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GENETIC AND MOLECULAR EPIDEMIOLOGY

Leukocyte Telomere Length and the Father's Age Enigma: Implications for Population Health and for Life Course

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What are the implications for population health of the demographic trend toward increasing paternal age at conception (PAC) in modern societies? We propose that the effects of older PAC are likely to be broad and harmful in some domains of health but beneficial in others. Harmful effects of older PAC have received the most attention. Thus, for example, older PAC is associated with an increased risk of offspring having rare conditions such as achondroplasia and Marfan syndrome, as well as with neurodevelopmental disorders such as autism. However, newly emerging evidence in the telomere field suggests potentially beneficial effects, since older PAC is associated with a longer leukocyte telomere length (LTL) in offspring, and a longer LTL is associated with a reduced risk of atherosclerosis and with increased survival in the elderly. Thus, older PAC may cumulatively increase resistance to atherosclerosis and lengthen lifespan in successive generations of modern humans. In this paper we: (i) introduce these novel findings; (ii) discuss potential explanations for the effect of older PAC on offspring LTL; (iii) draw implications for population health and for life course; (iv) put forth an evolutionary perspective as a context for the multigenerational effects of PAC; and (v) call for broad and intensive research to understand the mechanisms underlying the effects of PAC. We draw together work across a range of disciplines to offer an integrated perspective of this issue.

Introduction

In high-income countries, growing numbers of men as well as women are choosing to postpone parenthood. On average, both parents conceive their first child at an older age.[1,2] If sustained, this demographic shift may have manifold implications for the health of successive generations. We discuss here the evidence for a beneficial effect of increasing paternal age at conception (PAC) on the health of descendants.

Basic genetics offers a strong foundation for hypothesizing that increased PAC creates an increased risk for a host of disorders in offspring. *In utero*, the female germ cells undergo an estimated 22 cell divisions before

meiosis and two divisions during meiosis. However, as only one chromosome replication takes place during meiosis, the female germ cells undergo a total of 23 chromosome replications. Postnatally, the meiotic process is arrested at the first meiosis and this persists until puberty. Thus, between the mother's birth and the conception of her offspring, her germ cells undergo no chromosome replication and only one cell division (regardless of her age at conception).[3] In contrast, spermatogenesis goes on throughout most of the male's life course. For instance, the estimated cumulative numbers of germ-line stem cell (GSC) replications in men by the ages of 20 and 40 years are 150 and 610, respectively. This provides a greater chance for spontaneous, male-biased mutations.[3–5.]

It has long been recognised that rare conditions such as achondroplasia (the prevalence of which is ~one per twenty thousand) and Marfan syndrome (which has a prevalence of ~one per five thousand) may arise from mutations in the male GSCs.[6,7] However, in the past decade, a large number of studies have linked increased PAC to severe conditions that are not so rare in offspring, including autism, schizophrenia, and other neurodevelopmental disorders.[8–12] It is often assumed, but not proven, that this is also due to mutations in the male germ line. Perhaps because of the gravity of these diseases, their associations with PAC have generated substantial media attention and even entered public discourse.[13]

Studies now suggest, however, that older PAC may also confer benefits on the health of offspring. This poses a dilemma for public health. If increased PAC may have both adverse and beneficial effects, understanding the balance of its risks and benefits will require the consideration of a broad scope of relationships between increased PAC and offspring health. Yet we have only just begun to explore the potential benefits of older PAC, and the evidence for them is still not widely understood.

We therefore integrated work done across disciplines to articulate the case for a potentially major benefit of older PAC on the basis of an intriguing finding in recent studies that leukocyte telomere length (LTL) is on average longer in the offspring of older fathers.[14–19] This association of PAC with offspring LTL has no threshold, as it has been observed for increasing PAC from the age of ~20 up to 60 years.[15,17,18] As a longer LTL predicts reduced atherosclerotic risk[20–23] and longer survival in the elderly,[24–26] it is possible that older fathers, by endowing their offspring with a longer LTL, may also confer on them resistance to atherosclerosis and an advantage for increased longevity.

That older PAC is related to longer offspring LTL is an enigma. To some, it might even seem counter-intuitive, given the widespread awareness of genetic abnormalities related to both increased maternal age at conception (e.g., chromosomal aneuploidy) and PAC (e.g., *de novo* mutations). The PAC effect on offspring LTL is also perplexing on a deeper level, however, because of what it implies about age-related changes in the male germ line and how they are transmitted to offspring. Yet the outcome of these age-related changes, namely, longer telomere length (TL), is probably transmitted in Mendelian fashion. We discuss below how this enigma could be resolved.

For understanding of the following discussion, it is important to recognize four major aspects of TL in general and LTL in particular. First, telomeres are the TTAGGG tandem repeats at both ends of each of the mammalian chromosomes, and together with telomere-binding proteins they cap the chromosomes.[27] This capping stabilizes the telomere and prevents the chromosomal ends from being recognized by the DNA repair processes in cells as DNA break points and potential sites of chromosomal fusions. Second, as somatic cells replicate, their telomeres undergo progressive attrition because DNA polymerase cannot completely replicate the 3′ end of linear duplex DNA. This is referred to as the end-replication problem.[28,29] Once telomeres become very short, they often cause cells to exit from the replicative cycle and become senescent.[27] Third, LTL is a complex human genetic trait in that it is determined by many genes,[30,31] and its dynamics (birth LTL and age-dependent telomere attrition thereafter) reflect telomere dynamics in hematopoietic stem cells.[32,33] Fourth, because the hematopoietic system is probably the most proliferative system among somatic tissues, LTL, and by inference TL in hematopoietic stem cells, can become critically short during the long human life course, thereby imposing a limit on the longevity of some individuals.

The Effect of Paternal Age at Conception on the Leukocyte Telomere Length of Offspring

The mechanisms underlying the association of PAC with the LTL of offspring are not yet understood. Genome-wide association studies (GWAS) of LTL have deciphered a number of genes and genetic loci associated with LTL in the general population.[34–36] However, it is very unlikely that the PAC effect on offspring LTL is mediated through increased mutation load with age in the paternal germ line. Such mutations are too rare to explain the PAC effect on the offspring LTL,[37] for the reason that the effect of older PAC is manifested as a shift to a longer average LTL of the offspring in the population. Because there is no corresponding increase in variance of the offspring LTL,[15,17] this population shift does not merely reflect an increase in the small subset of persons with extremely long LTL.

An important clue to the causal mechanism of PAC on LTL is that while telomeres undergo age-dependent shortening in replicating somatic cells, TL is longer in sperm samples donated by older men

than in those donated by young ones.[17,38-40] Thus, postulated mechanisms for the PAC effect on LTL must ultimately explain the reason for why, on average, sperm cells of older men have longer TLs than sperm cells of younger men. One plausible explanation for this is age-related GSC selection in males. Each sperm is a distinct genetic package, ensuring genetic diversity among a father's offspring. Age might exert selection pressure at the level of the male GSCs such that surviving GSCs are those with relatively long telomeres. Indeed, there is some evidence for the 'overrepresentation' of sperm with longer telomeres in older men.[17]

Another explanation for the effect of PAC on LTL, not mutually exclusive with GSC selection, relates to the age-dependent elongation of telomeres in male GSCs. This could be due to the difference in telomerase activity between somatic cells and male germ-line cells. Telomerase is a reverse transcriptase that adds telomere repeats to the ends of chromosomes.[41] Telomerase activity is repressed after birth in most human somatic cells, including hematopoietic stem cells.[42,43] By contrast, telomerase displays robust activity in embryonic stem cells and in the testes of humans[44] and other mammals,[45,46] presumably because the enzyme is active in male GSCs. The activity of telomerase is usually fine-tuned to maintain the length of telomeres constant in telomerase-positive cells. It seems, however, that a small increase in TL (only a few base pairs) occurs with each replication of GSC in males,[40] suggesting that in these cells telomerase overshoots its mark. Because of the high number of replications of male GSCs, a small elongation would result in considerable lengthening of sperm-cell TL over many replications. Although sperm have a long TL, the TL of mammalian oocytes is relatively short and is evidently 'reset' upward during early embryogenesis.[47–49] However, regardless of mechanisms that affect TL in the embryo and fetus, human TL is evidently inherited in an allele-specific manner.[50,51] Accordingly, ordinary Mendelian principles would seem to suggest that since a child receives roughly half of its DNA from its father, the slope of its LTL vs. PAC should be approximately one half of the slope of TL in sperm vs. the ages of the sperm donors. Recent findings suggest that this is the case.[40]

Implications for Public Health and for Life Course

The magnitude of the PAC effect on offspring LTL is large, at ~15–20 base pairs of a longer LTL in the offspring for each year of PAC.[15,17,18] This is close to the average rate of age-dependent LTL attrition in adulthood, of ~20–30 base pairs per year.[17–19] Moreover, the PAC effect on offspring LTL appears to be cumulative across successive generations.[19]

Given the considerable magnitude of the PAC effect on offspring LTL and it's additive nature across successive generations,[19] current demographic trends of an upward shift in paternal age[1,2] might affect TL in future humans. From this standpoint, the PAC effect on LTL is also directly relevant to the biological limit of human longevity.[52] Short human telomeres could, in theory, impose a limit on human longevity, but the PAC effect suggests that human TL is malleable. It is therefore essential to factor in the PAC effect on TL dynamics in the offspring when considering the question of whether life expectancy is approaching its ultimate ceiling in modern humans.

The large magnitude of the PAC effect on offspring LTL also suggests that it could be worthwhile to use this knowledge to explore possibilities for improving population health. Before doing that, however, it is necessary to answer some basic questions about PAC and LTL in life-course and cross-generational epidemiological studies. The main determinants of LTL at any age are LTL at birth and the magnitude of its attrition during growth.[30] Yet the PAC effect has been studied only in adult offspring. The hypothesis of Mendelian transmission of a longer TL from the paternal germ line to the offspring predicts that offspring of older fathers would be conceived with a longer TL. By the time of conception, the TL of the paternal germ line would already have been lengthened by GSC selection or age-related elongation or both, and this longer TL would be inherited by the offspring. But this prediction of Mendelian inheritance of epigenetic changes has not yet been tested, leaving open the question of whether there might be some more complex process by which PAC exerts a latent effect on LTL that becomes evident *in utero* or during the first two decades of life.

The Evolutionary Perspective

We have noted above that increased PAC is associated with rare mutations and related diseases. If increased PAC also has beneficial effects on offspring health via increased TL, then we need to pose the following question: Might the PAC effect be understood from the perspective of natural forces that shape human biology with respect not only to disease but also to evolutionary fitness? We describe briefly research that may help answer this question.

Evolutionary theories suggest that delayed reproduction leads to increased longevity because of larger investment in maintenance and repair.[53] This feature has been displayed in model organisms. For instance, selection based on delayed reproduction causes a pronounced increase in the lifespan of the fruit fly *Drosophila melanogaster*.[53] Because increased PAC reflects delayed reproduction in humans, and longer LTL might predict increased lifespan, the PAC effect may be a manifestation in humans of the same phenomenon as seen in the fruit fly. Moreover, in aging male fruit flies, the number of GSCs is much smaller than that in younger male flies.[54] Such a phenomenon may be the result of a stochastic depletion of

GSCs or may reflect the ability of surviving GSCs to withstand the accruing burden of aging-related stress, primarily in the form of oxidative stress. The variant genetic and more likely epigenetic constitution that distinguishes the surviving GSCs from the non-surviving ones might provide a potential mechanism for transmitting increased fitness and longevity from fathers to offspring.

Studies across a variety of species suggest that TL and the expression of telomerase activity in somatic tissues have been fashioned by evolutionary forces. Consider, for instance, the body sizes of terrestrial mammals (among which humans are viewed as moderately sized mammals) and their life spans. Increased mammalian body size is associated with repression of telomerase, whereas increase in life span is associated with shorter telomeres.[55] Humans, the longest-living terrestrial mammals, have short telomeres and repressed telomerase activity in their somatic cells during extra-uterine life. In principle, TL might hence curtail lifespan in humans to a greater extent than in other mammals.

A postulated evolutionary explanation for repressed telomerase activity with increased body size and diminished TL with increased life span is that these features protect against cancer through the reproductive phase of the life span.[55] Because somatic cells from relatively large and long-living mammals tend to undergo many more replications for growth and maintenance than do those of small, short-living mammals, they should be subject to a greater risk of cancer. Thus far, however, there is no empirical evidence for associations of cancer risk with body size or longevity among mammals.[56] In this context, little is known about the effect among humans of inter-individual variation in TL with respect to the cost of having relatively short telomeres (perhaps less cancer risk early in life and more cardiovascular disease risk later in life) or long telomeres (perhaps more cancer risk early in life and less cardiovascular disease risk later in life).

Conclusions

The PAC effect on the health of offspring and, more broadly, on public health, requires fundamental re-thinking and new directions in research. Insight into this phenomenon and its links to human telomere biology will significantly advance the understanding of aging-related diseases in modern humans. Overall, the evidence supports the view that in some contexts the male germ line might drive the evolution of human TL. If so, this would represent a substantial addition to Haldane's conceptualization of the evolutionary force of male-biased mutations[57,58] and the subsequent recognition that the evolution of DNA sequences is largely driven through the numerous replications of the male germ line.[59]

Because TL at birth and its rapid attrition during early life strongly influence TL throughout the human life course,[30] an understanding of the PAC effect on offspring TL requires going straight to the source, namely, TL at birth and its attrition during childhood. Ongoing studies, exemplified by the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK[60,61] and the Norwegian Mother and Child Cohort Study (MoBa),[62] might be used to achieve this goal in a cost-effective manner. Lastly, it is clear that the enigma of the father's age and the health of his offspring are bound to engage telomere researchers, evolutionary biologists, epidemiologists, and demographers for quite some time. It also should enter the discourse on public health policies.

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KEY MESSAGES

- Older paternal age at conception is associated with a longer leukocyte telomere length in the offspring.
- A longer leukocyte telomere length has been shown to be associated with reduced atherosclerotic risk in adults and increased survival in the elderly.
- The association between paternal age at conception and the offspring's leukocyte telomere length probably stems from progressive age-dependent elongation of telomere length in the male germline.
- The underlying mechanisms for this elongation are not fully understood, but they might contribute to male-driven evolution of telomere length in humans.

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

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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.