News Release

Title: Common and specific features of genomic copy number variation in bipolar disorder, schizophrenia, and autism spectrum disorder

Key Points

- Large-scale comparative analyses of copy number variations (CNVs) were performed in bipolar disorder, schizophrenia, and autism spectrum disorder.
- Small (< 100 kb) deletions are more common in bipolar disorder, while large (> 500 kb) CNVs (deletions and duplications) are more common in schizophrenia and autism spectrum disorder.
- Known risk CNVs for neurodevelopmental disorders are implicated in the risk of the three disorders.
- Three genes (*PCDH15, ASTN2,* and *DLG2*) are associated with the risk of bipolar disorder.
- The three disorders share impaired chromatin function, while schizophrenia and autism spectrum disorder involve a broader and overlapping molecular pathophysiology (e.g., synapses).
- CNVs in non-coding regions may contribute to the risk of autism spectrum disorder and schizophrenia.

Summary

A research group led by professor Norio Ozaki at Nagoya University Graduate School of Medicine investigated the involvement of copy number variations (CNVs) in bipolar disorder, schizophrenia, and autism spectrum disorder. In detailed analysis of CNV data from 8,708 individuals (patients and controls), we found that small (< 100 kb) deletions are more common in bipolar disorder, while large (> 500 kb) CNVs are more common in autism spectrum disorder and schizophrenia. While known risk CNVs for neurodevelopmental disorders (e.g., autism spectrum disorder and intellectual disability) are significantly associated with the risk of each of the three disorders, the effect sizes of these CNVs for bipolar disorder are smaller than those for the other two disorders. We identified *PCDH15, ASTN2*, and *DLG2* as risk genes for bipolar disorder. Analysis of molecular pathophysiology based on the CNV data suggests an involvement of only chromatin function in bipolar disorder, while autism spectrum disorder and schizophrenia have more extensive and overlapping molecular pathophysiology. Finally, CNVs in non-coding regions were found to be involved in the risk of schizophrenia and autism spectrum disorder.

This study is a multicenter collaborative study involving more than 20 facilities in Japan and was supported by research grants from the Japan Agency for Medical Research and Development (AMED).

Research Background

It has been reported that relatives of patients diagnosed with bipolar disorder are more likely to have been diagnosed with autism spectrum disorder or schizophrenia. Risk variants common to the three disorders have also been identified. These findings suggest that the genetic factors for the three disorders may be partly overlapping.

The involvement of genomic copy number variations (CNVs: deletions or duplications) in autism spectrum disorder and schizophrenia has been reported by several research groups including our group (Kushima I et al., Cell Rep, 2018). Rare CNVs in specific loci (e.g., 22q11.2 deletion and 3q29 deletion) have been strongly associated with the risk of the two disorders. On the other hand, the association between bipolar disorder and CNVs is not clear. Few studies have directly and systematically compared CNV data in the three disorders. Furthermore, previous studies focused on CNVs in gene regions (coding regions), but the involvement of CNVs in non-coding regions (98% of the human genome) has not been fully investigated.

Research Results

We performed a large-scale CNV analysis of bipolar disorder, schizophrenia, and autism spectrum disorder. This is a multicenter collaborative study involving more than 20 facilities in Japan (Figure 1). Overall, 8,708 individuals (bipolar disorder: 1,818, schizophrenia: 3,014, autism spectrum disorder: 1,205, controls: 2,671) were analyzed using high-resolution array CGH. Focusing on rare CNVs (1% frequency in Japanese population), the characteristics of CNVs were systematically compared in the three disorders.

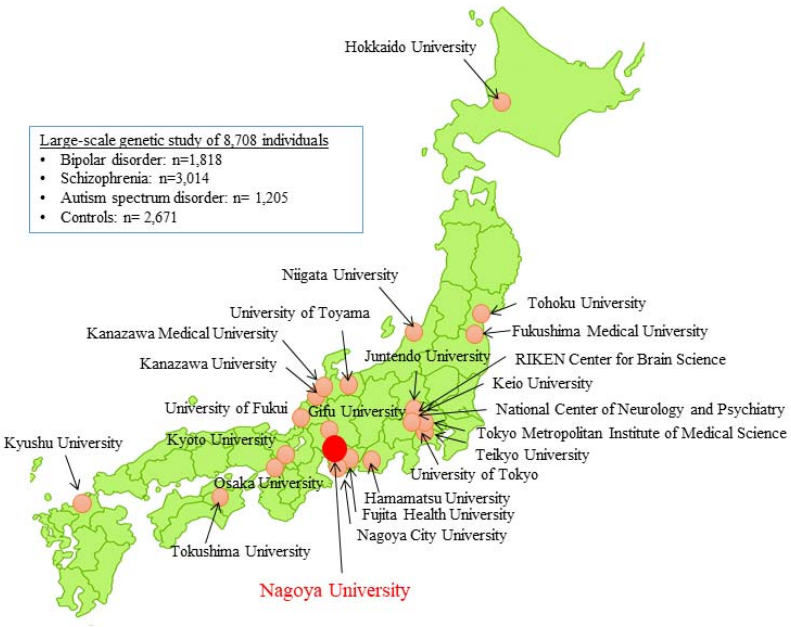

Figure 1 Multicenter collaborative study involving more than 20 facilities in Japan

This study revealed the following findings:

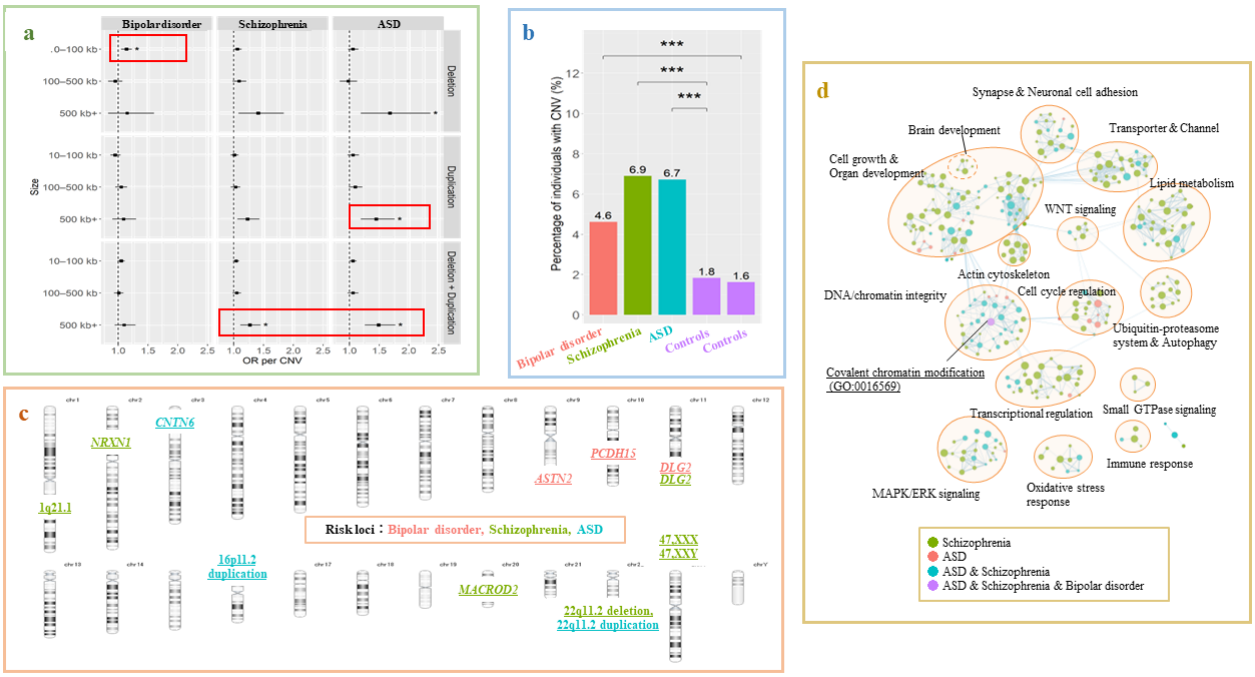

Figure 2 Comparative analysis of copy number variations (CNVs) in bipolar disorder, schizophrenia, and autism spectrum disorder (ASD)

1. Distribution of CNV size (Figure 2a)

As CNV size increases, the copy number of more genes changes, it is important to know the characteristics of its distribution. Comparison of CNVs in coding regions between patients and controls showed that small (< 100 kb) deletions are more common in bipolar disorder. This is different from enrichment of large (> 500 kb) CNVs (both deletions and duplications) in autism spectrum disorder and schizophrenia.

2. Association with known risk CNVs (Figure 2b)

There are many known risk CNVs for neurodevelopmental disorders (e.g., autism spectrum disorder and intellectual disability). Such risk CNVs were present in 4.6%, 6.9%, and 6.7% of patients with bipolar disorder, schizophrenia, and autism spectrum disorder, respectively. They were significantly higher than in controls (1.8%). This result indicates that known risk CNVs for neurodevelopmental disorders are implicated in the risk of the three disorders. The effect sizes (odds ratios) of risk CNVs were 2.9 in bipolar disorder, 3.7 in schizophrenia, and 4.2 in autism spectrum disorder.

3. Risk loci for three disorders (Figure 2c)

We examined the association between individual risk CNVs and each disorder. Twelve CNVs were significantly associated with the risk of any of the three diseases (3 for bipolar disorder, 6 for schizophrenia, and 3 for autism spectrum disorder). Three genes (*PCDH15, ASTN2, and DLG2)* were identified as risk genes for bipolar disorder. These genes were reported to be involved in the formation and function of neural circuits. We also found the association of 22q11.2 deletion, 1q21.1 deletion, *NRXN1* CNVs with schizophrenia, and 16p11.2 duplication, 22q11.2 duplication, *CNTN6* CNVs with autism spectrum disorder.

4. Analysis of molecular pathogenesis (Figure 2d)
We performed gene-set analysis based on gene ontology to identify biological pathways relevant to each disorder. The only biological pathway common to the three disorders was chromatin function. On the other hand, schizophrenia and autism spectrum disorder involved more extensive and overlapping pathways (synapses, oxidative stress response, transcriptional regulation).

5. Roles of CNVs in non-coding regions
Previous studies focused on CNVs in gene regions (coding regions). Since it was not known whether CNVs in the non-coding regions are involved in psychiatric disorders, we investigated this point. Non-coding regions (enhancers and promoters) that are active in brain tissues were available from database, and we evaluated whether CNVs in these regions are more common in each disease than in controls. As a result, we found that CNVs in non-coding regions are significantly more common in autism spectrum disorder and schizophrenia. This suggests that CNVs in non-coding regions may be involved in risk of the two disorders.

Research Summary and Future Perspective
This study suggests that CNVs are implicated in the risk of bipolar disorder as well as autism spectrum disorder and schizophrenia. The involvement of chromatin function in bipolar disorder is notable as chromatin function may be involved in the pharmacological effects of valproic acid, a medication for bipolar disorder. Previous studies suggested that genes associated with bipolar disorder (*PCDH15*, *ASTN2,* and *DLG2*) play a role in neural circuit function. Using iPS cells from bipolar disorder patients with *PCDH15* and *ASTN2* deletions and model mice generated based on these variants, we are currently investigating the molecular mechanisms by which these CNVs lead to the development of bipolar disorder. It is hoped that understanding the pathophysiological mechanisms of bipolar disorder will contribute to the development of therapeutic drugs.

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