Published in final edited form as:
Mutat Res. 2012 February 1; 730(1-2): 68–74. doi:10.1016/j.mrfmmm.2011.05.001.

Genetics of Leukocyte Telomere Length and its Role in Atherosclerosis

Abraham Aviv
The Center for Human Development and Aging, University of Medicine and Dentistry, New Jersey Medical School, Newark, New Jersey 07103, USA

Abstract

Humans display a large inter-individual variation in leukocyte telomere length (LTL), which is influenced by heredity, sex, race/ethnicity, paternal age at conception and environmental exposures. LTL dynamics (birth LTL and its age-dependent attrition thereafter) mirror telomere dynamics in hematopoietic stem cells (HSCs). LTL at birth is evidently a major determinant of LTL throughout the human lifespan, such that individuals endowed with short (or long) LTL at birth probably have short (or long) LTL later in life. Therefore, the associations of short LTL with atherosclerosis and with diminished survival in the elderly may relate to short birth LTL, accelerated age-dependent LTL attrition, or both. The mechanisms underlying these associations are still not well understood, but they stem in part from genetic factors in control of telomere maintenance and the rate of HSC replication.

Keywords

telomeres; aging; leukocytes; genetics; epigenetics

INTRODUCTION

Leukocyte telomere length (LTL) is a complex human trait. It is heritable [1–11] and modified by paternal age at conception (PAC) [12–15]. LTL displays large inter-individual variation at birth [16–19] and throughout the human lifespan [3,18,20,21]. Short telomeres in leukocytes and other organs have been observed in rare syndromes of Telomere Shortening [22–27] and considerable research has been devoted to the roles of telomere biology in human cancers [28–30]. But this communication focuses on LTL genetics in the general population and the potential role of LTL in human atherosclerosis.

LTL DYNAMICS

The last decade has seen remarkable progress in human telomere research with the majority of studies focusing on telomere dynamics (telomere length and its age-dependent rate of

Corresponding Author: Abraham Aviv, Room F-464 MSB, The Center for Human Development and Aging, University of Medicine and Dentistry of NJ, 185 South Orange Ave, Newark NJ 07103, Tel: 973-972-5280, Fax: 973-972-5576, avivab@umdnj.edu.

Conflict of Interest
None

shortening) in leukocytes. Why leukocytes? The studies that launched the discipline of telomere epidemiology probably examined leukocytes because they were readily available and convenient to handle [18,19]. It turned out that LTL is associated with a host of aging-related diseases and environmental circumstances that are linked to the aging of the cardiovascular system, primarily in the form of atherosclerosis [31–34].

The hematopoietic system is hierarchically arranged with mature leukocytes (erythrocytes and platelets) at its bottom and hematopoietic stem cells (HSCs) at its apex. At any age, LTL mirrors the length of telomeres in HSCs [35–37], although by and large LTL is shorter than telomere length in HSCs [but see 37]. Given that the hematopoietic system is the most proliferative among human tissues, age-dependent telomere shortening in this system, as expressed in LTL dynamics, does not reflect telomere shortening in other tissues that display less proliferation. In fact, in the general population, replicative senescence, which is one of the ultimate outcomes of telomere shortening, is unlikely to contribute to the aging of poorly proliferative tissues/cells [38,39] such as neurons, skeletal muscle and fat. That said, in rare syndromes of Telomere Shortening, organs such as lung and liver show functional compromise, which is apparently due to critically short telomeres (25,26,40,41).

What might be the factors that impact LTL dynamics? We know little about the variables in the developing fetus that account for the wide inter-individual variation in LTL at birth [16–20,37]. Moreover, most studies that have shown heritability of LTL [1–11] were based on findings in adults, although the work by Slagboom et al [1], the first to report LTL heritability, was based on twins aged 2–95 years. Akkad et al [17] observed a correlation between the LTLs of mothers and their newborns, suggesting that LTL heritability might already be expressed at birth. Whether or not the rate of LTL shortening during the post-natal period is also heritable, is unknown at present.

What we do know is that the rate of LTL shortening is extremely rapid early in life in both humans [18,19,42] and non-human primates [43] and that it slows down considerably during adulthood. HSCs have insufficient activity of telomerase [44–48], the reverse transcriptase that adds telomere repeats onto the ends of chromosomes [49], to prevent telomere shortening in leukocytes. Therefore, age-dependent LTL attrition reflects telomere shortening in HSCs. Although the length of telomeres and age-dependent telomere shortening in various leukocyte lineages may differ, there is a tight relationship in telomere length between these lineages and LTL [37]. Theoretical considerations [36] suggest that the rapid expansions of the pools of HCSs (by symmetric HSC replication) and hematopoietic progenitor cells (by asymmetric HSC replication) [50], in tandem with the growing soma, account for the fast pace of LTL shortening during the formative years. During adulthood, LTL shortening stems from ‘housekeeping’ functions of HSC replication to accommodate the homeostatic needs of the peripheral blood and probably replace HSCs that exit the replicative cycle due to a variety of causes. As shown in longitudinal studies, that is, repeated measures of LTL in the same persons over several years, there is a wide inter-individual variation in the rate of LTL shortening during adulthood [51–55]. Moreover, a number of these studies have suggested that a subset of individuals may even lengthen their LTL over time. However, recent work has concluded that the lengthening of LTL might be an artifact that reflects the measurement error of telomere length [56]. Although telomerase activity in activated T and B lymphocytes [57] might attenuate the rate of telomere shortening in these circulating cells, it is unlikely to cause LTL elongation with age.

LTL and Atherosclerosis

A consistent association has been observed between LTL and atherosclerosis. In general, individuals with clinical [58–61] and sub-clinical [34,62–65] manifestations of

atherosclerosis and those with increased risk for the disease because of a high BMI [3,65–68], sedentary lifestyle [69], insulin resistance [66,70–73] or cigarette smoking [4,65,67], display relatively shorter LTL than their peers, after adjustment for age, sex and race. Moreover, women have a longer LTL than men [2–4,15,64,65,73] and they are less likely to manifest atherosclerosis during the pre-menopausal period. Curiously, as a group African Americans have a longer LTL than whites [3, 73,74]. African Americans are also less prone than whites to coronary atherosclerosis, which is expressed in less coronary artery calcification [75–78]. Calcification is an important indicator of atherosclerotic plaque burden in the coronary arteries (79). A body of research indicates that independent of traditional risk factors, coronary artery calcification predicts coronary heart disease events (80–83). Even in the presence of multiple cardiac risk factors, persons with no evidence of coronary artery calcification have low near-term risk of having coronary artery disease events. However, whether the longer LTL and less coronary artery calcifications in African Americans than in whites are mechanistically connected is unknown at present.

The association of LTL with smoking [4,65,67], and sedentary lifestyle [69], suggests that in part the rate of LTL shortening is modified by environmental factors. The relatively short LTL in cigarette smokers might reflect an accelerated rate of LTL shortening [56], perhaps because of a cigarette smoke-mediated increase in the load of pro-inflammatory factors and pro-oxidants [84], two factors that might accelerate the rate of LTL shortening along the same lines that explain the short LTL in atherosclerosis. In fact, the proclivity of smokers to atherosclerosis is largely attributed to the pro-inflammatory and pro-oxidant effects of smoking. In As atherosclerosis is a state of chronic low-grade inflammation and increased oxidative stress [85,86], shortened LTL in patients with atherosclerosis might stem from a) an accelerated rate in HSC replication to replace leukocytes consumed in the inflammatory process, and b) the increase in the loss of telomere repeats per replication due to the sensitivity of the GGG triplets on telomeres to the hydroxyl radical [87,88]. But in and of itself an accelerated rate of LTL attrition hardly accounts for shortened LTL in all patients with clinical manifestations of atherosclerosis, because individuals with very short birth LTL probably have a relatively short LTL as adults regardless of their rate of age-dependent LTL shortening. This tenet is supported by the following findings: a) synchrony (equivalence) is observed in telomere length in utero [89], at birth [16,37] and to a great extent during adult life [37,90–92], and b) synchrony is also observed between LTL and telomere length in poorly proliferative tissues such as muscle [90] and fat [91]. As telomere length in poorly proliferative cells largely reflects telomere length during early development, and given the high inter-individual variation in LTL across newborns [16–19], it is safe to surmise that individuals with very short (or long) birth LTL are likely to display short (or long) LTL throughout their life course.

Accordingly, another potential model that explains the LTL-atherosclerosis connection focuses not on inflammation and oxidative stress that mark atherosclerosis but on repair mechanisms undertaken by the body to attenuate its progression. This repair is largely implemented by endothelial progenitor cells (EPCs), which originate from the bone marrow and integrate themselves into the site of vascular injury where they are engaged in endothelial repair [93,94]. Thus, EPCs are the endothelial repair offshoot of HSCs and both their numbers and replicative potential, which are essential for repair, depend on telomere length [95–98]. It follows that shortened telomere length in HSCs, expressed in compromised functions of EPCs, might be as much a part of atherosclerosis as the injurious part that results from inflammation and oxidative stress. In this sense, the hematopoietic repair arm of the vasculature depends on HSC telomere length.

LTL, Atherosclerosis, and Longevity

One of the fundamental questions that pertain to telomere biology in humans is whether LTL is linked to human longevity. If such a connection exists it is likely to be displayed in the elderly, i.e., individuals whose age approaches or has surpassed their life expectancy. Which raises this question: What is the main cause of death in the elderly? Without a doubt, the demise of the majority of the elderly in the USA and other modern societies relates in one way or another to cardiovascular disease, particularly in the form of atherosclerosis [99,100]. To put this statement in perspective, in 2005, approximately 35.5% of mortality in the US population was due to cardiovascular disease, which includes stroke and diabetes, the complication of which is accelerated atherosclerosis. However, in persons older than 85 years, 47.2% of mortality was the consequence of cardiovascular disease [101]. And these vital statistics do not account for death due to infection and dementia, which are much more common in elderly persons with severe cardiovascular disease. With regard to infection, the ultimate cause of death in the elderly is often listed as infection, e.g., influenza or pneumonia. However, the elderly easily succumb to infection due to immune senescence, which might be linked to LTL dynamics [102], and/or because of severely compromised cardiovascular functions. In this context, while the incidence of cardiovascular disease continues to climb exponentially with age, the incidence of cancer plateaus and even declines after the eighth decade [103]. Thus, the association or lack thereof of LTL with mortality in the elderly must be considered from the perspective of the role of cardiovascular disease in the death of the elderly. That said, a controversy once existed whether shortened LTL predicts mortality in the aged [104–109], but research examining the LTL-mortality connection in same-sex elderly twins has found that the co-twins with the shorter LTL were more likely to die first during the follow-up period [9,110]. Data derived from same-sex twins are particularly powerful with regard to the question about the LTL-longevity connection, since they require no statistical adjustments for age and sex of the co-twins and given that twins are more likely to be exposed to similar environmental conditions. Moreover, a recent study that focused on the LTL-mortality nexus in elderly persons participating in the Cardiovascular Health Study also found that individuals with short LTL are at a higher risk for premature death [73].

LTL Heritability and the Paternal Age at Conception (PAC) Effect on the Offspring's LTL

Studies in twins, siblings and families, a few of which were multigenerational, have found that LTL is heritable— estimated heritability between 0.36–0.84 (Table 1). Huda et al [111] found no evidence of LTL heritability based on a study in twins, whose telomere length was measured using Southern blots. The samples of the co-twins in each pair were not randomized; instead they were resolved in adjacent lanes. This probably exerted a 'gel-effect', which differs between samples resolved on different gels but not on those resolved on the same gel. Without randomizing the co-twins, the 'gel effect' might explain the inability of Huda et al to detect LTL heritability in their twins.

The mode of LTL heritability has been the focus of several studies (Table 1). Nawrot et al [4] reported that the inheritance of LTL is X-linked. Subsequent works reported a paternal mode of heritability [10] or a greater paternal than maternal LTL heritability [8,11]. In addition, Akkad et al [17] observed a robust correlation of LTL between mothers and their newborns. Thus, the evidence points to both maternal and paternal modes of LTL inheritance, although nuances in the exact modes of inheritance among studies are not well understood.

One of the most intriguing observations in telomere epidemiology (and telomere genetics) is the effect of PAC on the offspring's LTL (Table 2). The PAC effect was observed by Unryn et al in 2005 [13] in a small cohort and, except for one study in a relatively small sample [11], it has been replicated since in large cohorts [12,14,15], one of which [15] included participants in four different studies in the USA and Europe. It is expressed as a longer LTL in offspring of older fathers. Since all studies showing the PAC effect were performed in adult offspring, it has not been established whether PAC affects the offspring's LTL at birth and/or its age-dependent shortening afterwards. Several studies also reported association of maternal age at conception (MAC) with the offspring' LTL [8,12,14,15] (table 2), but given that the ages of the parents are usually highly correlated, the MAC effect is primarily attributed the PAC effect [12,14,15] (Table 2).

The root causes of the PAC effect are unknown. Interestingly, in contrast to age-dependent telomere shortening in proliferative somatic cells, telomere length is longer in sperm of older as opposed to younger men [10,112,113], a phenomenon that ostensibly relates to the 'emergence' of a subset of sperm with longer telomeres in older donors [15]. If telomere length reflects sperm 'fitness', it is possible that those stem cells of the germ line that display resiliency to aging give rise to sperm with longer telomeres. How this is brought about, and in what way longer telomeres in sperm of older donors might relate to the PAC effect, are unsolved enigmas. It is unlikely, however, that the PAC effect on the offspring's LTL stems from mutations that accumulate with age in the male germ line. A more plausible mechanism to explain the PAC effect might be altered gene expression, mediated by age-dependent changes in chromatin structure and DNA methylation of telomere-regulating genes or perhaps in the sub-telomeric region, which has been shown to affect telomere length [114]. Moreover, it is puzzling how these putative 'epigenetic' changes might be transmitted across generations without being erased during early gestation. And then another potential ramification of the PAC effect is whether by virtue of their longer LTL, offspring of older fathers are relatively resistant to atherosclerosis.

LTL-Regulating Genes in the General Population

Major mutations in telomere maintenance genes that involve the telomerase reverse transcriptase (*TERT*) and the telomerase RNA component (*TERC*), which encode the two subunits of telomerase, cause catastrophic diseases, marked by aplastic anemia and increased predilection to various forms of malignancies, pulmonary fibrosis and liver cirrhosis [22–27]. A subset of these diseases displays progressive shortening of telomeres across generations (genetic anticipation) — a phenomenon that presumably relates to the lack of telomerase activity during early gestation [115], which serves to elongate telomeres, and thereby prevent their shortening with cell replication. However, the specific (and rare) mutations that cause these diseases do not explain the wide inter-individual variation in LTL in the general population. In addition, genome-wide association studies (GWAS), which examine the associations of numerous single-nucleotide polymorphisms (SNPs) with specific phenotypes in many individuals, have found that the *TERT* locus is associated with adenocarcinomas of the lung [116–120], testicular germ cell cancers [121], gliomas [122], as well as other solid tumors [123]. However, only very recent works have deciphered through GWAS genetic loci that explain the inter-individual variation of LTL in the general population.

As LTL dynamics reflect telomere dynamics in HSCs, the genes that account for inter-individual variation in LTL presumably belong to at least two major categories: genes that are engaged in telomere maintenance in all cells and genes that modify directly or indirectly the pace of HSC replication. Recent GWAS support this supposition. These studies have found that SNPs in loci that harbor oligonucleotide/oligosaccharide-binding fold containing

1 gene (*OBFC1*), *TERC* and the chemokine (C-X-C motif) receptor 4 gene *(CXCR4*) are associated with LTL in the general population [124,125]. In addition, LTL was found to be associated with *TERC* in a study that used the candidate gene approach [126].

The telomere maintenance function of *TERC* is, of course, at the center of telomere biology. But *OBFC1*, the homologue of the yeast *Stn1*, is a newly discovered telomere maintenance gene in humans and its functions include the negative regulation of telomerase [127,128]. However, the functional impact of these SNPs associated with LTL through GWAS has not been demonstrated thus far.

While *TERC* and *OBFC1* are directly engaged in telomere maintenance in all cells, it is postulated that *CXCR4* might influence LTL by its central role in the trafficking of neutrophils across the bone marrow [129,130]. The rate of replication of HSCs of individuals with *CXCR4* variants that bring about slower mobilization of neutrophils from the bone marrow might be attenuated, resulting in a longer LTL. What's more, *CXCR*4 also plays a key role in the damage-repair feedback loop between HSCs and the endothelium, which is mediated by EPCs [131–134].

Previous GWAS have uncovered common genetic variants associated with aging-related diseases, including atherosclerosis. But as noted recently [135], many of these variants have so far provided little mechanistic insight into complex human traits. In contrast, the GWAS of LTL [12,125] have uncovered important mechanisms of LTL regulation by identifying loci that harbor variants of known telomere maintenance genes (*TERC, OBFC1*) and a gene engaged in HSC replication (*CXCR4*) that fit into the broader picture of the LTL-atherosclerosis connection. What might be the reason for this gap in outcomes between GWAS of aging-related diseases and GWAS of LTL?

Phenotypes of aging-related diseases such as atherosclerosis are many steps removed from the variant genes that contribute to their characteristics, and they often are poorly quantifiable. Myocardial infarction, a major complication of atherosclerosis, is a categorical trait (yes/no myocardial infarction). But such a trait might change with age, i.e., individuals without a history of myocardial infarction at the age when they were genotyped experience such an event later in life. In contrast, age-adjusted LTL is a quantitative trait that can be measured with relative accuracy. Therefore, using LTL as an intermediate phenotype narrows the spectrum of confounders and might facilitate identifying networks of genes that are engaged in telomere dynamics of the hematopoietic system and their impact on the aging vasculature. It follows that using LTL as an intermediate phenotype of atherosclerosis (and perhaps longevity) in humans might require relatively small samples for GWAS. For instance, 19,492 subjects participated in a GWAS of early-onset myocardial infarction that identified SNPs with genome-wide level of significance, including *CXCL12*— the ligand of *CXCR4* [136]. In contrast, the GWAS of LTL that uncovered *OBFC1*, *TERC* and *CXCR4* was based on 3,417 persons [124]. Most importantly, the identification of *TERC, OBFC1* and *CXCR4* as LTL-regulating genes provides the proof of concept that LTL dynamics mirror telomere dynamics in HSCs.

It is noteworthy, however, that LTL-regulating genes that have been discovered through GWAS explain only a small portion of the inter-individual variation in LTL, although it is likely that ongoing, large-scale GWAS of LTL will decipher more genes that explain this variation. Furthermore, thus far most of LTL GWAS have been performed primarily in Caucasians, providing no insight into the effect of race on LTL, a phenomenon that is probably driven by genetic factors, the potential ramifications of which to human health and longevity are unknown.

Conclusions

The essence of the LTL-atherosclerosis nexus comes down to the following paradigm: Atherosclerosis is an aging-related disease. The onset of the clinical (and sub-clinical) manifestations of the disease depends on the balance between the injurious and repair elements of the disease. An imbalance that is tilted towards injury over that of repair marks the onset of atherosclerosis, which probably occurs early in life in most individuals. The injurious element is partially attributed to the accruing burden of oxidative stress and inflammation on the vascular endothelium. In contrast, the repair element depends in large measure on HSC reserves, which are defined by HSC telomere length, as expressed in LTL. The pace of age-dependent LTL shortening, the index of the contraction rate of these reserves as humans get older, is accelerated by oxidative stress and inflammation.

Practically all humans, if they live long enough, develop atherosclerosis and LTL dynamics provide information about both the injurious and possibly the repair element of this age-related disease. The genes that thus far have been found to be associated with LTL in the general population appear to reaffirm this dichotomy. *OBFC1*—a gene that negatively regulates telomerase— and *TERC* are more likely to impact the size of the HSC reserves, as expressed in LTL, at birth. That is because telomerase activity is robust during early gestation [115] but repressed during extra-uterine life. In contrast, *CXCR4* probably impacts the rate of HSC reserve contraction, as mirrored in the rate of age-dependent LTL shortening. Whether PAC influences HSC reserves at birth, the rate of the contraction of these reserves, or both, is unknown at present.

Finally, given that atherosclerosis is a major determinant in human longevity and that LTL is associated with both atherosclerosis and longevity, it is only reasonable to propose that human longevity might depend to some extent on LTL-regulating genes and the PAC effect on the offspring's LTL.

Acknowledgments

The author's work was supported by NIH grants AG20132 AG21593 and AG30678

References

1. Slagboom PE, Droog S, Boomsma DI. Genetic determination of telomere size in humans: A twin study of three age groups. Am J Hum Genet. 1994; 55:876–882. [PubMed: 7977349]
2. Jeanclos E, Schork NJ, Kyvik KO, Kimura M, Skurnick JH, Aviv A. Telomere length inversely correlates with pulse pressure and is highly familial. Hypertension. 2000; 36:195–200. [PubMed: 10948077]
3. Hunt SC, Chen W, Gardner JP, Kimura M, Srinivasan SR, Eckfeldt JH, Berenson GS, Aviv A. Leukocyte telomeres are longer in African Americans than in whites: the National Heart, Lung, and Blood Institute Family Heart Study and the Bogalusa Heart Study. Aging Cell. 2008; 7:451–458. [PubMed: 18462274]
4. Nawrot TS, Staessen JA, Gardner JP, Aviv A. Telomere length and possible link to X chromosome. Lancet. 2004; 363:507–510. [PubMed: 14975611]
5. Vasa-Nicotera M, Brouilette S, Mangino M, Thompson JR, Braund P, Clemitson JR, Mason A, Bodycote CL, Raleigh SM, Louis E, Samani NJ. Mapping of a major locus that determines telomere length in humans. Am J Hum Genet. 2005; 76:147–151. [PubMed: 15520935]
6. Andrew T, Aviv A, Falchi M, Gardner JP, Lu X, Kimura M, Kato BS, Valdes AM, Spector TD. Mapping genetic loci that determine leukocyte telomere length in a large sample of unselected, female sibling-pairs. Am J Hum Genet. 2006; 78:480–486. [PubMed: 16400618]

7. Bischoff C, Graakjaer J, Petersen HC, Hjelmborg JB, Vaupel JW, Bohr V, Koelvraa S, Christensen K. The heritability of telomere length among the elderly and oldest-old. Twin Res Hum Genet. 2005; 8:433–439. [PubMed: 16212832]
8. Njajou OT, Cawthon RM, Damcott CM, Wu SH, Ott S, Garant MJ, Blackburn EH, Mitchell BD, Shuldiner AR, Hsueh WC. Telomere length is paternally inherited and is associated with parental lifespan. Proc Natl Acad Sci U S A. 2007; 104:12135–12139. [PubMed: 17623782]
9. Bakaysa SL, Mucci LA, Slagboom PE, Boomsma DI, McClearn GE, Johansson B, et al. Telomere length predicts survival independent of genetic influences. Aging Cell. 2007; 6:769–774. [PubMed: 17925004]
10. Nordfjäll K, Larefalk A, Lindgren P, Holmberg D, Roos G. Telomere length and heredity: Indications of paternal inheritance. Proc Natl Acad Sci U S A. 2005; 02:16374–16378.
11. Nordfjäll K, Svenson U, Norrback KF, Adolfsson R, Roos G. Large-scale parent-child comparison confirms a strong paternal influence on telomere length. Eur J Hum Genet. 2010; 18:385–389. [PubMed: 19826452]
12. Arbeev KG, Hunt SC, Kimura M, Aviv A, Yashin AI. Leukocyte telomere length, breast cancer risk in the offspring: The relations with father's age at birth. Mech Ageing Dev. 2011 Feb 25. [Epub ahead of print].
13. Unryn BM, Cook LS, Riabowol KT. Paternal age is positively linked to telomere length of children. Aging Cell. 2005; 4:97–101. [PubMed: 15771613]
14. De Meyer T, Rietzschel ER, De Buyzere ML, De Bacquer D, Van Criekinge W, De Backer GG, Gillebert TC, Van Oostveldt P, Bekaert S. Asklepios investigators. Paternal age at birth is an important determinant of offspring telomere length. Hum Mol Genet. 2007; 16:3097–3102. [PubMed: 17881651]
15. Kimura M, Cherkas LF, Kato BS, Demissie S, Hjelmborg JB, Brimacombe M, Cupples A, Hunkin JL, Gardner JP, Lu X, Cao X, Sastrasinh M, Province MA, Hunt SC, Christensen K, Levy D, Spector TD, Aviv A. Offspring's leukocyte telomere length, paternal age, and telomere elongation in sperm. PLoS Genet. 2008; 4(2):e37. [PubMed: 18282113]
16. Okuda K, Bardeguez A, Gardner JP, Rodriguez P, Ganesh V, Kimura M, Skurnick J, Awad G, Aviv A. Telomere length in the newborn. Pediatr Res. 2002; 52:377–381. [PubMed: 12193671]
17. Akkad A, Hastings R, Konje JC, Bell SC, Thurston H, Williams B. Telomere length in small-for-gestational-age babies. BJOG. 2006; 113:318–323. [PubMed: 16487204]
18. Rufer N, Brümmendorf TH, Kolvraa S, Bischoff C, Christensen K, Wadsworth L, Schulzer M, Lansdorp PM. Telomere fluorescence measurements in granulocytes and T lymphocyte subsets point to a high turnover of hematopoietic stem cells and memory T cells in early childhood. J Exp Med. 1999; 190:157–167. [PubMed: 10432279]
19. Frenck RW Jr, Blackburn EH, Shannon KM. The rate of telomere sequence loss in human leukocytes varies with age. Proc Natl Acad Sci U S A. 1998; 95:5607–5610. [PubMed: 9576930]
20. Alter BP, Baerlocher GM, Savage SA, Chanock SJ, Weksler BB, Willner JP, Peters JA, Giri N, Lansdorp PM. Very short telomere length by flow fluorescence in situ hybridization identifies patients with dyskeratosis congenita. Blood. 2007; 110:1439–1447. [PubMed: 17468339]
21. Barbieri M, Paolisso G, Kimura M, Gardner JP, Boccardi V, Papa M, Hjelmborg JV, Christensen K, Brimacombe M, Nawrot TS, Staessen JA, Pollak MN, Aviv A. Higher circulating levels of IGF-1 are associated with longer leukocyte telomere length in healthy subjects. Mech Ageing Dev. 2009; 130:771–776. [PubMed: 19913048]
22. Vulliamy TJ, Dokal I. Dyskeratosis congenita: the diverse clinical presentation of mutations in the telomerase complex. Biochimie. 2008; 90:122–130. [PubMed: 17825470]
23. Calado RT, Young NS. Telomere diseases. N Engl J Med. 2009; 361:2353–2365. [PubMed: 20007561]
24. Alder JK, Chen JJ, Lancaster L, Danoff S, Su SC, Cogan JD, Vulto I, Xie M, Qi X, Tuder RM, Phillips JA 3rd, Lansdorp PM, Loyd JE, Armanios MY. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci U S A. 2008; 105:13051–13056. [PubMed: 18753630]

25. Calado RT, Regal JA, Kleiner DE, Schrump DS, Peterson NR, Pons V, Chanock SJ, Lansdorp PM, Young NS. A spectrum of severe familial liver disorders associate with telomerase mutations. PLoS One. 2009; 4:e7926. [PubMed: 19936245]
26. Tsakiri KD, Cronkhite JT, Kuan PJ, Xing C, Raghu G, Weissler JC, Rosenblatt RL, Shay JW, Garcia CK. Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc Natl Acad Sci U S A. 2007; 104:7552–7557. [PubMed: 17460043]
27. Armanios M. Syndromes of telomere shortening. Annu Rev Genomics Hum Genet. 2009; 10:45–61. [PubMed: 19405848]
28. Murnane JP. Telomere loss as a mechanism for chromosome instability in human cancer. Cancer Res. 2010; 70:4255–4229. [PubMed: 20484032]
29. Artandi SE, DePinho RA. Telomeres and telomerase in cancer. Carcinogenesis. 2010; 31:9–18. [PubMed: 19887512]
30. Wentzensen IM, Mirabello L, Pfeiffer RM, Savage SA. The Association of Telomere Length and Cancer: A Meta–Analysis. Cancer Epidemiol Biomarkers Prev. 2011 Apr 5. [Epub ahead of print].
31. Butt HZ, Atturu G, London NJ, Sayers RD, Bown MJ. Telomere Length Dynamics in Vascular Disease: A Review. Eur J Vasc Endovasc Surg. 2010; 40:17–26. [PubMed: 20547081]
32. Samani NJ, van der Harst P. Biological ageing and cardiovascular disease. Heart. 2008; 94:537–539. [PubMed: 18411343]
33. Oeseburg H, de Boer RA, van Gilst WH, van der Harst P. Telomere biology in healthy aging and disease. Pflugers Arch. 2010; 459:259–268. [PubMed: 19756717]
34. Willeit P, Willeit J, Brandstätter A, Ehrlenbach S, Mayr A, Gasperi A, Weger S, Oberhollenzer F, Reindl M, Kronenberg F, Kiechl S. Cellular aging reflected by leukocyte telomere length predicts advanced atherosclerosis and cardiovascular disease risk. Arterioscler Thromb Vasc Biol. 2010; 30:1649–1656. [PubMed: 20508208]
35. Shepherd BE, Guttorp P, Lansdorp PM, Abkowitz JL. Estimating human hematopoietic stem cell kinetics using granulocyte telomere lengths. Exp Hematol. 2004; 32:1040–1050. [PubMed: 15539081]
36. Sidorov I, Kimura M, Yashin A, Aviv A. Leukocyte Telomere Dynamics and Human Hematopoietic Stem Cell Kinetics during Somatic Growth. Exp Hematol. 2009; 37:514–524. [PubMed: 19216021]
37. Kimura M, Gazitt Y, Cao X, Zhao X, Lansdorp PM, Aviv A. Synchrony of telomere length among hematopoietic Cells. Exp Hematol. 2010; 38:854–859. [PubMed: 20600576]
38. Spalding KL, Bhardwaj RD, Buchholz BA, Druid H, Frisén J. Retrospective birth dating of cells in humans. Cell. 2005; 122:133–143. [PubMed: 16009139]
39. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, Blomqvist L, Hoffstedt J, Näslund E, Britton T, Concha H, Hassan M, Rydén M, Frisén J, Arner P. Dynamics of fat cell turnover in humans. Nature. 2008; 453:783–787. [PubMed: 18454136]
40. Armanios M, Chen JL, Chang YP, Brodsky RA, Hawkins A, Griffin CA, Eshleman JR, Cohen AR, Chakravarti A, Hamosh A, Greider CW. Haploinsufficiency of telomerase reverse transcriptase leads to anticipation in autosomal dominant dyskeratosis congenita. Proc Natl Acad Sci U S A. 2005; 102:15960–15964. [PubMed: 16247010]
41. Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, Lawson WE, Xie M, Vulto I, Phillips JA 3rd, Lansdorp PM, Greider CW, Loyd JE. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med. 2007; 356:1317–1326. [PubMed: 17392301]
42. Zeichner SL, Palumbo P, Feng Y, Xiao X, Gee D, Sleasman J, Goodenow M, Biggar R, Dimitrov D. Rapid telomere shortening in children. Blood. 1999; 93:2824–2830. [PubMed: 10216076]
43. Baerlocher GM, Rice K, Vulto I, Lansdorp PM. Longitudinal data on telomere length in leukocytes from newborn baboons support a marked drop in stem cell turnover around 1 year of age. Aging Cell. 2007; 6:121–123. [PubMed: 17156085]
44. Broccoli D, Young JW, de Lange T. Telomerase activity in normal and malignant hematopoietic cells. Proc Natl Acad Sci U S A. 1995; 92:9082–9086. [PubMed: 7568077]
45. Yui J, Chiu CP, Lansdorp PM. Telomerase activity in candidate stem cells from fetal liver and adult bone marrow. Blood. 1998; 91:3255–3262. [PubMed: 9558381]

46. Chiu CP, Dragowska W, Kim NW, Vaziri H, Yui J, Thomas TE, Harley CB, Lansdorp PM. Differential expression of telomerase activity in hematopoietic progenitors from adult human bone marrow. Stem Cells. 1996; 14:239–248. [PubMed: 8991544]
47. Morrison SJ, Prowse KR, Ho P, Weissman IL. Telomerase activity in hematopoietic cells is associated with self-renewal potential. Immunity. 1996; 5:207–21. [PubMed: 8808676]
48. Engelhardt M, Kumar R, Albanell J, Pettengell R, Han W, Moore MA. Telomerase regulation, cell cycle, and telomere stability in primitive hematopoietic cells. Blood. 1997; 90:182–193. [PubMed: 9207452]
49. Blackburn EH. Telomeres and telomerase: their mechanisms of action and the effects of altering their functions. FEBS Lett. 2005; 579:859–862. [PubMed: 15680963]
50. Morrison SJ, Kimble J. Asymmetric and symmetric stem-cell divisions in the development of cancer. Nature. 2006; 441:1068–1074. [PubMed: 16810241]
51. Ehrlenbach S, Willeit P, Kiechl S, et al. Influences on the reduction of relative telomere length over 10 years in the population-based Bruneck Study: introduction of a well-controlled high-throughput assay. Int J Epidemiol. 2009; 38:1725–1734. [PubMed: 19666704]
52. Aviv A, Chen W, Gardner JP, et al. Leukocyte telomere dynamics: longitudinal findings among young adults in the Bogalusa Heart Study. Am J Epidemiol. 2009; 169:323–329. [PubMed: 19056834]
53. Nordfjäll K, Svenson U, Norrback KF, Adolfsson R, Lenner P, Roos G. The individual blood cell telomere attrition rate is telomere length dependent. PLoS Genet. 2009; 5(2):e1000375. [PubMed: 19214207]
54. Farzaneh-Far R, Lin J, Epel E, Lapham K, Blackburn E, Whooley MA. Telomere Length Trajectory and Its Determinants in Persons with Coronary Artery Disease: Longitudinal Findings from the Heart and Soul Study. PloS One. 2010; 5(1):e8612. [PubMed: 20072607]
55. Farzaneh-Far R, Lin J, Epel ES, Harris WS, Blackburn EH, Whooley MA. Association of Marine Omega-3 Fatty Acid Levels With Telomeric Aging in Patients With Coronary Heart Disease. JAMA. 2010; 303:250–257. [PubMed: 20085953]
56. Chen W, Kimura M, Kim S, Cao X, Srinivasan SR, Berenson GS, Kark JD, Aviv A. Longitudinal vs. Cross-Sectional Evaluations of Leukocyte Telomere Length Dynamics: Age-Dependent Telomere Shortening is the Rule. J Gerontol Biol Sci Med Sci. 2011; 66:312–319.
57. Kaszubowska L. Telomere shortening and ageing of the immune system. J Physiol Pharmacol. 2008; 59:169–186. [PubMed: 19261979]
58. Samani NJ, Boultby R, Butler R, Thompson JR, Goodall AH. Telomere shortening in atherosclerosis. Lancet. 2001; 358:472–473. [PubMed: 11513915]
59. Brouilette SW, Moore JS, McMahon AD, Thompson JR, Ford I, Shepherd J, Packard CJ, Samani NJ. Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: a nested case-control study. Lancet. 2007; 369:107–114. [PubMed: 17223473]
60. van der Harst P, van der Steege G, de Boer RA, Voors AA, Hal AS, Mulder MJ, Van Gilst WH, van Veldhuissen DJ. Telomere length of circulating leukocytes is decreased in patients with chronic heart failure. J Am Coll Cardiol. 2007; 49:1459–1464. [PubMed: 17397675]
61. Samani NJ, van der Harst P. Biological ageing and cardiovascular disease. Heart. 2008; 94:537–539. [PubMed: 18411343]
62. Benetos A, Gardner JP, Zureik M, Labat C, Xiaobin L, Adamopoulos C, Temmar M, Bean KE, Aviv A. Short telomeres are associated with increased carotid artery atherosclerosis in hypertensive subjects. Hypertension. 2004; 43:182–185. [PubMed: 14732735]
63. O'Donnell CJ, Demissie S, Kimura M, Levy D, Gardner JP, White C, D'Agostino RB, Wolf PA, Polak J, Cupples A, Aviv A. Leukocyte telomere length and carotid artery intimal medial thickness: The Framingham Heart Study. Arterioscler Thromb Vasc Biol. 2008; 28:1165–1171. [PubMed: 18388332]
64. Mainous AG 3rd, Codd V, Diaz VA, Schoepf UJ, Everett CJ, Player MS, Samani NJ. Leukocyte telomere length and coronary artery calcification. Atherosclerosis. 2010; 21:262–267. [PubMed: 19945703]

65. Vasan RS, Demissie S, Kimura M, Cupples LA, Rifai N, White C, Wang TJ, Gardner JP, Cao X, Benjamin EJ, Levy D, Aviv A. Association of leukocyte telomere length with circulating biomarkers of the renin-angiotensin-aldosterone system: the Framingham Heart Study. Circulation. 2008; 117:1138–1144. [PubMed: 18268147]
66. Gardner JP, Li S, Srinivasan SR, Chen W, Kimura M, Lu X, Berenson GS, Aviv A. Rise in insulin resistance is associated with escalated telomere attrition. Circulation. 2005; 111:2171–2177. [PubMed: 15851602]
67. Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LM, Aviv A, Spector TD. Increased body mass and cigarette smoking are associated with short telomeres in women. Lancet. 2005; 366:662–664. [PubMed: 16112303]
68. Prescott J, McGrath M, Lee IM, Buring JE, De Vivo I. Telomere length and genetic analyses in population-based studies of endometrial cancer risk. Cancer. 2010; 116:4275–4782. [PubMed: 20549820]
69. Cherkas LF, Hunkin JL, Kato BS, Richards JB, Gardner JP, Surdulescu GL, Kimura M, Lu X, Spector TD, Aviv A. The association between physical activity in leisure time and leukocyte telomere length. Arch Intern Med. 2009; 168:154–158. [PubMed: 18227361]
70. Aviv A, Valdes A, Gardner JP, Swaminathan R, Kimura M, Spector TD. Menopause modifies the association of leukocyte telomere length with insulin resistance and inflammation. J Clin Endocrinal Metab. 2006; 91:635–640.
71. Demissie S, Levy D, Benjamin EJ, Cupples LA, Gardner JP, Herbert A, Kimura M, Larson MG, Meigs JB, Keaney JF, Aviv A. Insulin resistance, oxidative stress, hypertension, and leukocyte telomere length in men from the Framingham Heart Study. Aging Cell. 2006; 5:325–330. [PubMed: 16913878]
72. Atzmon G, Cho M, Cawthon RM, Budagov T, Katz M, Yang X, Siegel G, Bergman A, Huffman DM, Schechter CB, Wright WE, Shay JW, Barzilai N, Govindaraju DR, Suh Y. Evolution in health and medicine Sackler colloquium: Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians. Proc Natl Acad Sci U S A. 2010; 107(Suppl 1):1710–1717. [PubMed: 19915151]
73. Fitzpatrick AL, Kronmal RA, Kimura M, Gardne JP, Psaty BM, Jenny NS, Tracy RP, Hardikar S, Aviv A. Leukocyte Telomere Length and Mortality in the Cardiovascular Health Study. J Gerontol Biol Sci Med Sci. 2011; 66:421–429.
74. Zhu H, Wang X, Gutin B, Davis CL, Keeton D, Thomas J, Stallmann-Jorgensen I, Mooken G, Bundy V, Snieder H, van der Harst P, Dong Y. Leukocyte telomere length in healthy Caucasian and African-American adolescents: relationships with race, sex, adiposity, adipokines, and physical activity. J Pediatr. 2011; 158:215–220. [PubMed: 20855079]
75. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: Results from the multi-ethnic study of atherosclerosis (MESA). Circulation. 2006; 113:30–37. [PubMed: 16365194]
76. Loria CM, Liu K, Lewis CE, Hulley SB, Sidney S, Schreiner PJ, Williams OD, Bild DE, Detrano R. Early adult risk factor levels and subsequent coronary artery calcification. The CARDIA Study. J Am Coll Cardiol. 2007; 49:2013–2020. [PubMed: 17512357]
77. Aiyer AN, Kip KE, Marroquin OC, Mulukutla SR, Edmundowicz D, Reis SE. Racial differences in coronary artery calcification are not attributed to differences in lipoprotein particle sizes: The heart strategies concentrating on risk evaluation (Heart SCORE) Study. Am Heart J. 2007; 153:328–324. [PubMed: 17239697]
78. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial ethnic groups. New Engl J Med. 2008; 358:1336–1345. [PubMed: 18367736]
79. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, et al. American Heart Association Committee on Cardiovascular ImagingIntervention; American Heart Association Council on Cardiovascular RadiologyIntervention; American Heart Association Committee on Cardiac Imaging Council on Clinical Cardiology. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation. 2006; 114:1761–1791. [PubMed: 17015792]

80. Church TS, Levine BD, McGuire DK, Lamonte MJ, Fitzgerald SJ, Cheng YJ, Kimball TE, Blair SN, Gibbons LW, Nichaman MZ. Coronary artery calcium score, risk factors, and incident coronary heart disease events. Atherosclerosis. 2007; 190:224–31. [PubMed: 16540111]
81. Shaw LJ, Raggi P, Berman DS, Callister TQ. Coronary artery calcium as a measure of biologic age. Atherosclerosis. 2006; 188:112–119. [PubMed: 16289071]
82. Hopkins PN, Ellison RC, Province MA, Pankow JS, Carr JJ, Arnett DK, Lewis CE, Heiss G, Hunt SC. Association of coronary artery calcified plaque with clinical coronary heart disease in the National Heart, Lung, and Blood Institute's Family Heart Study. Am J Cardiol. 2006; 97:1564–1569. [PubMed: 16728214]
83. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four ethnic groups. New Engl J Med. 2008; 358:1336–1345. [PubMed: 18367736]
84. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. Chest. 2007; 131:1557–1566. [PubMed: 17494805]
85. Weber C, Zernecke A, Libby P. The multifaceted contributions of leukocyte subsets to atherosclerosis: lessons from mouse models. Nat Rev Immunol. 2008; 8:802–815. [PubMed: 18825131]
86. Ross R. Atherosclerosis— an inflammatory disease. N Engl J Med. 1999; 340:115–126. [PubMed: 9887164]
87. Tchirkov A, Lansdorp PM. Role of oxidative stress in telomere shortening in cultured fibroblasts from normal individuals and patients with ataxia-telangiectasia. Hum Mol Genet. 2003; 12:227–232. [PubMed: 12554677]
88. Sitte N, Saretzki G, von Zglinicki T. Accelerated telomere shortening in fibroblasts after extended periods of confluency. Free Radic Biol Med. 1998; 24:885–893. [PubMed: 9607597]
89. Youngren K, Jeanclos E, Aviv H, Kimura M, Stock J, Hanna M, Skurnick J, Bardeguez A, Aviv A. Synchrony in telomere length of the human fetus. Hum Genet. 1998; 102:640–643. [PubMed: 9703424]
90. Gardner JP, Kimura M, Chai W, Durrani JF, Tchakmakjian L, Cao X, Lu X, Li G, Peppas AP, Skurnick J, Wright WE, Shay JW, Aviv A. Telomere dynamics in macaques and humans. J Gerontol A Biol Sci Med Sci. 2007; 62:367–374. [PubMed: 17452729]
91. Granick M, Kimura M, Kim S, Daniali L, Cao X, Herbig U, Aviv A. Telomere dynamics in keloids. Eplasty. 2011; 11:e15. [PubMed: 21436892]
92. von Zglinicki T, Serra V, Lorenz M, Saretzki G, Lenzen-Grossimlighaus R, Gessner R, Risch A, Steinhagen-Thiessen E. Short telomeres in patients with vascular dementia: an indicator of low antioxidative capacity and a possible risk factor? Lab Invest. 2000:1739–1747. [PubMed: 11092534]
93. Fadini GP, Agostini C, Sartore S, Avogaro A. Endothelial progenitor cells in the natural history of atherosclerosis. Atherosclerosis. 2007; 194:46–54. [PubMed: 17493626]
94. Werner N, Nickenig G. Endothelial progenitor cells in health and atherosclerotic disease. Ann Med. 2007; 39:82–90. [PubMed: 17453672]
95. Satoh M, Ishikawa Y, Takahashi Y, Itoh T, Minami Y, Nakamura M. Association between oxidative DNA damage and telomere shortening in circulating endothelial progenitor cells obtained from metabolic syndrome patients with coronary artery disease. Atherosclerosis. 2008; 198:347–353. [PubMed: 17983621]
96. Imanishi T, Hano T, Nishio I. Angiotensin II accelerates endothelial progenitor cell senescence through induction of oxidative stress. J Hypertens. 2005; 23:97–104. [PubMed: 15643130]
97. Oeseburg H, Westenbrink BD, de Boer RA, van Gilst WH, van der Harst P. Can critically short telomeres cause functional exhaustion of progenitor cells in postinfarction heart failure? J Am Coll Cardiol. 2007; 50:1909–1913. [PubMed: 17980260]
98. Kissel CK, Lehmann R, Assmus B, Aicher A, Honold J, Fischer-Rasokat U, Heeschen C, Spyridopoulos I, Dimmeler S, Zeiher AM. Selective functional exhaustion of hematopoietic progenitor cells in the bone marrow of patients with postinfarction heart failure. J Am Coll Cardiol. 2007; 49:2341–2349. [PubMed: 17572250]

99. Aronow WS. Heart disease and aging. Med Clin North Am. 2006; 90:849–862. [PubMed: 16962846]
100. Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. Clin Geriatr Med. 2009; 25:563–577. [PubMed: 19944261]
101. Deaths and death rates by leading causes of death and age: 2005 (Table 115). US Census Bureau. The 2009 Statistical Abstract, the National Data Book. http://www.census.gov/compendia/statab/cats/births_deaths_marriages_divorces.html
102. Effros RB. Telomere/telomerase dynamics within the human immune system: effect of chronic infection and stress. Exp Gerontol. 2011; 46:135–140. [PubMed: 20833238]
103. Driver JA, Djoussé L, Logroscino G, Gaziano JM, Kurth T. Incidence of cardiovascular disease and cancer in advanced age: prospective cohort study. BMJ. 2008; 337:a2467. [PubMed: 19066258]
104. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. Association between telomere length in blood and mortality in people aged 60 years or older. Lancet. 2003; 361:393–395. [PubMed: 12573379]
105. Bischoff C, Petersen HC, Graakjaer J, Andersen-Ranberg K, Vaupel JW, Bohr VA, et al. No association between telomere length and survival among the elderly and oldest old. Epidemiology. 2006; 17:190–194. [PubMed: 16477260]
106. Martin-Ruiz CM, Gussekloo J, van Heemst D, von Zglinicki T, Westendorp RG. Telomere length in white blood cells is not associated with morbidity or mortality in the oldest old: a population-based study. Aging Cell. 2005; 4:287–290. [PubMed: 16300480]
107. Harris SE, Deary IJ, MacIntyre A, Lamb KJ, Radhakrishnan K, Starr JM, Whalley LJ, Shiels PG. The association between telomere length, physical health, cognitive ageing, and mortality in non-demented older people. Neurosci Lett. 2006; 406:260–264. [PubMed: 16919874]
108. Honig LS, Schupf N, Lee JH, Tang MX, Mayeux R. Shorter telomeres are associated with mortality in those with APOE epsilon 4 and dementia. Ann Neurol. 2006; 60:181–187. [PubMed: 16807921]
109. Njajou OT, Hsueh WC, Blackburn EH, Newman AB, Wu SH, Li R, Simonsick EM, Harris TM, Cummings SR, Cawthon RM. Health ABC study. Association between telomere length, specific causes of death, and years of healthy life in health, aging, and body composition, a population-based cohort study. J Gerontol A Biol Sci Med Sci. 2009; 64:860–864. [PubMed: 19435951]
110. Kimura M, Hjelmborg JV, Gardner JP, Bathum L, Brimacombe M, Lu X, Christiansen L, Vaupel JW, Aviv A, Christensen K. Short leukocyte telomeres forecast mortality: a study in elderly Danish twins. Am J Epidemiol. 2008; 167:799–806. [PubMed: 18270372]
111. Huda N, Tanaka H, Herbert BS, Reed T, Gilley D. Shared environmental factors associated with telomere length maintenance in elderly male twins. Aging Cell. 2007; 6:709–713. [PubMed: 17725691]
112. Baird DM, Britt-Compton B, Rowson J, Amos NN, Gregory L, Kipling D. Telomere instability in the male germline. Hum Mol Genet. 2006; 15:41–51.
113. Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, Greider CW, Harley CB. Telomere length predicts replicative capacity of human fibroblasts. Proc Natl Acad Sci USA. 1992; 89:10114–10118. [PubMed: 1438199]
114. Blasco MA. The epigenetic regulation of mammalian telomeres. Nat Rev Genet. 2007; 8:299–309. [PubMed: 17363977]
115. Wright WE, Piatyszek MA, Rainey WE, Byrd W, Shay JW. Telomerase activity in human germline and embryonic tissues and cells. Dev Genet. 1996; 18:173–179. [PubMed: 8934879]
116. McKay JD, Hung RJ, Gaborieau V, Boffetta P, Chabrier A, Byrnes G, Zaridze D, Mukeria A, et al. Lung cancer susceptibility locus at 5p15.33. Nat Genet. 2008; 40:1404–406. [PubMed: 18978790]
117. Landi MT, Chatterjee N, Yu K, Goldin LR, Goldstein AM, Rotunno M, Mirabello L, Jacobs K, et al. A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. Am J Hum Genet. 2009; 85:679–691. [PubMed: 19836008]

118. Kohno T, Kunitoh H, Shimada Y, Shiraishi K, Ishii Y, Goto K, Ohe Y, Nishiwaki Y, et al. Individuals susceptible to lung adenocarcinoma defined by combined HLA-DQA1 and TERT genotypes. Carcinogenesis. 2010; 31:834–841. [PubMed: 20061363]

119. Truong T, Hung RJ, Amos CI, Wu X, Bickeböller H, Rosenberger A, Sauter W, Illig T, et al. Replication of lung cancer susceptibility loci at chromosomes 15q25, 5p15, and 6p21: a pooled analysis from the International Lung Cancer Consortium. J Natl Cancer Inst. 2010; 102:959–971. [PubMed: 20548021]

120. Hsiung CA, Lan Q, Hong YC, Chen CJ, Hosgood HD, Chang IS, Chatterjee N, Brennan P, et al. The 5p15.33 locus is associated with risk of lung adenocarcinoma in never-smoking females in Asia. PLoS Genet. 2010; 6(8):pii, e1001051. [PubMed: 20700438]

121. Turnbull C, Rapley EA, Seal S, Pernet D, Renwick A, Hughes D, Ricketts M, Linger R, et al. Variants near DMRT1, TERT and ATF7IP are associated with testicular germ cell cancer. Nat Genet. 2010; 42:604–607. [PubMed: 20543847]

122. Shete S, Hosking FJ, Robertson LB, Dobbins SE, Sanson M, Malmer B, Simon M, Marie Y, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet. 2009; 41:899–904. [PubMed: 19578367]

123. Rafnar T, Sulem P, Stacey SN, Geller F, Gudmundsson J, Sigurdsson A, Jakobsdottir M, Helgadottir H, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet. 2009; 41:221–227. [PubMed: 19151717]

124. Levy D, Neuhausen BL, Hunt SC, Kimura M, Hwang S-H, Chen W, Bis JC, Fitzpatrick AL, Smith E, Andrew D, Gardner JP, Srinivasan SR, Schork N, Rotter JI, Herbig U, Psaty BM, Sastrasinh M, Murray SS, Vasan RS, Province MA, Glazer NL, Lu X, Cao X, Kronmal R, Mangino M, Soranzo N, Spector TD, Berenson GS, Aviv A. Genome-wide Association Identifies *OBFC1* as a Locus Involved in Human Leukocyte Telomere Biology. Proc Nat Acad Sci USA. 2010; 107:9293–9298. [PubMed: 20421499]

125. Codd V, Mangino M, van der Harst P, Braund PS, Kaiser M, Beveridge AJ, Rafelt S, Moore J, Nelson C, Soranzo N, Zhai G, Valdes AM, Blackburn H, Leach IM, de Boer RA, Kimura M, Aviv A, Goodall AH, Ouwehand W, van Veldhuisen DJ, van Gilst WH, Navis G, Burton PR, Tobin MD, Hall AS, Thompson JR, Spector T, Samani NJ. Wellcome Trust Case Control Consortium. Common variants near TERC are associated with mean telomere length. Nat Genet. 2010; 42:197–199. [PubMed: 20139977]

126. Njajou OT, Blackburn EH, Pawlikowska L, Mangino M, Damcott CM, Kwok PY, Spector TD, Newman AB, Harris TB, Cummings SR, Cawthon RM, Shuldiner AR, Valdes AM, Hsueh WC. A common variant in the telomerase RNA component is associated with short telomere length. PLoS One. 2010 Sep 27.5(9):e13048. [PubMed: 20885959]

127. Wan M, Qin J, Songyang Z, Liu D. OB-fold containing protein 1 (OBFC1), a human homologue of yeast Stn1, associates with TPP1 and is implicated in telomere length regulation. J Biol Chem. 2009; 284:26725–26731. [PubMed: 19648609]

128. Li S, Makovets S, Matsuguchi T, Blethrow JD, Shokat KM, Blackburn EH. Cdk1-dependent phosphorylation of Cdc13 coordinates telomere elongation during cell-cycle progression. Cell. 2009; 136:50–61. [PubMed: 19135888]

129. Eash KJ, Means JM, White DW, Link DC. CXCR4 is a key regulator of neutrophil release from the bone marrow under basal and stress granulopoiesis conditions. Blood. 2009; 113:4711–4719. [PubMed: 19264920]

130. Furze RC, Rankin SM. Neutrophil mobilization and clearance in the bone marrow. Immunology. 2008; 125:281–288. [PubMed: 19128361]

131. Tang YL, Zhu W, Cheng M, Chen L, Zhang J, Sun T, Kishore R, Phillips MI, Losordo DW, Qin G. Hypoxic preconditioning enhances the benefit of cardiac progenitor cell therapy for treatment of myocardial infarction by inducing CXCR4 expression. Circ Res. 2009; 104:1209–1216. [PubMed: 19407239]

132. Egan CG, Caporali F, Huqi AF, Zito MC, Focardi M, Mondillo S, Pierli C, Marzilli M, Sorrentino V. Reduced levels of putative endothelial progenitor and CXCR4+ cells in coronary artery disease: kinetics following percutaneous coronary intervention and association with clinical characteristics. Thromb Haemost. 2009; 101:1138–1146. [PubMed: 19492159]

133. Brunner S, Winogradow J, Huber BC, Zaruba MM, Fischer R, David R, Assmann G, Herbach N, Wanke R, Mueller-Hoecker J, Franz WM. Erythropoietin administration after myocardial infarction in mice attenuates ischemic cardiomyopathy associated with enhanced homing of bone marrow-derived progenitor cells via the CXCR-4/SDF-1 axis. FASEB J. 2009; 23:351–361. [PubMed: 18827024]

134. Xiao Q, Ye S, Oberhollenzer F, Mayr A, Jahangiri M, Willeit J, Kiechl S, Xu Q. SDF1 gene variation is associated with circulating SDF1alpha level and endothelial progenitor cell number: the Bruneck Study. PLoS One. 2008; 3(12):e4061. [PubMed: 19115008]

135. McClellan J, King MC. Genetic heterogeneity in human disease. Cell. 2010; 141:210–217. [PubMed: 20403315]

136. Myocardial Infarction Genetics Consortium. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet. 2009; 41:334–341. [PubMed: 19198609]

Table 1

Heritability.

1st Author	Ref	Twins/Non-twins*	Sample size	Est. Heritability	Mode
Slagboom	1	Twins	246	0.78	—
Jeanclos	2	Twins	98	0.84	—
Hunt	3	Non-twins	2968	0.73	—
Nawrot	4	Non-twins	327	0.70	X-chromosome
Vasa-Nicotera	5	Non-twins	383	0.82	—
Andrew	6	Twins	2050	0.36	—
Bischoff	7	Twins	574	0.36	—
Njajou	8	Non-twins	907	0.44	Paternal>Maternal
Bakayasa	9	Twins	360	0.56	—
Nordfjäll	10	Non-twins	132		Paternal
Nordfjäll	11	Non-twins	962		Paternal>Maternal
Huda	111	Twins	686	None	—

*Families or sibs;—no information

Table 2

Paternal Age at Conception Effect on the Offspring's LTL

1st Author	Ref	Sample Size	PAC	MAC	PAC/MAC
Unryn	13	125	Yes	No	—
De Meyer	14	2433	Yes	Yes	Yes
Njajou	8	907	Yes	Yes	—
Kimura[a]	15	432	Yes/No*	No	Yes**
Kimura[b]	15	847	Yes	Yes	Yes
Kimura[c]	15	132	Yes	No	Yes
Kimura[d]	15	1954	Yes	No	Yes
Nordfjäll	11	227	No	No	—
Arbeev	12	2177	Yes	Yes	Yes

PAC, paternal age at conception; MAC, maternal age at conception; PAC/MAC, paternal age at conception adjusted for maternal age at conception;

[a]The Framingham Heart Study;

[b]The Family Heart Study;

[c]The Longitudinal Study of Aging Danish Twins;

[d]TwinsUK;

*Yes for sons, No for daughters;

**Only for sons; — no information