Promoter Polymorphism in the \textit{Serotonin Transporter (5-HTT)} Gene Is Significantly Associated with Leukocyte Telomere Length in Han Chinese

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Abstract

The \textit{serotonin transporter} gene (5-HTT-linked polymorphic region (5-HTTLP) plays an important role in modulating mood and behavior by regulating 5-HTT expression and thereby controlling the concentration of serotonin (5-HT) in brain synapses: The homozygous shorter allele (S/S) in 5-HTTLP results in lower 5-HTT expression coupled with stronger psycho-pathological reactions to stressful experiences compared to the homozygous long (L/L) and heterozygous (S/L) alleles. Psychological insults and mood disorders have been shown to cause accelerated telomere shortening, a marker of biological aging, however, it is currently unclear whether the allelic variants of 5-HTTLP affect telomere length (TL) in the healthy population without mood disorders. In the present study, we determined the relationship between TL and the 5-HTTLP variants in healthy Han Chinese. The 5-HTTLP genotyping and leukocyte TL analysis of 280 young female Han Chinese freshmen showed a significantly shorter TL in 149 of them carrying the 5-HTTLP S/S version compared to those (131) with the L/S or L/S plus L/L genotypes (mean ± SD: 0.533±0.241 for S/S vs 0.607±0.312 for L/S, $P = 0.034$; or vs 0.604±0.313 for L/S plus L/L, $P = 0.038$). Similar results were achieved in the other cohort including 220 adult healthy individuals of different age, gender and profession (0.691±0.168 for S/S vs 0.729±0.211 for L/S, $P = 0.046$, or vs 0.725±0.213 for L/S plus L/L, $P = 0.039$). Taken together, shorter leukocyte TL is significantly associated with the 5-HTTLP S/S allele variant, which may be implicated in psychological stress-related health problems.

Introduction

Telomeres, tandem arrays of repetitive TTAGGG sequences associated with their binding factors, form protective caps at chromosome termini and are essential to maintain genomic integrity and stability [1,2]. Telomeric DNA is synthesized by telomerase, an RNA-dependent DNA polymerase [2,3]. In human somatic cells, telomeres are 8 to 20 kb long and shorten progressively with each round of cell division or with increased age owing to “the end replication problem” and lack of telomerase activity [1–3]. When telomeres become too short (dysfunctional) to protect chromosomes, the DNA damage response is activated, thereby triggering the permanent growth arrest of cells (replicative senescence) [1,2,4]. Recent evidence has accumulated that the same scenario also occurs in vivo, thereby contributing to human aging [3,4]. Moreover, it has been shown that individuals with shorter leukocyte telomeres, exhibit a higher risk to develop age-related diseases such as heart diseases, stroke and cancer [1–4]. More importantly, a close correlation between shorter telomeres and increased mortality has been documented in published reports [5–8].

In addition to the cell replication- and aging-mediated telomere shortening, many other factors may significantly affect telomere length (TL). For instance, an impact of psychosocial factors and mood disorders on TL has been observed. In 2004, Epel et al [9] first reported significantly shorter telomeres in leukocytes derived from women experiencing high levels of life stress, and they thus suggested the accelerated telomere erosion as a link between psychological stress and early onset of age-related diseases. Since then, the relationship between TL and different kinds of psychological adversity has been extensively investigated, and most of the study results consistently confirmed this inverse relationship [10–13].

The monoamine neurotransmitter serotonin or 5-hydroxytryptamine (5-HT) is involved in the regulation of diverse brain functions including emotional and behavioral activities through interactions with different 5-HT receptor subtypes in the central nervous system (CNS) [14]. Appropriate levels of 5-HT at brain synapses is essential for these functions and one key regulator of 5-
HT is serotonin transporter (5-HTT) on the presynaptic neuron [14]. 5-HTT removes 5-HT released into the synaptic cleft, thereby terminating serotonergic neurotransmission. 5-HTT protein is encoded by the \( SLC6A4 \) gene whose transcriptional activity is regulated by a number of variations [14]. Among these, the serotonin transporter gene (5-HTT)-linked polymorphic region (5-HTTLPR), composed of short (S/S), or long (L/L), homozygous, or heterozygous (S/L) allelic versions, has been well characterized to affect 5-HTT expression: The S and L alleles in the 5-HTTLPR result in lower and higher levels of 5-HTT expression, respectively [14,15]. People carrying the S/S version in general exhibit lower transcriptional start site. S and L variants contain 14 and 16 repeats, respectively (22 bps/repeat). The specific PCR primers span the LPR region and genomic DNA derived from 500 healthy individuals was amplified. Shown are the representative S/S, L/S and L/L genotypes: SS: Lanes 2, 6 and 8; LS: Lanes 3, 5 and 7; LL: Lane 4. Lane 1: DNA marker.

HTTLPR genotype distribution of each age group among 220 healthy individuals.

| Age (years) | S/S (%) | L/S (%) | L/L (%) | Total |
|-------------|---------|---------|---------|-------|
| 16          | 1 (100) | 0 [0]   | 0 [0]   | 1     |
| 17          | 13 (44.8)| 9 (31.0)| 7 (24.2)| 29    |
| 18          | 71 (54.2)| 46 (35.1)| 14 (10.7)| 131   |
| 19          | 55 (37.3)| 38 (26.9)| 3 (2.1) | 96    |
| 20          | 8 (42.1)| 10 (52.6)| 1 (5.3) | 19    |
| 21          | 1 (25.0)| 2 (50.0)| 1 (25.0)| 4     |
| Total       | 149 (53.2)| 105 (37.5)| 26 (9.3)| 280   |

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Significantly shorter telomeres in the individuals carrying the 5-HTTLPR S/S variant

Leukocyte TL was determined using quantitative real-time PCR (qPCR). In the cohort of 280 freshmen aged 16 to 21 years, there was no correlation between age and TL (data not shown). The relative TL (mean ± SD) was 0.533 ± 0.241, 0.607 ± 0.312, and 0.591 ± 0.319 for the S/S, L/S and L/L carriers, respectively (Table 4), and a statistically significant difference was found between S/S and L/S groups (\( P = 0.034 \)). A similar result was obtained when the comparison was made between S/S and L/L plus L/L group (0.533 ± 0.241 vs 0.604 ± 0.313, \( P = 0.038 \)) (Table 4). However, there was no difference in TL between the S/S and L/L groups, largely due to too few L/L carriers (26 individuals) in this cohort. In addition, TL of L/S and L/L carriers did not differ.

Table 2. 5-HTTLPR genotype distribution of each age group among 220 healthy individuals.

| Age (years) | S/S (%) | L/S (%) | L/L (%) | Total |
|-------------|---------|---------|---------|-------|
| 21 – 29     | 27 (52.9)| 22 (43.1)| 2 (4.0)| 51    |
| 30 – 39     | 26 (47.3)| 24 (43.6)| 5 (9.1)| 55    |
| 40 – 49     | 21 (58.3)| 14 (38.9)| 1 (2.8)| 36    |
| 50 – 59     | 18 (42.9)| 22 (52.4)| 2 (4.7)| 42    |
| 60 – 69     | 4 (57.1)| 2 (28.6)| 1 (14.3)| 7    |
| 70 – 79     | 7 (30.4)| 13 (56.5)| 3 (13.1)| 23    |
| 80 – 85     | 2 (33.3)| 3 (50.0)| 1 (16.7)| 6    |
| Total       | 105 (47.7)| 100 (45.5)| 15 (6.8)| 220   |

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Table 3. 5-HTTLPR variant distribution between male and female individuals.

| Gender | S/S (%) | L/S (%) | L/L (%) | Total |
|--------|---------|---------|---------|-------|
| Male   | 53 (43.3)| 58 (47.5)| 11 (9.1)| 122   |
| Female | 52 (53.0)| 42 (42.9)| 4 (4.1)| 98    |
| Total  | 105 (47.7)| 100 (45.5)| 15 (6.8)| 220   |

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age. When the L/S and L/L carriers were pooled together, this group had a significantly longer TL than S/S carriers (0.725 ± 0.213 vs 0.691 ± 0.168, P = 0.038) (Table 4). Once again, there were no differences in TL between the S/S and L/L carriers, mainly because of too few of individuals (15) in the latter group.

**Discussion**

In the present study, we explored the relationship between TL and 5-HTTLPR genotypes by studying two cohorts of 500 healthy Han Chinese adults. In 280 young female freshmen, we observed a significantly shorter leukocyte TL in the homozygous S/S carriers compared to those harboring heterozygous L/S or a combined group including both L/S and homozygous L/L individuals. This correlation was further verified in another cohort of 220 healthy adults of different age, gender and profession. The findings collectively suggest that the healthy individuals carrying the S/S 5-HTTLPR variant undergo accelerated telomere erosion.

Previous studies have shown that perceived stress and different psychological insults are associated with an increased rate of telomere shortening, suggesting a strong psychological impact on telomere homeostasis [9–11]. All of the healthy individuals included in the present study were free of mood disorders, however, there has long been a link of the neurobehavioral effects of the 5-HTTLPR s-variant with hypervigilance, an enhanced sensitivity to motivationally relevant environmental stimuli [14]. For example, they exhibit exaggerated reactivity in the amygdala and increased startle responses to pictures of fearful faces, a stronger attentional bias for negatively valenced words, difficulty with disengaging attention from threat-related stimuli, increased fear responses to a shock-predicting stimulus, and so on [17–24]. Alternatively, the S/S carriers may display much lower threshold reactivity in the amygdala and increased startle responses to pictures of fearful faces, a stronger attentional bias for negatively valenced words, difficulty with disengaging attention from threat-related stimuli, increased fear responses to a shock-predicting stimulus, and so on [17–24].

**Table 4.** Difference in telomere length among different 5-HTTLPR genotypes.

| Genotype  | N   | TL* (mean ± SD) | P value |
|-----------|-----|----------------|---------|
| Freshmen cohort |     |                |         |
| S/S       | 149 | 0.533 ± 0.241   | 0.034 (S/S vs L/S) |
| L/S       | 105 | 0.607 ± 0.312   | >0.05 (L/S vs L/L)  |
| L/L       | 26  | 0.591 ± 0.319   | >0.05 (L/L vs S/S)  |
| L/S + L/L | 131 | 0.604 ± 0.313   | 0.038 (S/S vs L/S + L/L) |
| Second cohort |     |                |         |
| S/S       | 105 | 0.691 ± 0.168   | 0.046 (S/S vs L/S)  |
| L/S       | 100 | 0.729 ± 0.211   | >0.05 (L/S vs L/L)  |
| L/L       | 15  | 0.697 ± 0.235   | >0.05 (L/L vs S/S)  |
| L/S + L/L | 115 | 0.725 ± 0.213   | 0.039 (S/S vs L/S + L/L) |

*TL: Telomere length.

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(such as physical abuse, parental divorce, unemployment or drug use) during their childhood, had shorter telomeres [28]. Likely, telomere homeostasis is vulnerable to various negative factors including psychological insults in childhood because of psychologically rapid telomere erosion in this period [29]. Of note, the TL difference between the 5-HTTLPR S/S and L/S variant carriers was smaller in the second cohort of individuals (5.5%) than in the freshmen one (13.9%). Because the second cohort included more senior adults, it would be interesting to probe whether senior S/S carriers may become less sensitive to various environmental stimuli, and re-gain net TL to a certain degree.

In the initial pilot study, we selected a relatively homogenous cohort of individuals, young female Chinese Han freshmen, for the following reasons: First, TL is highly variable within individuals and among different races [30–32]. Second, TL is equal between the sexes at birth, but age-mediated telomere shortening occurs more rapidly in males than in females [33]. Third, TL is affected by many lifestyles and environmental factors, such as smoking, night-shift work, and certain professions [25,34]. By making this selection, we wanted to minimize other effects on TL in the studied subjects. Therefore, the observed differential TL may reflect true difference between the 5-HTTLPR S/S and L/S/L/L carriers. Further support for such a difference comes from the other cohort of 220 adult individuals with different age, gender and profession.

It is well established that the presence of shorter telomeres is a feature of many age-related conditions and diseases including immunosenescence, cardiovascular disease, stroke, cancer, sarcopenia, osteoporosis, osteoarthritis, and skin aging [1,4,5–8,35–40]. Therefore, the observed shorter telomere among individuals experiencing psychological insults may provide an explanation for early demonstrations of psychopathological conditions-mediated premature onset of aging. It is currently unclear whether 5-HTTLPR S/S carriers have a higher risk to develop aging-related diseases. Given the present finding, it is conceivable that this may happen and is thus worth of evaluating such possibility.

We identified 50.8% S/S, 41.0% L/S and 8.2% L/L for 5-HTTLPR variants in these 500 Chinese Han healthy adults. The total frequency for L and S alleles is 28.7% and 71.3%, respectively, which is rather different from the variant distribution observed in Europeans (57% for L allele; 95% CI: 49.9–61.8%), however, consistent with the results obtained from Asians (27% for L allele; 95% CI: 23.9–32.9%) [16]. It is unclear whether there is a negative correlation between the 5-HTTLPR S/S genotype and...
reduced TL in the European population, or whether such differential distribution of the 5-HTTLPR variants influences TL between eastern and western worlds, thereby contributing to the differential frequencies of aging-related diseases. Further studies are required to address these important issues.

In summary, our present study shows the accelerated telomere attrition in the Chinese Han 5-HTTLPR S/S variant carriers, however, the underlying mechanism is unclear. Given the accumulated evidence that the 5-HTTLPR S/S variant is strongly associated with the enhanced sensitivity to motivationally relevant environmental stimuli, we are currently investigating whether the S/S genotype mimics adverse psychological insults, thereby resulting in reduced TL.

**Materials and Methods**

**Participants and sample collection**

The study included two cohorts of Chinese Han healthy individuals, one with 280 young female freshmen enrolled in Shandong University in 2012 and the other with 220 adult healthy volunteers of different professions. Both cohorts of participants were free from depression or mood disorders, and did not take statins, estrogens, or other medicines regularly according to their medical history. Age of freshmen was from 16 to 21 years (median age 18 years). The cohort of 220 adults included 98 females and 122 males. The median age of females was 38 years (range 21 to 81 years). Men had median age of 43 years (range 22 to 85 years) (For details see Tables 1 and 2). Peripheral blood was collected in the morning before breakfast, leukocytes were isolated with red blood cell lysis buffer (Tiangen, China) and the cells were then used immediately or stored at ~80°C. The study was approved by the ethics committee and review board of Shandong University Nursing School. The oral informal consent, which is consistent with the institutional regulation and approved by the ethics committee of Shandong University Nursing School, was obtained from the participants or guardians if <18 years and documented in the study subject list. Blood was collected only from those who agreed.

**DNA extraction and 5-HTTLPR genotyping**

Genomic DNA was extracted from participants’ peripheral blood leukocytes using a DNA extraction kit (TianGen, China). The analysis of the 5-HTTLPR variant was done using PCR. The following primer pair was designed to span the variant region in the 5-HTT promoter: 5'-GGCGTTGCCGCTCTGAATGC-3' (forward) and 5'-GAGGGACTGAGCTGGACAACCAC-3' (reverse). PCR was performed with the annealing temperature at 62°C for 33 cycles. The PCR products were subjected to electrophoresis in 2% agarose gels, stained with ethidium bromide and visualized under UV light.

**Telomere length assessment**

TL was determined using qPCR as described [41,42]. Two ng of DNA were used for each PCR reaction and PCR was carried out in an ABI7700 sequence detector (Applied Biosystems, Foster City, CA). The primer sequences for human telomere (Tel1b and Tel2b) and β-globin (HBG3 and HBG4) were: Tel1b: 5'-CGGTTTTGTTGGTTTGGGTT-3', Tel2b: 5'-GGCTTGCCTTACCCTACCCTTACCC-TTACCCT-3', HBG3: 5'-TGTGCTGGCCCATCACTTTG-3', and HBG4: 5'-ACCAGCCA-CCACTTTCTGATAGG-3'. T/ HBG values were determined using the formula T/S = 2^(-ΔΔCt), where ΔΔCt = average Ct_telmere - average Ct_β-globin. The T/S ratio was arbitrarily expressed as TL.

**Statistical analyses**

Differences in TL between different 5-HTTLPR genotypes were analyzed using an analysis of ANCOVA, among which age and/or gender as covariates were corrected for TL. The relationship between TL and age was determined using Pearson’s correlation analysis. All the tests were two-tailed and computed using SigmaStat3.1 software (Systat Software, Inc., Richmond, CA). P values of <0.05 were regarded as statistically significant.
Author Contributions
Conceived and designed the experiments: PL TL JL QZ FK GC. Analyzed the data: PL TL FK CZ. Wrote the paper: PL MB DX.

References
1. Shay JW, Wright WE (2007) Hallmarks of telomeres in ageing research. J Pathol 211: 214–23.
2. Daniel M, Peek GW, Tollefsbol TO (2012) Regulation of the human catalytic subunit of telomerase (hTERT). Gene 498: 135–46.
3. Nicholls C, Li H, Wang JQ, Lau JP (2012) Molecular regulation of telomerase activity in aging. Protein Cell 2: 726–38.
4. Lopez-Ortin C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153: 1194–217.
5. Lee J, Sandrini AJ, Connell JE, Van J, Mui T, et al. (2012) The relationship between telomere length and mortality in chronic obstructive pulmonary disease (COPD). PLoS One 7: e35567. doi: 10.1371/journal.pone.0035567.
6. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. (2003) Association between telomere length in blood and mortality in people aged 60 years or older. Lancet 361: 393–5.
7. Honig LS, Kang MS, Schupf N, Lee JH, Mayeux R. (2012) Association of shorter leukocyte telomere repeat length with dementia and mortality. Arch Neurol 2012: 69: 1332–9.
8. Deelen J, Beekman M, Codd V, Trompet S, Broer L, Hagg S, et al. (2014) Leukocyte telomere length associates with prospective mortality independent of immune-related parameters and known genetic markers. Int J Epidemiol doi: 10.1093/ije/dyu267.
9. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, et al. (2004) Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A 101: 17312–5.
10. De Meyer T (2011) Telomere length integrates psychological factors in the successful aging story, but what about the biology? Psychosom Med 73: 524–7.
11. Kiecolt-Glaser JK, Glaser R (2010) Psychological stress, telomeres, and telomerase. Brain Behav Immun 24: 529–30.
12. Damjanovic AK, Yang Y, Glaser R, Kiecolt-Glaser JK, Nguyen H, et al. (2007) Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. J Immunol 179: 4249–54.
13. Price LH, Kao HT, Burgers DI, Carpenter LL, Tyra AR. (2013) Telomeres and early-life stress: an overview. Biol Psychiatry 73: 15–23.
14. Homberg JR, Lesch KP (2012) Looking on the bright side of serotonin transporter gene variation. Biol Psychiatry 69: 513–9.
15. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, et al. (1996) Association between reduced serotonin transporters and emotional startle. Mol Psychiatry 11: 1106–12.
16. Li Q (2006) Cellular and molecular alterations in mice with deficient and normal subunit of telomerase (hTERT). Gene 498: 135–46.
17. Brocke B, Armbruster D, Muller J, Hensch T, Jacob CP, et al. (2006) Serotonin transporter gene promoter region (5-HTTLPR) polymorphism with biased attention for emotional stimuli. J Abnorm Psychol 118: 670–81.
18. Beevers CG, Gibb BE, McGeary JE, Miller IW (2007) Serotonin transporter genetic variation and biased attention for emotional word stimuli among psychiatric inpatients J Abnorm Psychol 116: 208–12.
19. Beevers CG, Wells TT, Ellis AJ, McGeary JE. (2009) Association of the serotonin transporter gene promoter region (5-HTTLPR) polymorphism with biased attention for emotional stimuli. J Abnorm Psychol 118: 670–81.
20. Fox E, Edgwell A, Ashwin C (2009) Looking on the bright side: biased attention and the human serotonin transporter gene. Proc Biol Sci 276: 1747–51.
21. Osinsky R, Reuter M, Kupper Y, Schmitz A, Kozycz E, et al. (2008) Variation in the serotonin transporter gene modulates selective attention to threat. Emotion 8: 564–8.
22. Thomason ME, Henry ML, Paul Hamilton J, Joormann J, Pine DS, et al. (2010) Neural and behavioral responses to threatening emotion faces in children as a function of the short allele of the serotonin transporter gene. Biol Psychol 85: 38–44.
23. Gibb BE, Benas JS, Grassia M, McGeary J (2009) Children's attentional biases and 5-HTTLPR genotype: potential mechanisms linking mother and child depression. J Clin Child Adolesc Psychol 38: 415–26.
24. Lin J, Epel E, Blackburn E (2012) Telomeres and lifestyle factors: roles in aging. Mutat Res 730: 85–9.
25. Wikgren M, Maripuu M, Karlsson T, Nordfjall K, Berglind J, et al. (2012) Short telomeres in depression and the general population are associated with a hypocortisolism state. Biol Psychiatry 71: 294–300.
26. Wolkowitz OM, Epel ES, Reus VI, Mellon SH (2010) Depression gets old fast: do stress and depression accelerate cell aging? Depress Anxiety 27: 327–38.
27. Surtees PG, Wainswright NW, Pooley KA, Luben RN, Khaw KT, et al. (2011) Life stress, emotional health, and mean telomere length in the European Prospective Investigation into Cancer (EPIC)-Norfolk population study. J Gerontol A Biol Sci Med Sci 66: 1152–62.
28. Frenck RW Jr., Blackburn EH, Shannon KM (1998) The rate of telomere sequence loss in human leukocytes varies with age. Proc Natl Acad Sci U S A 95: 5607–10.
29. Geronimus AT, Hicken MT, Pearson JA, Seashols SJ, Brown KL, et al. Do US Black Women Experience Stress-Related Accelerated Biological Aging? A Novel Theory and First Population-Based Test of Black-White Differences in Telomere Length. Hum Nat 21: 19–38.
30. Aviv A, Valdes AM, Spector TD (2006) Human telomere biology: pitfalls of moving from the laboratory to epidemiology. Int J Epidemiol 35: 1424–9.
31. Takubo K, Inoumiya-Shimomura N, Honma N, Nosabe M, Arai T, et al. (2002) Telomere lengths are characteristic in each human individual. Exp Gerontol 37: 523–31.
32. Barrett EL, Richardson DS (2011) Sex differences in telomeres and lifespan. Aging Cell 10: 913–21.
33. Valdes AM, Andrew T, Gardner JP, Kimura M, Ochsnar E, et al. (2005) Obesity, cigarette smoking, and telomere length in women. Lancet 366: 662–4.
34. Weischer M, Nordestgaard BG, Cawthon RM, Freiberg JJ, et al. (2013) Short telomere length, cancer survival, and cancer risk in 47102 individuals. J Natl Cancer Inst 105: 459–68.
35. Aviv A (2009) Leukocyte telomere length, hypertension, and atherosclerosis: are there potential mechanistic explanations? Hypertension 53: 390–1.
36. Morla M, Busquets X, Pou J, Saulela J, MacNee W, et al. (2006) Telomere shortening in smokers with and without COPD. Eur Respir J 27: 525–48.
37. Martin-Ruiz C, Dickinson HO, Keys B, Rowan E, Kennay RA, et al. (2006) Telomere length predicts poststroke mortality, dementia, and cognitive decline. Ann Neurol 60: 174–80.
38. Halvorsen TL, Beattie GM, Lopez AD, Seashols SJ, Brown KL, et al. Do US Black Women Experience Stress-Related Accelerated Biological Aging? A Novel Theory and First Population-Based Test of Black-White Differences in Telomere Length. Hum Nat 21: 19–38.
39. Aviv A (2009) Leukocyte telomere length, hypertension, and atherosclerosis: are there potential mechanistic explanations? Hypertension 53: 390–1.
40. Weischer M, Nordestgaard BG, Cawthon RM, Freiberg JJ, et al. (2013) Short telomere length, cancer survival, and cancer risk in 47102 individuals. J Natl Cancer Inst 105: 459–68.
41. Andrews NP, Fuji H, Gronowicz JY, Weyand GM (2010) Telomeres and immunological diseases of aging. Gerontology 56: 390–403.
42. Li P, Hou M, Lou F, Bjorkholm M, Xu D (2012) Telomere dysfunction induced by chemotherapeutic agents and radiation in normal human cells. Int J Biochem Cell Biol 44: 1531–40.
43. Cawthon RM (2002) Telomere measurement by quantitative PCR. Nucleic Acids Res 30: e47.