telomeres) and Hispanics having higher PRS (predicting shorter telomeres) compared to Whites. These findings were independent of socioeconomic factors (education and total assets), age, and gender and confirmed using a genetic principal components approach with components strongly associated with race/ethnicity. Interestingly, self-reported race performed nearly as well as genetic ancestry for these telomere-associated polymorphisms. In a subset of 5808 HRS participants with available data on TL, the authors also confirmed longer telomeres in African-Americans, and intriguing associations between TL and select genetic principal components. Data on individual SNPs presented in the supplementary tables will also fuel future research.

These findings suggest that African-Americans share a genetic predisposition to longer TL, and Hispanics to shorter TL, and that these subgroups experience different rates of TL shortening over their lives relative to Whites. Thus, observed differences in TL may be due to traditional risk factors (possibly other than socioeconomic status). This provides one possible explanation for the contradictory findings regarding
race and TL elsewhere in the literature, but further research using telomere-related clinical endpoints (e.g., cancer diagnosis) and specific exposures is needed to establish clinical significance for these findings. If validated, telomeres may be a useful tool for assessing health risks related to racial/ethnic minority status in the US, and potentially for improving early diagnosis and/or prevention of the many age-related health conditions driving the observed racial/ethnic health disparities. In addition, these results will need to be confirmed in other populations (as noted by the authors in their discussion of potential survivorship bias in the HRS). Nonetheless, these findings provide new insight into the trajectory of telomere shortening over time in multiple demographic subgroups. Confirming via longitudinal studies the distribution of the genetic determinants of TL in the US population could greatly enhance our understanding of the epidemiology of age-related diseases and lead to breakthroughs in new personalized detection and prevention efforts.

Disclosure

The authors declared no conflicts of interest.

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