Telomere Length in a Population of Long-Lived People of the Northwestern Region of Russia


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Abstract—An interdisciplinary study was carried out of the telomere length and polymorphism of genes of the renin-angiotensin (ACE) and serotonin (5HTR2A and 5HTTLPR) systems in a population of old and very old inhabitants of northwestern Russia, as well as on their relationships to data from clinical and geriatric anamneses and psychological characteristics. By the method of factor analysis, a firm association was revealed between the telomere length and respondents’ age in subgroups of old and long-living respondents.

Keywords: telomeres, longevity, polymorphism of ACE genes, 5HTR2A, HTTLPR

INTRODUCTION

In studying the primary mechanisms of aging of organisms, terminal sites of eukaryotic chromosomes—telomeres—are one of the most widely studied potential factors determining lifespan at present. The increased interest in these specialized complexes is due to the unique functions that they perform by maintaining the integrity of the cell genome (Blackburn, 2001). In addition to preventing chromosome fusion, telomeres are responsible for their attachment to the nuclear membrane (Podgornaya et al., 2000; Hediger et al., 2002), for mitotic and meiotic chromosome segregation (Conrad et al., 1997; Kirk et al., 1997; Dynek and Smith, 2004) and meiotic coupling (Rockmill and Roeder, 1998), for stabilization of ruptured chromosomes (Jager and Philippsen, 1989; Pennaneach et al., 2006), and for protection from their reparation systems (Mirska et al., 2008), as well as affecting expression of genes (Baur et al., 2001; Pedham et al., 2006).

At each cell division, the telomere DNA areas are shortened (Olovnikov, 1973; Allsop et al., 1992), thereby performing a peculiar buffer function (Ohki et al., 2001) to prevent more significant informational DNA sites from the so-called terminal underreplication (Olovnikov et al., 1971; Grach, 2009). According to the telomeric theory of aging, due to this molecular mechanism, the total number of cell divisions in the absence of telomeric activity is restricted a some limit—Hayflick’s limit (Hayflick and Moorhead, 1961)—while depletion of the proliferative potential of the cell in some tissue areas might be sufficient for the appearance of diseases associated with aging (Mikhelson, 2001; Herbig et al., 2006; Aubert and Lansdorp, 2008; Mikhelson and Gamaley, 2008). Increase of the telomere erosion rate is thought to be associated with the effect on the organism of adverse stressogenic factors, including constant increase of the level of oxidative (Aviv, 2002; Saretzki and von Zglinicki, 2002; Demissie et al., 2006) and psychological stress (Epel et al., 2004; Simon et al., 2006; Damjanovic et al., 2007).

A serious confirmation of a correction of the telomere theory of aging has been found using the results of working with cells of people suffering from progerias—hereditary diseases of premature aging. Here, a clear correlation is traced between aging at molecular, cellular, and organism levels: in cells of patients with Hutchinson–Guilford syndrome and ataxia–teleangiectasia, telomeres turned out to be have been sharply shortened since birth and the Heyflick’s limit decreased. Phenotypical manifestations of aging develop in such patients significantly earlier than in healthy persons (Allsop et al., 1992).

However, the literature data on the interaction of telomere length with lifespan are contested. In several works, no relationship has been revealed between the telomere length and mortality in people of advanced age (Bischoff et al., 2006; Martin-Ruiz et al., 2005). At the same time, in most studies, a dependence of the

length of telomere repeats on age and sex has been detected. It has been shown that telomeres of blood mononuclears in 100-year-old people are shorter than in young people, while in women they are longer than in men of the same age (Frenck et al., 1998; Tauchi et al., 1999). Nevertheless, the values of telomere lengths in different individuals are within rather wide limits and thus far no clear correlation has been revealed between telomere length and time of tissue turnover in vivo. This allows it to be concluded that telomere length is an individual characteristic, rather than a marker of biological age (Takubo et al., 2002). At the same time, a group of researchers, including E.H. Blackburn—the 2009 Nobel Prize winner in physiology and medicine for discovery of the telomere structure and of the mechanism of maintenance of their length—managed to show in 2004 for the first time that stress accumulated over a lifetime led to telomere shortening (Epel et al., 2004). In 2011, the same group of scientists discovered that positive psychological action (meditation) tends to produce the opposite result—telomeres in such people shorten at a significantly slower rate (Jacobs et al., 2011). Thereby, changes in the telomere length show the effect of the acting stress factor, while a decrease or increase of the rate of this change is a marker of positive or negative stress action. Thus, there was even an elongation of telomeres in women on long-term estrogen therapy that was noted (Lin et al., 2011). The combined effect of quite diverse stresses on the telomere length and association of these changes with these changes with processes of aging at the organism level is a topic being currently widely discussed in the scientific literature (Puterman et al., 2010).

Due to numerous discrepancies in the literature data, we decided to carry out our own study of the telomere length in geriatric age groups and determine whether the shortening rate of chromosome telomeres depends on the presence of pathologies and other stresses or is more or less constant in their absence. In addition, such investigations have not been performed in the population of the northwestern region of Russia.

MATERIALS AND METHODS

The group studied comprised 170 persons (40 men, 130 women), patients of St. Petersburg City Geriatric Center from 55 to 101 years of age (mean age of 79.98 ± 8.72 years). All respondents were Russian-speakers and participated in the study voluntarily.

Physical health (active longevity) was estimated by specific gerontological methods (“Index of the Ability to Take Care of Oneself”), and necessary data on anamnesis were taken from the respondents’ disease histories, (diabetes, strokes, heart attacks, oncological diseases, etc.). To evaluate psychological state and level of psychoemotional stress, all respondents were asked to undergo psychological testing composed of a package of standard procedures that we have described earlier (Spivak et al., 2009).

Isolation of DNA from venous blood was performed by the standard method with use of proteinase K end phenol–chloroform (Sambrook et al., 1989). The highly molecular DNA was air-dried and dissolved in TE buffer; in such a form, DNA was stored at –20°C.

The telomere length in lymphocytic fraction of peripheral blood was analyzed by the method of online polymerase chain reaction (cPCR) from the original protocol (Cawthon, 2002), in specific primers that do not form dimers during performance of cPCR were used, which was achieved owing to their incomplete complementarity to telomere repeats: Tel-1: 5'-GGTTTTTGAGGGTGAGGTAGGAGTGGTGGTGTTAGGG-3'; Tel-2: 5'-TCCCCGACTATCCTATCCCTATCCCCATATCCCTA-3'. The mean telomere length in a sample (in kb) was calculated by an original procedure (O’Callaghan et al., 2008) using dilutions of a calibrator—an 84-member synthetic oligonucleotide composed of telomere repeats TTAGGG. The mean telomere length per genome was calculated by standardization of the number of copies of telomere repeats per number of copies of gene of ribosomal phosphoprotein PO 36B4 (T/S) located on chromosome 12 and represented in cells in a single copy (Boulay et al., 1999). To amplify the gene of ribosomal phosphoprotein, the following primers were used: 36B4u: 5'-CAGCAAGTGGGAAGGTGGCT-3'; 36B4d: 5'-CCCATTCTATCATCCCTATCCCTA-3'.

Results of measurement of telomere lengths were compared with data of anamnesis from materials of disease histories and psychological characteristics with performance of factor analysis of all observed variables with use of orthogonal rotation of the normalized load matrix Varimax, the main components being applied in the method of isolation of factors.

RESULTS AND DISCUSSION

In comparing all the obtained data with those for patients older than 50 years (cf. the dotted diagram), we failed to find a clear link between telomere and age; the spread of data presented in Fig. 1 was too high.

When considering respondents of the senior age group (older than 80) with the long-lived people (older than 90), we observed an interesting dynamic. In the senior age group (Fig. 2), distribution of the telomere lengths, like in Fig. 1, did not decrease with age; however, in long-lived people (Fig. 3), and inverse relation of telomere lengths with age was observed.

At present, a great amount of experimental data have been accumulated connecting age-associated diseases both with telomere length and with polymorphisms of different genes (Farzaneh–Far et al., 2010; Hoen et al., 2011). The insertional/deletional (I/D) polymorphism of the gene of the angiotensin-convert-ting enzyme (ACE) (Rigat et al., 1990) has been tradi-