Ribosomal DNA gene copies are increased in blood and brain of Japanese schizophrenia patients

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日本人統合失調症患者の血液・脳試料におけるリボソーマル DNA 遺伝子コピー数の増加

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＜**Abstract**＞

Background

Ribosomes are essential structures in all living organisms that synthesize proteins, composed of RNA and proteins encoded by multi-copy genes in humans. Several lines of evidence have indicated that ribosomal DNA transcriptional activity may play a key role in neuronal plasticity. Dysfunctional neural plasticity has been proposed as a key pathophysiological mechanism in schizophrenia (SCZ), which is associated with genetic factors. Past evidence has indicated increased ribosomal DNA copy number (rDNAcn) in the blood of patients with SCZ among European populations. Here, for the first time, we investigated rDNAcn of SCZ in East Asian populations as well as in blood and brain tissues.

Materials and methods

The study design and related procedures were performed in accordance with the Declaration of Helsinki. This study was approved by the Ethical Committee for Genetic Studies of Kobe University Graduate School of Medicine. Written informed consent was obtained from all living participants and the families of deceased individuals.

Blood samples were taken from 81 living patients with SCZ and 98 healthy controls, while brain tissue samples were obtained from autopsies conducted on 10 SCZ patients and 23 non-psychiatric control individuals. All participants were of Japanese descent, and patients with SCZ were diagnosed based on the DSM-IV criteria by a psychiatrist. Autopsies were conducted at Kobe University Graduate School of Medicine, and DNA was extracted from the dorsolateral prefrontal cortex (DLPFC).

Measurement of rDNAcn was done by quantitative polymerase chain reaction (qPCR) using standard curve base analysis. To estimate rDNAcn, amplicons targeting 18S and 28S coding regions of rDNA were used, with amplicons corresponding to the coding regions of the albumin gene (ALB) as an endogenous control. The ratio of ribosomal DNA to that of the reference endogenous control gene in each sample was determined as the 18S or 28S / ALB ratio.

The Kolmogorov-Smirnov test was used to assess the normality of the data. Regression analyses using generalized linear models or multiple linear regression were applied to analyze between-group comparisons of rDNAcn, with covariates (age and sex), as needed. Spearman's rho tests were performed to assess the relationship between 18S rDNAcn and 28S rDNAcn. Statistical significance was defined as a two-tailed $p < 0.05$.

Results

The correlation between the individual values of 18S and 28S rDNAcn was strong in healthy controls (Spearman's rho = 0.76, $p < 0.001$) and moderate in patients with SCZ (Spearman's rho = 0.57, $p < 0.001$). The correlation between the individual values of 18S and 28S rDNAcn was strong in both non-psychiatric controls ($p < 0.001$) and patients with SCZ ($p = 0.002$) for DLPFCs. The distribution of

18S/28S rDNAcns in blood samples was skewed ($p < 0.05$), patients with SCZ had significantly increased rDNAcn compared to controls for both 18S ($p = 0.034$) and 28S rDNAcn ($p = 0.004$). The distribution of 18S/28S rDNAcns in DLPFC samples was normalized ($p = 0.43$), patients with SCZ had a significant increase in 18S rDNAcn ($p = 0.047$) compared to controls, but not in 28S rDNAcn ($p = 0.203$).

Discussion

This study successfully replicated previous findings of increased rDNAcn in the blood of European patients with SCZ using an East Asian cohort, suggesting a potential link between increased rDNA content and the global and basic pathophysiology of SCZ. We also provided the first evidence of increased rDNAcn in the DLPFC of SCZ patients, a region associated with SCZ vulnerability. Meanwhile, the study acknowledged several limitations, including the use of post-mortem brain samples, technical limitations of the qPCR method, small sample sizes, and the need for further research on other brain regions and rRNA synthesis in SCZ. In conclusion, our findings shed light on further research into rDNA towards an improved understanding of SCZ-related pathophysiology.