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Accelerated leukocyte telomere erosion in schizophrenia: Evidence from the present study and a meta-analysis

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ABSTRACT

Human telomeres consist of tandem nucleotide repeats (TTAGGG) and associated proteins, and telomere length (TL) is reduced progressively with cell division over the lifespan. Telomere erosion might be accelerated or prevented to varying degrees when exposure to serious medical illnesses. In previous studies, an association between TL decrease and schizophrenia has been extensively reported; however, the results remain largely controversial. To further investigate TL in schizophrenia patients and reconcile this controversy, we first measured leucocyte TL (LTL) in our samples (52 paranoid schizophrenia, 89 non-paranoid patients and 120 controls), and then conducted a comprehensive meta-analysis of the existing results of LTL in patients of schizophrenia compared to healthy subjects. Totally, 11 studies encompassing 1243 patients of schizophrenia and 1274 controls were included in the final meta-analysis model. In our samples, significant reduction of LTL in paranoid schizophrenia was observed compared to controls ($F = 50.88$, $P < 0.001$); whereas there was no significant difference in LTL between non-paranoid schizophrenia and controls ($F = 0.842$, $P = 0.360$). For meta-analysis, random-effects model showed significant LTL decrease in patients of schizophrenia when compared to controls ($Z = 2.07$, $P = 0.039$, SMD = −0.48, 95% CI = −0.94 to −0.03). Moreover, a marginal decrease in LTL was observed in medicated patients ($Z = 1.92$, $P = 0.055$, SMD = −0.58, 95% CI = −1.18–0.01) and those patients with poor response to antipsychotics ($Z = 1.76$, $P = 0.078$, SMD = −0.60, 95% CI = −1.27–0.07). In conclusion, we observed significant reduction of LTL in individuals with schizophrenia compared with controls. However, all the studies included in the meta-analysis were cross-sectional, and better controlled long-term studies are needed to replicate this result.

1. Introduction

Telomeres are nucleoprotein complexes which consists of tandem nucleotide repeats, $(TTAGGG)_n$ in mammals, and associated proteins, and form the ends of linear chromosomes. The functions of telomere include protection of chromosomal termini from the loss of genetic information, as well as from end-to-end fusion, which are crucial for maintenance of chromosomal integrity (de Lange, 2002).

Telomeres length (TL) is known to be in part genetically controlled, with heritability ranging from 0.36 to 0.84 (Aviv, 2012). Variation in many genes, including *TERT*, *TERC* and *OBFC1*, has been reported to be associated with mean TL (Codd et al., 2010, 2013). Epigenetic regulation and adversity over the lifespan have effect on TL as well (Aviv, 2012). Normally, leukocyte telomere length (LTL) decreases gradually over the lifespan, with an estimate of 32.2–45.5 bp attrition per year in healthy populations according to

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a longitudinal study (Muezzinler et al., 2013) and aging-related telomere detrition has been detected in cell types including fibroblasts and lymphocytes (Frenck et al., 1998). However, serious medical illnesses may accelerate or prevent telomere erosion to varying degree. Such diseases included atherosclerosis, diabetes mellitus, cancer and psychiatric disorders (Mourkioti et al., 2013; Verhoeven et al., 2016; Walsh et al., 2014).

Schizophrenia is a neurodevelopmental and neurodegenerative disease, in which genetic risk variants (i.e. *ZNF804A*, *CACNA1C*, etc.) and environmental factors play important roles in its development (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Paranoid schizophrenia is one subtype of schizophrenia and has stable clinical characteristics, mainly positive symptoms (i.e. hallucinations and delusions). Although the pathophysiology of schizophrenia remains largely elusive, it has been reported that schizophrenia is associated with impaired antioxidant defense, which might not be due to antipsychotic medications since oxidative stress abnormalities are found in first-episode psychosis (Flatow et al., 2013). Moreover, since schizophrenia shares some lifelong characteristics (i.e. pattern of mortality and cognitive impairment) with elderly people, and risk factors for other aging-related diseases also contribute to schizophrenia, some authors proposed that schizophrenia was one syndrome of accelerated aging (Okusaga, 2014). Considering the fact that both aging and oxidative stress are main drivers of telomere shortening (Wolkowitz et al., 2011), TL might be decreased in schizophrenia patients than healthy subjects.

In previous studies, an association between decreased LTL and schizophrenia has been extensively reported although the sample size used was relatively small. For example, Kao et al. detected significant telomere erosion in patients of schizophrenia ($N = 51$), when compared to healthy family members ($N = 24$) and independent controls ($N = 53$) (Kao et al., 2008). Similarly, in a cross-sectional study consisting of 36 schizophrenia patients and 41 healthy subjects, significant telomere content decrease was found in schizophrenia (Fernandez-Egea et al., 2009). As for paranoid schizophrenia (98 cases and 109 controls), shorter LTL was also observed by Rao et al. (2016). However, other studies did not confirm this observation. Nieratschker et al. found that TL in individuals with schizophrenia was longer than controls in a large sample of medicated schizophrenia ($N = 539$) and controls ($N = 519$) (Nieratschker et al., 2013).

In the present study, we first investigated the association of LTL with schizophrenia in our independent sample consisting of 141 patients of schizophrenia (52 paranoid cases and 89 non-paranoid patients) and 120 controls, and then performed a comprehensive meta-analysis of LTL in schizophrenia with the largest sample size available (1243 patients of schizophrenia and 1274 controls).

2. Methods

2.1. Participants

In this study, a total of 141 unrelated schizophrenia patients (68 males and 73 females, aged 38.0 ± 4.7 years), including 52 paranoid schizophrenia and 89 non-paranoid schizophrenia patients, were recruited from the Affiliated Hospital of Southwest Medial University between April 2014 and December 2015. Patients were clinically diagnosed as schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria and evaluated based on the Structured Clinical Interview for DSM-IV (SCID). Subjects with the following conditions were excluded from this study: any other Axis I Disorders and Axis II Disorders; unstable psychiatric features; history of serious medical or neurological disorders; serious medical disorders, such as cancer and cardiovascular diseases; alcoholism; drug abuse; and so on. Meanwhile, 120 unrelated healthy subjects (67 males and 53 females, aged 39.2 ± 5.3 years) were recruited as controls from local communities. The exclusion criteria for controls were similar to that for patients.

All the subjects provided written informed consent to participate in this study. The study design and procedures were in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of Southwest Jiaotong University.

2.2. LTL measurement by quantitative polymerase chain reaction (qPCR)

Peripheral blood sample (5 ml) was collected in EDTA tube from each participant. Genomic DNA was isolated from peripheral blood leukocytes using the FlexiGene DNA kit (QIAGEN, USA) according the manufacturer's instructions (Rao et al., 2015).

The mean LTL was measured by qPCR and the mean LTL for each sample was indicated as the ratio of telomere repeat length (T) to copy number for a single-copy gene (S). The detailed procedures and calculation method were described in our previous study (Rao et al., 2016).

The primers for the telomere PCR were 270 nM Tel1 (5′-GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT-3′) and 900 nM Tel2 (5′-TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA-3′); for single copy gene, the hemoglobin gene (Hgb), the primers were 300 nM Hgb1 (GCTTCTGACACAACTGTGTTCACTAGC) and 700 nM Hgb2 (CACCAACTTCATCCACGTTCACC). The cycling conditions for telomere were 95 °C for 5 min, followed by 40 cycles of 95 °C for 10 s and 54 °C for 2 min with plate read. The profile of *Hgb* included initial incubation step at 95 °C for 5 min, followed by 40 cycles of amplification with 10 s at 95 °C, 30 s at 58 °C and 20 s at 72 °C with data collection.

All qPCR reactions were conducted on a CFX96 Real-Time PCR Detection System (Bio-Rad, Hercules, CA). Each sample was run in triplicate using 25 ng DNA templates in a 25 μl reaction volume. The telomere and single copy gene were amplified on separate runs with the same samples located in precisely the same well positions, in order to minimize variations between plates.

2.3. Study searching and data collection for meta-analysis

We searched candidate studies in PubMed (http://www.ncbi.nlm.nih.gov), Scopus (http://www.scopus.com), EMBASE (http://www.elsevier.com/online-tools/embase) and ISIWeb of Knowledge (http://apps.webofknowledge.com/) with the following searching terms: "telomere" and ("schizophrenia" or "psychosis"). Publications written in English before the 1st of January 2016 were considered. The references of retrieved articles were also reviewed to identify other eligible studies that were not indexed by the above-mentioned databases.

Any studies with available LTL (the average and standard deviation) of schizophrenia patients as well healthy controls were included. For each eligible study, two independent investigators (Rao and Yao) extracted the following data: 1) first author and publication year; 2) the sample size, gender ratio and age distribution of patients and controls; 3) LTL measurement method; 4) mean and standard deviation of LTL in schizophrenia and controls; 5) other useful information, i.e. medication and clinical assessment. If required information was not available, we requested from the authors.

2.4. Statistical analysis

All analyses were performed using the SPSS 17.0 and Stata 12.0