News Release

Title

Identification of copy number variations associated with schizophrenia and elucidation of molecular pathogenesis

Key Points

○ Copy number variations (CNVs) associated with schizophrenia (SCZ) were identified in 9% of patients.
○ In patients with CNVs associated with SCZ, 40% had a history of congenital/developmental phenotypes, and the rate of treatment resistance was significantly higher.
○ There is a possibility that genomic instability and impaired oxidative stress response are involved in pathogenesis of SCZ.

Summary

Prof. Norio Ozaki (Department of Psychiatry) in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.) and collaborators in Tokyo Metropolitan Institute of Medical Science, Osaka University, Niigata University, Toyama University, Fujita Health University, RIKEN Brain Science Institute, Tokushima University, and Chang Gung University identified CNVs associated with SCZ in 9% of SCZ patients and elucidated their clinical characteristics and molecular pathogenesis.
CNV contributes substantially to human evolution, normal phenotypic variation, and human disease. To date, thousands of different genomic duplications and deletions, each spanning hundreds to millions of base pairs, have been mapped genome-wide, and collectively account for a significant fraction of human genetic variation. The importance of rare CNVs for neuropsychiatric disease is now well-established. The research group performed a high-resolution genome-wide CNV analysis on a mainly (92%) Japanese population (1699 SCZ cases & 824 controls). The group demonstrated the high genetic heterogeneity of SCZ and its clinical features and raises the possibility that genomic instability is involved in its pathogenesis, which may be related to the increased burden of de novo CNVs and variable expressivity of CNVs.

Research Background

Recent schizophrenia (SCZ) studies have reported an increased burden of de novo copy number variants (CNVs) and identified specific high-risk CNVs, although with variable phenotype expressivity. However, the pathogenesis of SCZ has not been fully elucidated.

Research Results

Using array comparative genomic hybridization, we performed a high-resolution genome-wide CNV analysis on a mainly (92%) Japanese population (1699 SCZ cases and 824 controls) and

identified 7066 rare CNVs, 70.0% of which were small (100 kb). Clinically significant CNVs were significantly more frequent in cases than in controls (odds ratio = 3.04, $P = 9.3 \times 10^{-9}$, 9.0% of cases). We confirmed a significant association of X-chromosome aneuploidies with SCZ and identified 11 de novo CNVs (e.g., MBD5 deletion) in cases. In patients with clinically significant CNVs, 41.7% had a history of congenital/developmental phenotypes, and the rate of treatment resistance was significantly higher (odds ratio = 2.79, P = 0.0036). We found more severe clinical manifestations in patients with two clinically significant CNVs. Gene set analysis replicated previous findings (e.g., synapse, calcium signaling) and identified novel biological pathways including oxidative stress response, genomic integrity, kinase and small GTPase signaling. Furthermore, involvement of multiple SCZ candidate genes and biological pathways in the pathogenesis of SCZ was suggested in established SCZ-associated CNV loci.

Research Summary and Future Perspective

Our study shows the high genetic heterogeneity of SCZ and its clinical features and raises the possibility that genomic instability is involved in its pathogenesis, which may be related to the increased burden of de novo CNVs and variable expressivity of CNVs.

Publication

Kushima I, Aleksic B, Nakatochi M, Shimamura T, Shiino T, Yoshimi A, Kimura H, Takasaki Y, Wang C, Xing J, Ishizuka K, Oya-Ito T, Nakamura Y, Arioka Y, Maeda T, Yamamoto M, Yoshida M, Noma H, Hamada S, Morikawa M, Uno Y, Okada T, Iidaka T, Iritani S, Miyashita M, Kobori A, Arai M, Itokawa M, Cheng MC, Chunag YA, Chen CH, Suzuki M, Takahashi T, Hashimoto R, Yamamori H, Yasuda Y, Watanabe Y, Nunokawa A, Someya T, Ikeda M, Toyota T, Yoshikawa T, Numata S, Ohmori T, Kunimoto S, Mori D, Yamamoto T, Iwata N, Ozaki N. High-resolution copy number variation analysis of schizophrenia in Japan. *Molecular Psychiatry*. May, 31, 2016.

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