Genetic copy number variation (CNV) contributes substantially to human evolution, normal phenotypic variation, and human disease. To date, thousands of genetic copy number variations are present in the human genome. Among them, copy number variations are present in the human genome. CNVs are defined as copy number variations that range from one kilobase (kb) to megabases (Mbs) in size. Recently, several rare CNVs (<1% in population) have been associated with the risk of schizophrenia with odds ratios (ORs) of 2 to over 50. Such CNVs include deletions at 1q21.1, NKSN1, 1q21.1, 1q11.2, 19q13.3, and 22q11.2 and duplications at 1q21.1, 1p12, 3q29, 15q11.2, 16p13.1, and 16p11.2. These CNVs were classified into two major categories: (i) neurodevelopmental and psychiatric disorders (variable expressivity of CNVs). Despite the progress, small CNVs (<100 kb) have not been fully studied in schizophrenia. Furthermore, the pathogenesis of this disorder has not been elucidated. Thus, we performed a high-resolution genome-wide CNV analysis to address these issues.

CNV analysis
Using a microarray technology called array comparative genomic hybridization, we performed a high-resolution genome-wide CNV analysis of 1699 schizophrenia patients and 824 healthy controls. Our study revealed high genetic heterogeneity of schizophrenia and its clinical features and raised the possibility that genomic instability is involved in its pathogenesis, which may be related to the increased burden of de novo CNVs and the variable expressivity of CNVs.

Phenotypic analysis
To characterize clinical features of patients with clinically significant CNVs, we examined clinical information in detail. As a result, 61.7% of patients with such CNVs had a history of congenital phenotypes (e.g., congenital heart defects) or premorbid developmental problems (e.g., intellectual disability). In addition, the rate of treatment resistance to antipsychotics (primary medication for schizophrenia) was significantly higher in patients with such CNVs than in those without them (36.1% vs 16.9%, odds ratio = 2.79, P = 0.0036). This indicated that CNV findings may be useful in predicting the response to antipsychotics in patients with schizophrenia. We also found more severe clinical manifestations in patients with two clinically significant CNVs.

Pathogenic analysis
Identification of pathogenic pathways is critical for understanding its pathogenesis and development of novel treatment. For that purpose, we performed bioinformatic analysis (i.e., gene set analysis) using our CNV dataset. As a result, we identified multiple biological pathways implicated in the pathogenesis of this disorder: oxidative stress response, genomic instability, gene expression regulation, cell adhesion, neuronal signaling, kinase, synapse, small GTPase signaling, and endocytosis are affected by CNVs. Disruption of genomic integrity and oxidative stress response induces genomic instability, which is involved in germline CNV formation and somatic CNV formation in neurons. The former account for an increased rate of de novo or rare CNVs and the latter for the variable expressivity of CNVs.

Although increased oxidative stress has been reported in these patients, its role in the pathogenesis remains unclear. Furthermore, genomic instability is essential for normal neuronal and normal neuronal function. This pathway includes DNA repair, DNA replication, and DNA recombination, which are involved in major mechanisms of CNV formation. Therefore, CNVs in patients which affect the oxidative stress response or genomic integrity may promote genomic instability that underlies de novo CNV rates and a greater burden of rare CNVs in schizophrenia. In addition, genomic instability may influence the genome of somatic cells (neurons) and increase somatic mutations. Consistent with this, an increased copy number of rare CNVs has been recently reported in schizophrenia. Somatic mutations (mosaicism) are also implicated in variable expressivity of CNVs. Finally, a genetic model of schizophrenia is provided in Figure.

References