

Commentary: The evolutionary biology of the paternal age effect on telomere length

Dan TA Eisenberg^{1,2*} and Christopher W Kuzawa^{3,4}

¹Department of Anthropology, University of Washington, Seattle, WA, USA, ²Center for Studies in Demography and Ecology, University of Washington, Seattle, WA, USA, ³Department of Anthropology, Northwestern University, Evanston, IL, USA and ⁴Cells to Society: the Center for Social Disparities and Health, Institute for Policy Research, Northwestern University, Evanston, IL, USA

*Corresponding author. Department of Anthropology, University of Washington, Box 353100, Seattle, WA 98195-3100, USA.
E-mail: dtae@dtae.net

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Telomeres are repeating sequences of DNA found at the ends of chromosomes, that shorten in most proliferating tissues as we age and our cells replicate. Shortened telomeres result in a reduced capacity for cell proliferation, and in adults have been shown to predict increased morbidity and earlier mortality. Whereas telomeres tend to shorten with cell replications in most tissues, sperm telomere length appears to run counter to this trend by increasing with each cell division, leading to a lengthening of sperm telomeres as men age.¹ As a result, offspring of older fathers have longer telomere lengths. This finding suggests that the age at which a man conceives his offspring might have important influences on his children's health and longevity by altering the length of telomeres that they inherit. Abraham Aviv and Ezra Susser are leaders in considering this paternal age at conception (PAC) effect on offspring telomere lengths, and their article in this issue is an important review of this topic.² In addition to discussing the basic molecular biology and health implications of the PAC effect, they also briefly consider some of the evolutionary dynamics that are implied by this unusual phenomenon. Here we elaborate on the evolutionary significance of the PAC effect and note some points where our interpretations of the literature differ slightly from those of Aviv and Susser.

Telomeres and the evolutionary biology of aging

Aviv and Susser draw a parallel between the PAC effect on telomeres and the observation that fruit flies selected for delayed reproduction have increased life expectancies. The fruit fly genetics literature illuminates key principles of evolutionary theory that pertain to the evolution of species differences in the pace of senescence, which are helpful to review. A

prominent explanation for the evolution of species differences in the pace of ageing derives from three key assumptions^{3,4}: (i) organisms have limited energy which must be allocated between different functions, (ii) organisms may invest resources in reproduction or in maintenance functions that extend lifespan (e.g. antioxidants, DNA repair), but not both and (iii) the optimal balance of reproductive versus maintenance expenditures is determined by the prevailing level of unavoidable (extrinsic) mortality that members of a species (or breeding population) face, which shifts the organism's optimism about living into the future. As unavoidable mortality increases, organisms have less optimism about the future, and therefore are expected to invest more in current reproduction (and less in maintenance), and vice versa.

Mechanistically, this trade-off between reproductive and maintenance expenditures occurs over many generations as the frequencies of alleles that influence energy allocation within the body change via natural selection: with decreased unavoidable mortality rates over many generations, alleles that promote increased maintenance efforts are selected because their bearers leave more descendants than peers with alleles that shunt lifespan-extending maintenance resources into rapid and early reproduction. We agree with Aviv and Susser that the trade-off between maintenance and reproduction provides important clues into the forces that have shaped the PAC effect on telomere lengths. However, the nucleotide sequences that build telomeres change rapidly within single generations, making them a fascinating scenario of molecular evolution that does not cleanly fit within conventional models of natural selection.^{5,6} The genotype of a young man is the same as his genotype as an older man, but the telomeres (nucleotide sequence) he transmits to his offspring increase in length as he ages. Thus, the PAC effect shares more with phenotypic plasticity and transgenerational epigenetic

effects (or an unusual example of genetic plasticity of the germ line) than with natural selection operating on the germ line.

We have hypothesized that the PAC effect is a case of an adaptive intergenerational phenotypic plasticity.^{5,6} Phenotypic or developmental plasticity are common forms of adaptation that allow individual organisms to modify their phenotypes in response to ecological changes occurring within a generation or two, which is far more rapid than can be accommodated by natural selection operating on gene frequencies.⁷ In our evolutionary past, having been born to an older father likely indicated a greater probability of growing up within a social/ecological environment with lower extrinsic mortality and/or with greater opportunities for reproduction at later ages. Thus men with the ability to extend sperm telomere lengths with age and to transmit these modified telomeres to offspring might have increased Darwinian fitness because their offspring were better able to calibrate their reproductive and maintenance expenditures across the likely duration of their lifespans within the variable environments that human populations have confronted.

Although having been born to an older father likely indicates an environment in which living to old age is more probable, a man who at the age of 20 years has one child and at the age of 50 has another would transmit different telomere lengths to his offspring despite living in the same environment. Because paternal age in any one generation varies due to birth order and other factors, we predicted that the PAC effect would exhibit a multigenerational character, integrating a running average signal of the age at reproduction not just of the father, but of recent male ancestors extending back further in time.⁵ As has been argued recently for other forms of epigenetic inheritance,⁷ this type of ‘intergenerational inertia’ in which current phenotypes reflect lingering cumulative impacts of past ancestral experience could provide a more stable and thus reliable signal of local ecological conditions (in this case schedules of mortality and reproduction) upon which to base adaptive decisions about resource allocation.

Our recent work in a large multi-generational cohort in the Philippines supports the multi-generational PAC hypothesis, but only among paternal grandfathers.⁶ That is, if your paternal grandfather was older when he conceived your father, you were predicted to have longer telomeres, independent of and adding to the effect of your father’s age at your own conception. Intriguingly, the lengthening of telomeres predicted by a 1-year delay in age at reproduction was the same for father’s age and grandfather’s age, and very similar to the yearly decline in telomere length measured in middle- to older-aged mothers of the cohort members. It is not clear why we do not see similar effects through the matriline (maternal grandfather’s age), or whether this finding will be replicated in other populations. If so, this would suggest

that any paternal age-related effect on telomere length is explained primarily by the average ages of reproduction among direct patrilineal male ancestors. The multi-generational nature of the PAC effect hints at a means by which human lineages might gradually shift expenditures on maintenance, and potentially prolong lifespans, as unavoidable mortality is consistently low and optimism about living into the future is high.

Are shorter telomeres “thrifty”?

An evolutionary perspective also reminds us that increased longevity does not necessarily equate to increased fitness. This raises an important question: if longer telomeres promote increased longevity, what is the selective pressure against having long telomeres? Aviv and Susser briefly review the prominent hypothesis that longer telomeres promote increased cancer risk. This hypothesis makes intuitive sense, since having a cell lineage with the ability to replicate more times should allow cancerous mutations more time to accumulate. However, the empirical evidence, including prospective research and studies examining the association of telomere-length related genetic polymorphisms to cancer risk, suggest on balance that inheriting longer telomeres might in fact protect against the development of cancer.^{5, 8–10, 11} We have suggested that one possible explanation for these surprising findings is that shorter telomere length impairs immune function, and that this increases cancer risk because a robust immune system is an important factor in combating cancer.⁵

If longer telomeres in humans do not increase cancer risk, they must be costly in other ways. Because telomeres help regulate cell proliferation, one possibility is that shorter telomeres might be ‘thrifty’ in the sense that they reduce maintenance effort particularly in tissue repair and immune function.⁵ In our evolutionary past, resources (e.g. calories and micronutrients) were likely more limited than in modern industrialized contexts. In resource-constrained environments, investment in maintenance and tissue repair to allow a long life (when such investments might otherwise be invested in growth or reproduction) can be maladaptive if unavoidable mortality rates are so high that future reproductive returns on this investment are unlikely to be realized. Telomere length might help directly mediate the evolutionary trade-off between maintenance and reproduction.

Although much remains to be learned about the dynamics and health effects of telomere length within and across generations, the example of the PAC effect illustrates how an evolutionary perspective can help shed light on health-related phenomena, including those that underlie ageing. Ageing is regulated by machinery that evolved not to maximize longevity, but to balance trade-offs in ways that optimize Darwinian

fitness. Since the conditions that we experience change more rapidly than natural selection can change our genome, mechanisms to detect environmental variation and to rapidly respond have likely evolved. The multi-generational character of the PAC effect may give us rare insights into a mechanism that evolved to allow lineages to adjust strategies of resource allocation within the body rapidly as ecological conditions change. Like Aviv and Susser, we think the PAC effect on offspring telomere lengths may have important health consequences and should be rigorously considered from multiple perspectives, including that of evolutionary biology.

Conflict of interest: None declared.

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