News Release

Title　Synaptic dysfunction is involved in the pathogenesis of eating disorders: findings from genomic analysis of Japanese patients.

Key Points

- Genomic copy number variation is associated with the risk of eating disorders
- Eating disorders and neurodevelopmental disorders share similarities in terms of genetic factors
- Disruption of synaptic function may play a role in the pathogenesis of eating disorders

Summary

A research group led by Norio Ozaki, specially-appointed professor at Nagoya University Graduate School of Medicine, Itaru Kushima, clinical lecturer at the Medical Genomics Center, Nagoya University Hospital, Miho Imaeda, assistant professor at the Department of Chemotherapy, Nagoya University Hospital, and Satoshi Tanaka, deputy director at the National Hospital Organization Higashi Owari Hospital/Nagoya Medical Center found that genomic copy number variations (CNVs) are involved in the risk of developing eating disorders, which are highly prevalent among young women. Risk CNVs known to be associated with neurodevelopmental disorders (NDD-associated CNVs) were found in 10% of female patients with severe eating disorders and they were associated with risk of the disorders. Most of the CNVs found in patients affected genes related to neuronal synapses. We also confirmed that patient CNVs were significantly enriched in synapse-related genes, and for the first time, elucidated that synaptic dysfunction is involved in the pathogenesis of eating disorders.

This research was supported by the Strategic Research Program for Brain Sciences (Project for Elucidation of Mechanisms of Psychiatric and Neurological Diseases) of the Japan Agency for Medical Research and Development (AMED), "Elucidation of Pathogenesis by Integration of Multi-Hierarchical Information in Schizophrenia and Autistic Spectrum Disorder," and the Strategic Promotion Program for Brain Science Research (Research on Overcoming Developmental Disorders and Schizophrenia), " Development of Diagnostic and Therapeutic Methods Based on the Results of Genome Analysis of Schizophrenia and Autism Spectrum Disorder," and "Research on Neural Circuitry and Molecular Pathogenesis Based on Genetic Variants in Psychiatric Disorders," funded by the Project for Elucidation of the Entire Functional Brain Network Using Innovative Technology. The research results will be published in Psychiatry and Clinical Neurosciences.

Research Background

Eating disorders are a group of disorders characterized by persistent disturbances in eating behavior that impair physical health and psychosocial functioning. Among them, anorexia

nervosa (AN) is found in about 1% of young women and patients with AN have a strong fear of weight gain, distorted body image, low body weight due to food restriction, and a high mortality rate (about 5% per 10 years). The pathogenesis of eating disorders is unknown, and there is currently no effective drug treatment. Epidemiological studies have suggested that genetic factors are strongly involved in the development of eating disorders and may partially overlap with genetic factors in other psychiatric disorders. Genomic copy number variations (CNVs), a subtype of genomic variation, are reported to be involved in the development of psychiatric disorders, including autism spectrum disorder and schizophrenia. Previous studies of eating disorders have found CNVs associated with risk of psychiatric disorders in a subset of patients. However, the association between eating disorders and CNVs has not yet been definitively determined, and it is unclear whether they are a risk for the development of the disorder.

Research Results

In this study, CNV analysis was performed in 70 patients with eating disorders and 1036 healthy subjects (all study subjects were Japanese women). Patients were diagnosed with severe eating disorders: anorexia nervosa or avoidant/restrictive food intake, with a minimum BMI of 15 or less. The genetic analysis was conducted using high-resolution array CGH, which is capable of detecting small CNVs. Since CNVs are known to be involved in the development of NDDs based on previous reports, we focused our investigation on such CNVs. As a result, NDD-associated CNVs were found in 10% (7/70) of patients with eating disorders and 2.3% (24/1036) of healthy controls. Statistical analysis confirmed that NDD-associated CNVs were significantly associated with the risk of eating disorders (odds ratio = 4.69, P = 0.0023). The CNVs found in patients included 45,X (Turner syndrome), KATNAL2 deletion, DIP2A deletion, PTPRT deletion, RBFOX1 deletion, CNTN4 deletion, MACROD2 deletion and FAM92B deletion. Among these, PTPRT, DIP2A, RBFOX1, and CNTN4 were reported to function at neuronal synapses. To further investigate the involvement of synaptic dysfunction, we performed gene set analysis. Patient CNVs were significantly enriched in the gene set associated with synaptic signaling (odds ratio = 2.55, P = 0.0254), suggesting that synaptic signaling may be involved in the pathogenesis.

Research Summary and Future Perspective

This study indicates that NDD-associated CNVs are involved in the development of eating disorders. Furthermore, the study revealed the involvement of synaptic dysfunction in the pathogenesis of eating disorders. Since the sample size of this study was relatively small (70 patients), it is necessary to confirm the reproducibility of the results in larger samples. Based on the CNVs found in patients, future analyses using patient-derived iPS cells and model animals are expected to advance our understanding of the pathophysiology of eating disorders from the viewpoint of synaptic dysfunction. These research results are also expected to contribute to the development of early diagnostic methods and new therapeutic agents for eating disorders.

Publication

Journal: Psychiatry and Clinical Neurosciences

Title: Contribution of copy number variations to the risk of severe eating disorders.

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DOI: 10.1111/pcn.13430

Japanese ver.

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