Opinion piece

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The mitochondrial genome, paternal age and telomere length in humans

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Telomere length (TL) in humans is highly heritable and undergoes progressive age-dependent shortening in somatic cells. By contrast, sperm donated by older men display comparatively long telomeres, presumably because in the male germline, telomeres become longer with age. This puzzling phenomenon might explain why TL in the offspring correlates positively with paternal age. The present communication proposes that mitochondrial DNA polymorphisms and heteroplasmy cause variation in the production of reactive oxygen species, which, in turn, mediate age-dependent selection of germ stem cells with long telomeres and hence sperm with long telomeres. These long telomeres are then inherited by the offspring. The effect of paternal age on the offspring TL might be an evolutionarily driven mechanism that helps regulate TL across the human population.

This article is part of the theme issue 'Understanding diversity in telomere dynamics'.

1. Introduction

In humans, stem cells in the male germline undergo many more replications than those in the female germline [1]. This is the reason that the paternal lineage in humans and perhaps other primates is the main source of *de novo* germline mutations in the offspring [2–4]. The numerous replications of stem cells in the human male germline might also explain the recently discovered phenomenon of the paternal-age-at-conception (PAC) effect on telomere length (TL).

While somatic stem cells experience age-dependent telomere shortening, sperm of older males show comparatively longer telomeres [5–7], which are apparently inherited by the offspring [8,9]. Thus, offspring conceived by older fathers have longer telomeres than their peers [5,10–12]. The PAC effect on TL has also been observed in chimps [13], suggesting that its yet unknown evolutionary role might be of significance in hominids.

Such findings highlight another curious observation related to the mode of inheritance of TL in humans. Although the telomere literature provides conflicting results on the mode of TL inheritance [14–16], convincing findings indicate that TL is more strongly affected through the maternal than paternal lineage [17,18]. Thus, offspring TL is influenced through distinct channels of maternal (greater inheritance) and paternal (PAC) effects; and these effects are already evident in newborns [17]. Notably, the mode of inheritance and parental age effect differ in various species. For instance, TL is heritable in the free-ranging sand lizard and shows a PAC effect on TL in male offspring [19]. In birds, TL is also inherited [20–23], principally through the maternal lineage [21–23], and may show a maternal-age-at-conception effect on the offspring TL [23].

2. The mitochondrial genome and telomere length dynamics in the human male and female germlines

Findings showing that newborn TL is influenced more through the maternal than paternal lineage [17] suggest that the mitochondrial genome may play a

role in TL dynamics during embryonic/fetal development. This is because the mitochondria are inherited solely from the mother.

The DNA of the human mitochondria, the main source of endogenous reactive oxygen species (ROS), is highly polymorphic, presumably because of evolution-mediated adaptation to different environmental and geographical settings [24]. Mitochondrial DNA (mtDNA) is not only polymorphic but also heteroplasmic, i.e. two or more mtDNA alleles might coexist in different proportions in different cells of the same lineage [24]. Thus, mtDNA polymorphisms and heteroplasmy may, respectively, engender variation in ROS production across individuals and across cells of the same lineage within the individual. As ROS augment replication-dependent TL shortening [25,26], cells that produce lower amounts of ROS should experience less replication-dependent TL shortening.

Owing to the uniparental (asexual) mode of mitochondrial inheritance, the outcomes of mitochondrial mutations cannot be attenuated through germline recombination. However, 'purifying selection' of mitochondria occurs in primordial stem cells of the female germline, presumably to cull deleterious mutations in the mitochondrial genome, which displays a higher mutational rate than the nuclear genome and increased susceptibility to mutational drift [27,28]. However, little is known about mitochondrial selection dynamics, if any, in the male germline.

Importantly, mitochondria in the male germline are not transmitted to the offspring. Still, in the light of the numerous replications of male germ cells [1], variation in the production of ROS due to underlying mtDNA polymorphism and heteroplasmy might differentially influence TL in sperm, which would be transmitted to offspring. Moreover, while 'purifying selection' in the female germline principally occurs during embryonic development, in theory, germ stem cell selection in the male germline might occur during extra-uterine life throughout the male's long reproductive period.

3. Linking reactive oxygen species production with telomere lengthening in the male germline

Given the difficulties in obtaining human oocytes for research and reliance on TL measurements in a single oocyte (compared with millions of sperm) at a time, information about TL dynamics in the human female germline is scant. That said, there is good consensus that age-dependent telomere lengthening does not occur in the female germline [29]. How then can we explain age-dependent telomere lengthening in the human male germline?

Telomerase, the reverse transcriptase that offsets replication-mediated telomere shortening [30], is largely silent in somatic cells of humans and other long-lived large mammals [31]. By contrast, telomerase activity is robust in the testes and presumably germ stem cells (but not mature spermatozoa) of males in humans [32] and other mammals [33,34]. Given that the male germline undergoes numerous replications during extra-uterine life, it makes intuitive sense that telomerase would minimize or eliminate replication-mediated telomere shortening, thereby avoiding critically short telomeres in the germline, which might compromise fitness. The longer telomeres in sperm of older men suggest, however, that telomerase 'overshoots', adding telomere repeats to the ends of the chromosomes over and above those lost due to the replication of male germ stem cells [7].

But, there might be another potential explanation for telomere elongation in sperm, namely, age-dependent survival, i.e. selection, of male germ stem cells that produce lower amounts of ROS. These selected germ stem cells would display less TL shortening per replication. If telomerase in the male germline adds a constant amount of telomere repeats with each germ cell replication, age-dependent enrichment of germ stem cells that produce a lower amount of ROS would result in progressively longer telomeres in the germline of older males. In fact, indirect evidence, derived from research in twins, suggests a PAC-mediated preferential selection of germ stem cells with longer telomeres in the male germline [35]. Moreover, as the mitochondria in the male germline are not transmitted to the offspring, mitochondrial variants that produce more ROS would not be selected out across generations of males. Thus, the PAC effect would repeat itself generation after generation.

4. Conclusion

TL is a complex genetic trait whose dynamics during the individual's life course (including intra-uterine growth and development) might be influenced by the parental nuclear genetics and maternal (mitochondrial) genetics. This communication synthesizes evidence from diverse disciplines to explain the puzzling findings of long telomeres in sperm of older men and hence the PAC effect on the offspring TL. Whatever the underlying mechanisms of the PAC effect on the offspring TL might be, such a phenomenon adds another dimension of 'plasticity' to trans-generational TL dynamics. We view the PAC effect as a process whereby older fathers endow their offspring with longer telomeres, but another perspective is that younger fathers endow their offspring with shorter telomeres. In this way, in addition to a host of inherent and environmental factors, paternal age in humans might be a unique mechanism through which TL is regulated across generations.

While TL dynamics in the growing fetus/newborn might be influenced by polymorphisms in the maternal mtDNA, in the end, the PAC effect on the offspring TL might largely (and ironically) reflect variation in the mitochondrial genome that is derived from the offspring's paternal grandmother. The collective influences stemming from the mitochondrial genomes of the paternal grandmother (through PAC) and the mother on the offspring's TL suggest that human TL might be more female-driven than male-driven.

Finally, the proposed model of mitochondria-based stem cell selection in the male germline is founded on the premise that the PAC effect on the offspring TL reflects underlying mechanisms that produce long telomeres in sperm of older versus younger males. However, no study has examined sperm TL dynamics based on longitudinal evaluation of sperm donated by the same men as they get older. Analysis based on longitudinal evaluation of the relationship between sperm TL dynamics and mtDNA polymorphisms and heteroplasmy might thus provide the answer about whether the PAC effect on the offspring TL is driven by mitochondrial genetics in the male germline.

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References

1. Crow JF. 2000 The origins, patterns and implications of human spontaneous mutation. *Nat. Rev. Genet.* **1**, 40–47. (doi:1038/35049558)

2. Shimmin LC, Chang BH, Li WH. 1993 Male-driven evolution of DNA sequences. *Nature* **362**, 745–747. (doi:10.1038/ng1097-182)

3. Li WH, Yi S, Makova K. 2002 Male-driven evolution. *Curr. Opin. Genet. Dev.* **12**, 650–656. (doi:10.1016/S0959-437X(02)00354-4)

4. Kong A *et al.* 2012 Rate of *de novo* mutations and the importance of father's age to disease risk. *Nature* **488**, 471–475. (doi:10.1038/nature11396)

5. Kimura M *et al.* 2008 Offspring's leukocyte telomere length, paternal age, and telomere elongation in sperm. *PLoS Genet.* **4**, e37. (doi:10.1371/journal.pgen.0040037)

6. Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, Greider CW, Harley CB. 1992 Telomere length predicts replicative capacity of human fibroblasts. *Proc. Natl Acad. Sci. USA* **89**, 10 114–10 118. (doi:10.1073/pnas.89.21.10114)

7. Aston KI, Hunt SC, Susser E, Kimura M, Factor-Litvak P, Carrell D, Aviv A. 2012 Divergence of sperm and leukocyte age-dependent telomere dynamics: implications for male-driven evolution of telomere length in humans. *Mol. Hum. Reprod.* **18**, 517–522. (doi:10.1093/molehr/gas028)

8. Baird DM, Rowson J, Wynford-Thomas D, Kipling D. 2003 Extensive allelic variation and ultrashort telomeres in senescent human cells. *Nat. Genet.* **33**, 203–207. (doi:10.1038/ng1084)

9. Graakjaer J, Der-Sarkissian H, Schmitz A, Bayer J, Thomas G, Kolvraa S, Londoño-Vallejo JA. 2006 Allele-specific relative telomere lengths are inherited. *Hum. Genet.* **119**, 344–350. (doi:10.1007/s00439-006-0137-x)

10. Unryn BM, Cook LS, Riabowol KT. 2005 Paternal age is positively linked to telomere length of children. *Aging Cell* **4**, 97–101. (doi:10.1111/j.1474-9728.2005.00144.x)

11. De Meyer T, Rietzschel ER, De Buyzere ML, De Bacquer D, Van Criekinge W, De Backer GG, Gillebert TC, Van Oostveldt P, Bekaert S. 2007 Paternal age at birth is an important determinant of offspring telomere length. *Hum. Mol. Genet.* **16**, 3097–3102. (doi:10.1093/hmg/ddm271)

12. Eisenberg DT, Hayes MG, Kuzawa CW. 2012 Delayed paternal age of reproduction in humans is associated with longer telomeres across two generations of descendants. *Proc. Natl Acad. Sci. USA* **109**, 10 251–10 256. (doi:10.1073/pnas.1202092109)

13. Eisenberg DT, Tackney J, Cawthon RM, Cloutier CT, Hawkes K. 2017 Paternal and grandpaternal ages at conception and descendant telomere lengths in chimpanzees and humans. *Am. J. Phys. Anthropol.* **162**, 201–207. (doi:10.1002/ajpa.23109)

14. Eisenberg DT. 2014 Inconsistent inheritance of telomere length (TL): is offspring TL more strongly correlated with maternal or paternal TL? *Eur. J. Hum. Genet.* **22**, 8–9. (doi:10.1038/ejhg.2013.202)

15. De Meyer T, Vandepitte K, Denil S, De Buyzere ML, Rietzschel ER, Bekaert S. 2014 A non-genetic, epigenetic-like mechanism of telomere length inheritance? *Eur. J. Hum. Genet.* **22**, 10–11. (doi:10.1038/ejhg.2013.255)

16. De Meyer T, Eisenberg DT. 2015 Possible technical and biological explanations for the 'parental telomere length inheritance discrepancy' enigma. *Eur. J. Hum. Genet.* **23**, 3–4. (doi:10.1038/ejhg.2014.65)

17. Factor-Litvak P, Susser E, Kezios K, McKeague I, Kark JD, Hoffman M, Kimura M, Wapner R, Aviv A. 2016 Leukocyte telomere length in newborns: implications for the role of telomeres in human disease. *Pediatrics* **137**, e20153927. (doi:10.1542/peds.2015-3927)

18. Broer L *et al.* 2013 Meta-analysis of telomere length in 19 713 subjects reveals high heritability, stronger maternal inheritance and a paternal age effect. *Eur. J. Hum. Genet.* **21**, 1163–1168. (doi:10.1038/ejhg.2012.303)

19. Olsson M, Pauliny A, Wapstra E, Uller T, Schwartz T, Blomqvist D. 2011 Sex differences in sand lizard telomere inheritance: paternal epigenetic effects increases telomere heritability and offspring survival. *PLoS ONE* **6**, e17473. (doi:10.1371/journal.pone.0017473)

20. Atema E, Mulder E, Dugdale HL, Briga M, van Noordwijk AJ, Verhulst S. 2015 Heritability of telomere length in the zebra finch. *J. Ornithol.* **156**, 1113–1123. (doi:10.1007/s10336-015-1212-7)

21. Horn T, Robertson BC, Will M, Eason DK, Elliott GP, Gemmell NJ. 2011 Inheritance of telomere length in a bird. *PLoS ONE* **6**, e17199. (doi:10.1371/journal.pone.0017199)

22. Reichert S, Rojas ER, Zahn S, Robin JP, Criscuolo F, Massemin S. 2015 Maternal telomere length inheritance in the king penguin. *Heredity* **114**, 10–16. (doi:10.1038/hdy.2014.60)

23. Asghar M, Bensch S, Tarka M, Hansson B, Hasselquist D. 2015 Maternal and genetic factors determine early life telomere length. *Proc. R. Soc. B* **282**, 20142263. (doi:10.1098/rspb.2014.2263)

24. Wallace DC. 2015 Mitochondrial DNA variation in human radiation and disease. *Cell* **163**, 33–38. (doi:10.1016/j.cell.2015.08.067)

25. Von Zglinicki T. 2003 Replicative senescence and the art of counting. *Exp. Gerontol.* **38**, 1259–1564. (doi:10.1016/j.exger.2003.09.015)

26. Houben JM, Moonen HJ, van Schooten FJ, Hageman GJ. 2008 Telomere length assessment: biomarker of chronic oxidative stress? *Free Radic. Biol. Med.* **44**, 235–246. (doi:10.1016/j.freeradbiomed.2007.10.001)

27. Stewart JB, Freyer C, Elson JL, Larsson NG. 2008 Purifying selection of mtDNA and its implications for understanding evolution and mitochondrial disease. *Nat. Rev. Genet.* **9**, 657–662. (doi:10.1038/nrg2396)

28. Wallace DC. 2010 Colloquium paper: bioenergetics, the origins of complexity, and the ascent of man. *Proc. Natl Acad. Sci. USA* **107**(Suppl. 2), 8947–8953. (doi:10.1073/pnas.0914635107)

29. Keefe DL, Liu L. 2009 Telomeres and reproductive aging. *Reprod. Fertil. Dev.* **21**, 10–14. (doi:10.1071/RD08229)

30. Blackburn EH. 2005 Telomeres and telomerase: their mechanisms of action and the effects of altering their functions. *FEBS Lett.* **579**, 859–862. (doi:10.1016/j.febslet.2004.11.036)

31. Gomes NM *et al.* 2011 Comparative biology of mammalian telomeres: hypotheses on ancestral states and the roles of telomeres in longevity determination. *Aging Cell* **10**, 761–768. (doi:10.1111/j.1474-9726.2011.00718.x)

32. Wright WE, Piatyszek MA, Rainey WE, Byrd W, Shay JW. 1996 Telomerase activity in human germline and embryonic tissues and cells. *Dev. Genet.* **18**, 173–179. (doi:10.1002/(SICI)1520-6408(1996))

33. Nasir L, Devlin P, McKevitt T, Rutteman G, Argyle DJ. 2001 Telomere lengths and telomerase activity in dog tissues: a potential model system to study human telomere and telomerase biology. *Neoplasia* **3**, 351–359. (doi:10.1038/sj/neo/7900173)

34. Gardner JP *et al.* 2007 Telomere dynamics in macaques and humans. *J. Gerontol. A Biol. Sci. Med. Sci.* **62**, 367–374. (doi:10.1093/gerona/62.4.367)

35. Hjelmborg JB *et al.* 2015 Paternal age and telomere length in twins: the germ stem cell selection paradigm. *Aging Cell* **14**, 701–703. (doi:10.1111/acel.12334)