A non-genetic, epigenetic-like mechanism of telomere length inheritance?

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We have read with great interest the manuscript by Broer *et al*, 'Meta-analysis of telomere length in 19 713 subjects reveals high heritability, stronger maternal inheritance and a paternal age effect', recently accepted for publication in the *European Journal of Human Genetics*.[1] While providing the scientific community with particularly valuable information regarding telomere length (TL) inheritance, we believe that an important implication of the authors' findings has not been addressed, ie, that TL inheritance might be direct and only modulated by genetics. But first we will briefly sketch the relevance of this discussion.

The length of telomeres, the several kilobase long TTAGGG repeats capping human chromosomes, has been repeatedly demonstrated to be an independent predictive factor of certain aging related diseases, such as cardiovascular diseases, and their outcome. Although causality remains to be validated, it has been suggested that replicative senescence triggered by critically shortened telomeres might be a driver of these diseases. Whereas telomeres shorten with aging in somatic tissues, with additional modulation by external factors such as oxidative stress, the average TL of an individual's different tissues is very similar and predominantly determined at birth.[2]

As a shorter TL at birth might therefore imply an increased risk for aging related diseases, the exact mechanism and magnitude of TL inheritance is of real importance. The first major report on this topic already dates back from 1994, demonstrating major TL heritability of 78% in monozygotic twins.[3] After this seminal paper, it however took almost 20 years to identify the exact mode of TL inheritance. Originally, X-linked and paternal inheritance were proposed.[4,5] Yet, both modes were finally proven inaccurate by the recent pivotal study by Broer *et al*,[1] a meta-analysis including 1244 father–offspring and 1388 mother–offspring pairs. Their results – even upon adjustment for shared environmental factors – support both paternal and maternal inheritance. However, the study by Broer *et al*[1] also leads to a new fundamental telomere biology question, which was – despite some intriguing clues in their results – not brought forward by the authors. More specifically, what is the exact nature of TL inheritance: does a subject's TL particularly reflect his/her genetic composition, ie, genetic inheritance, or does it predominantly reflect the TL of the original germ cells that gave rise to the subject? We argue that the results by Broer *et al*[1] hint at the latter possibility.

Genetic inheritance has since long been suggested as the primary mechanism of TL inheritance, as early results suggested that TL is completely reset during early mammalian embryogenesis. In the course of this process, telomeres are elongated again by a specific enzyme called telomerase, reportedly to a predetermined TL 'set point' at birth.[6] The fact that several SNPs in the vicinity of genes involved in the telomerase machinery have been associated with leukocyte TL through GWAS, eg,[7] therefore indicates that there is indeed a certain genetic component involved, as pointed out by Broer *et al*.[1] On the other hand, the authors also validated that the paternal age at a child's conception is an important determinant of its TL,[8] most likely due to telomerase-dependent telomere elongation in sperm cells over time. This not only proves that TL is at least not fully reset during embryogenesis, but also that the original spermatozoon TL is still visible in the offspring. Therefore, this indicates that a subject's TL at least partially reflects the TL of his/her parents' specific germ cells. Note that this direct mechanism, which is also supported by studies in mice,[9] is indeed straightforward and has been suggested before by us and others.[8,10] However, it is an unlikely mechanism in case of X-linked or paternal inheritance. The report by Broer *et al*,[1] indicating both maternal and paternal inheritance, therefore calls for a thorough evaluation of this direct mechanism of TL inheritance, which we consider to be epigenetic-like.

Indeed, in case of a direct mechanism, TL can be considered to fulfill the definition of an epigenetic trait,[11] as it is mitotically and meiotically heritable, but does not rely on the actual DNA sequence. That is, the information is encoded in the length of the telomeres, not in the repeated TTAGGG sequence. Note that there is indeed an effect of genetic variants on TL,[7] but this also the case for DNA-methylation,[12] simply implying that epigenetic(-like) features are also partially under genetic control. Importantly, together with the telomeres, a stable phenotype is inherited as well, ie, absence of replicative senescence, with associated gene expression pattern. Similar to epigenetic marks, TL inheritance is not fully stable, with clear impact of the environment, and there might be a major interaction with other epigenetic features. For example, in addition to an effect of genetics,[7] telomerase activity is also regulated by DNA-methylation[13] and lifestyle/environment,[14] and perhaps even their interplay. However, it is unclear to which extent this additional epigenetic layer of TL control might also be meiotically inherited.

The non-genetic inheritance mechanism has several consequences. First, stronger inheritance will be observed when the germ cells' TL better reflects the parents' TL. In women, primary oocytes are present from birth until ovulation without additional division, whereas in men there is continuous mitosis of spermatogonia of which a fraction will result in spermatozoa. Importantly, it can be expected that stochastic effects during these divisions will yield a greater variation in spermatozoon TL than will be the case for oocytes. A plausible consequence of this putative difference is that there will be a stronger maternal than paternal inheritance, see the observations by Broer *et al*.[1] Note that additional explanations are required for the observation of (stronger) paternal inheritance in other populations.[15] Second, in case of epigenetic inheritance, transgenerational effects may be present. For example, this implies a cumulated impact of the paternal age at conception effect, with potential health risk effects, as suggested by Eisenberg *et al*.[16]

In summary, the outcome of the endeavor by Broer *et al*[1] has far more consequences than initially anticipated. The fact that TL is both maternally and paternally inherited implies the possibility of direct, non-genetic TL transmission through the germ cells, which we consider to be an epigenetic-like mechanism. Additional genetic modulation is present, particularly through telomerase activity during early embryogenesis, but the quantitative impact of each inheritance mechanism remains to be elucidated.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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