Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Shorter telomere length in people with schizophrenia: A preliminary study from Australia

Cherrie Galletly [a,b,c,*], Varinderpal S. Dhillon [d], Dennis Liu [a,b], Ryan P. Balzan [e], Lisa A. Hahn [a,c], Michael F. Fenech [d]

[a] Discipline of Psychiatry, University of Adelaide, Adelaide, SA, Australia
[b] Northern Adelaide Local Health Network, Adelaide, SA, Australia
[c] Ramsay Health Care (SA) Mental Health, Australia
[d] Nutrigenomics & DNA Damage Diagnostics, CSIRO Health and Biosecurity, Adelaide, SA, Australia
[e] School of Psychology, Flinders University, Adelaide, SA, Australia

A R T I C L E I N F O

Article history:
Received 16 August 2016
Received in revised form 28 February 2017
Accepted 2 March 2017
Available online xxxx

Keywords:
Telomere
Telomerase
DNA
Schizophrenia
Psychosis
Diet
Lifestyle

A B S T R A C T

Schizophrenia is a complex mental illness affecting the normal functioning of the brain, interfering with the ability to think, feel and act. It can be conceptualised as a syndrome of accelerated ageing, with early onset of cardiovascular disease and high rates of premature mortality. Telomere attrition increases with oxidative stress and is considered a biomarker of ageing. Previous studies have assessed abnormalities in telomere length in schizophrenia, but the results are inconsistent. The present study used a case-control design to assess whether people with schizophrenia have shortened telomeres, indicative of accelerated ageing. Subjects were all male, aged 25–35 years, living in the same urban region of Adelaide, South Australia. Telomere length was measured using a quantitative real-time polymerase chain reaction (PCR) method. We found significantly shorter telomeres in people with schizophrenia relative to healthy controls. This is the first study to show telomere attrition among people with schizophrenia in Australia. Shorter telomere length may indicate the common pathways that schizophrenia shares with other neuropsychiatric and neurodevelopmental disorders associated with increased cellular senescence. Further well-controlled larger studies in people with schizophrenia are required to fully understand (i) the role of variables that have the potential to modulate telomere length such as use of antipsychotic drugs, medical conditions, parental age, smoking, alcohol abuse and use of illicit drugs; (ii) effective treatments to slow telomere erosion and (iii) mechanisms responsible for accelerating and reducing telomere damage.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Telomeres are DNA-protein complexes that consist of hexameric $(TTAGGG)_n$ tandem repeats of DNA associated with shelterin proteins that control maintenance of telomere length (Erdel et al., 2017; Martinez and Blasco, 2015). They are crucial for maintaining chromosomal integrity by preventing telomere end fusions (Martinez and Blasco, 2015; Blackburn and Epel, 2012). Telomeres act as molecular clocks and shorten as a consequence of each cell division and also due to inability to completely replicate the ends of chromosomes (Blackburn et al., 2015). Many factors such as oxidative stress, chronic inflammation, psychological stress and depression can accelerate telomere attrition (Steptoe et al., 2017; Pedrini et al., 2012; Needham et al., 2015; Lindqvist et al., 2015; Steptoe et al., 2017; Udomsinprasert et al., 2016).

Several lines of evidence have implicated abnormal telomere length in various somatic and psycho-somatic diseases such as cardiovascular disorders (Mourkioti et al., 2013), cancer (Walsh et al., 2014), hypertension (Morgan et al., 2014), type 2 diabetes (Willeit et al., 2014), Alzheimer's disease (Tedone et al., 2015), systemic inflammation (Shin and Baik, 2016), and chronic pain (Sibille et al., 2012). In addition, there is an increasing body of evidence linking telomere length with psychiatric disorder including anxiety and depression (Lindqvist et al., 2015; Kananen et al., 2010; Verhoeven et al., 2016).

People with schizophrenia have significantly lower average life expectancy (Hjorthøj et al., 2017) which has led to the suggestion that schizophrenia may be associated with accelerated biological ageing (Lindqvist et al., 2015; Schnack et al., 2016); such accelerated ageing might be associated with shortened telomeres. However, current studies are not conclusive, with some showing shortening of telomeres (Kao et al., 2008; Yu et al., 2008; Kota et al., 2015; Czepielewski et al., 2016) while others show either no difference (Malaspina et al., 2014; Mansour et al., 2011) or longer telomeres compared to the healthy population (Nieratschker et al., 2013). Telomerase is an enzyme that

* Corresponding author at: Discipline of Psychiatry, University of Adelaide, Adelaide, SA, Australia.
E-mail address: cherrie.galletly@adelaide.edu.au (C. Galletly).

http://dx.doi.org/10.1016/j.schres.2017.03.007
0920-9964/© 2017 Elsevier B.V. All rights reserved.

ARTICLE IN PRESS

protects telomeres and maintains telomere length, and Porton et al. (2008) found lower levels of telomerase in people with schizophrenia compared to controls, although telomerase levels varied considerably between subjects. Recent meta-analyses have shown a trend towards shorter telomere length in people with schizophrenia compared to controls (Polho et al., 2015; Rao et al., 2016).

Among people with schizophrenia, there are gender and age differences that may explain differences in telomere length (Wolkowitz et al., 2017). For example, Malaspina et al. (2014) reported that older paternal age was associated with longer telomeres in men with schizophrenia, and shorter telomeres in women. In addition, a number of other unexplored environmental factors could directly or indirectly influence telomere length, including years of education, employment and marital status, income, nutrition and lifestyle. As many of these factors can vary between clinical and non-clinical groups (Van Nierop et al., 2013), they should be taken into account when assessing telomere length in people with schizophrenia. The current study aimed to control for these potential confounding factors by restricting the study population to males with schizophrenia and healthy male controls, matching for age and region of domicile, and obtaining data on parental age at birth, marital status, employment and income. We hypothesised that even after controlling for these variables, people with schizophrenia would have shorter telomeres relative to matched healthy controls.

2. Materials and methods

2.1. Study participants

A total of 48 males with schizophrenia and 51 healthy male controls without a psychiatric diagnosis were included. Participants were 25–35 years old, and lived within the Northern Adelaide Local Health Network (NALHN) catchment area; this is a socio-demographically deprived region. Schizophrenia participants were outpatients receiving community care from the NALHN mental health service. Electronic records were used to identify subjects who were male, aged 25–35 years, non-Indigenous (not Aboriginal), and lived in the included postcodes. Subjects were included if they had capacity to give informed consent, sufficient English language skills to complete the study measures, were not intellectually disabled, and were not considered a risk to the safety of research staff. Potential participants were selected randomly and invited to participate. Healthy controls were typically staff or visitors to the Lyell McEwin Hospital, male, aged 25–35 years, non-Indigenous, and living in the NALHN catchment area. They were screened for a lifetime diagnosis of a psychiatric disorder and excluded if this was present. The study was approved by the Queen Elizabeth Hospital Ethics Committee and all participants provided written informed consent.

2.2. Assessment

Patients with a clinical diagnosis of schizophrenia were screened using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and the diagnosis of schizophrenia was confirmed clinically using DSM-IV-TR by a trained psychiatric research nurse. Their age at the onset of symptoms, and the number of hospitalisations, was recorded. Data was collected for all participants which included marital and employment status, years of education, income, welfare support, and current living arrangements. A health questionnaire was used to collect relevant data including parental age, any known birth trauma, any chronic medical diagnosis, personal and family history of cancer, frequency and duration of alcohol, tobacco, illicit drug usage and current medication, including vitamins and supplements. Body mass index (BMI) was calculated using height and current weight. The 14-item Perceived Stress Scale (PSS) (Cohen et al., 1983) was used to assess stress over the past month, and the International Physical Activity Questionnaire (Craig et al., 2003) was implemented to measure physical activity over the previous week. All participants provided a blood sample for measurement of leukocyte telomere length.

2.3. Telomere length assessment

Genomic DNA was extracted from whole blood using the QIAamp DNA blood mini kit (Qiagen, Australia). Purified DNA samples were quantified using NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, Australia) and diluted as per experimental requirements (5 ng/μl). Telomere length was measured using quantitative real-time PCR (Cawthon, 2002, 2009; Dhillon et al., 2017). The ratio of the telomere (T) repeat copy number to the single-copy gene (S) was determined for each sample using ABI 7300 Real-Time PCR Detection System (Life Technologies, USA). The final concentrations of the PCR reagents were 1 × SYBR Green Mix (Life Technologies, USA), 20 ng sample DNA, 0.2 μmol of telomere specific primers (F: 5′-GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGA GGGT-3′; R: 5′-TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA-3′) and 0.3 μmol of 36B4 primers (F: 5′-CAGCAAGTGGGAAGGTGTAATCC-3′; R: 5′-CCCATTCTATCATCAACGGGTACAA-3′). The reactions were performed in triplicates using telomere and 36B4 specific primers in a 96-well plate, and each plate included a reference DNA sample. A five point serial dilution (five DNA concentrations of 1301 cell line DNA over an 8.4 fold range were generated by serial dilution, dilution factor being 1.68 and the final amounts per well ranged from 0.63 to 5.02 ng) standard curve of DNA concentration *versus* T/S ratio using DNA isolated from the 1301 cell line (which has a mean telomere length of 23,000 base pairs) was established in each plate. The standard curve was then used to convert the T/S ratio into telomere length (TL) in base pairs (bp) using following equation: Absolute TL (bp) = 2433.23X + 3109.51 where X = T/S ratio, 2433.23 is the slope and 3109.51 is the intercept of the standard curve. A standard curve with a high correlation factor ($R^2 \geq 0.97$) was required to accept the results from each plate. We calculated intra-assay and inter-assay coefficient of variation (CV) to assess the variation of results within each data set and also to ensure plate-to-plate consistency, respectively. The intra-assay CV between triplicates for telomeres was 2.3% and 2.1% for the single-copy gene, whereas the inter-assay CV between plates was 0.5% for telomeres and 0.88% for single-copy gene.

2.4. Statistical analyses

All analyses were conducted using IBM SPSS 19.0. A saturated ANCOVA model was established to investigate telomere length in relation to schizophrenia diagnosis, age, relationship status, employment, number of medical conditions, smoking status, alcohol and illicit drug use. The saturated model controlled for categorical and continuous variables and then significant terms were only included into the model by backward eliminating non-significant variables. All significant predictor variables were controlled in the final lean model. Within the schizophrenia group, an independent samples *t*-test was used to compare telomere length in those taking antipsychotic medications with those not taking these medications. Only main effects of each variable were incorporated into the model. Based on the standard deviation of 1255 bp, with 48 subjects per group, the study has 90% power to detect a difference of 840 bp in telomere length at $p < 0.05$.

3. Results

3.1. Participants and telomere length

Details of participants are given in Table 1. The mean age (years) was 31.27 ± 0.44 for schizophrenia subjects and 29.16 ± 0.44 for normal healthy controls. Table 1 also shows the mean (S.E.) telomere length, for the two groups. Fig. 1 shows the distribution of telomere length by group indicating a trend for lower telomere length in the schizophrenia

Please cite this article as: Galletly, C., et al., Shorter telomere length in people with schizophrenia: A preliminary study from Australia, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.03.007

Download English Version:

https://daneshyari.com/en/article/6822382

Download Persian Version:

https://daneshyari.com/article/6822382

Daneshyari.com