News Release

Title

Variable psychiatric manifestations in patients with 16p11.2 duplication:
A case series of four patients

Key Points

• This case series reported the detailed psychiatric phenotypes of four Japanese patients with 16p11.2 duplication.

• We revealed that the patients with 16p11.2 duplication show variable psychiatric manifestations in each patient.

•The results of this study are expected to lead to the establishment of a clinical treatment for 16p11.2 duplication and to the elucidation of the pathological mechanism.

Summary

Prof. Norio Ozaki, Dr. Itaru Kushima and Dr. Yu Hayashi (Department of Psychiatry, Nagoya University Graduate School of Medicine) and collaborators have retrospectively investigated the longitudinal clinical data of four psychiatric patients with 16p11.2 duplication（i.e. two schizophrenia (SCZ) and two autism spectrum disorder (ASD) patients）. As a result, the detailed longitudinal clinical data of these four patients showed a variety of psychiatric symptoms other than the main diagnosis, and the two SCZ patients were resistant to drug treatment.

Recent genomic studies have identified several genomic variants that are strongly associated with psychiatric disorders. One of them, the 16p11.2 duplication, are associated with SCZ, ASD, intellectual disability, and bipolar disorder, and is known as one of the cross-disorder risk variants. On the other hand, few studies have reported psychiatric phenotypes and responsiveness to medication in these patients.

Professor Norio Ozaki and his research group analyzed genomic copy number variants (CNVs) in the 16p11.2 region using the array comparative genomic hybridization (aCGH) in a previous study, and identified 16p11.2 duplication in two SCZ patients and two ASD patients. We retrospectively investigated the longitudinal clinical data of the four patients, and revealed that the 16p11.2 duplication may be associated with variable psychiatric manifestations within individual patients as well as across different patients.

The results of this study are expected to provide the insight to the diagnosis and understanding of the pathogenesis of 16p11.2 duplication.

Research Background

Genomic copy number variants (CNVs) are one type of genomic variant, and some rare CNVs are associated with the risk of psychiatric and neurodevelopmental disorders. One of them, the 16p11.2 duplication,

contains 20 to 30 genes in its duplicated region. Some of these genes (such as *MAPK3, KCTD13, and TAOK2*) are known to play important roles in neuronal development. Previous studies have revealed that 16p11.2 duplication was implicated in intellectual disability (ID), autism spectrum disorder (ASD), schizophrenia (SCZ), attention-deficit/hyperactivity disorder (ADHD), and bipolar disorder (BP). On the other hand, detailed psychiatric characteristics and treatment response of 16p11.2 duplication have not been fully investigated.

Research Results

We retrospectively investigated longitudinal clinical data of two SCZ cases (cases 1 and 2) and two ASD cases (cases 3 and 4) with 16p11.2 duplication from medical record, including developmental history, age at onset, psychiatric symptoms (including symptoms below the diagnostic threshold), duration of hospitalization, medications and their effectiveness, and results of brain imaging, laboratory tests, and cognitive tests.

As a result, case 1 showed symptoms of ASD and ADHD at an early age, and was also diagnosed with mild ID on intelligence test at the age of 6. At the age of 20, she developed SCZ and subsequently showed BP-related manic and depressive symptoms. She was judged to be treatment resistant to high dosese of antipsychotics and had a history of hospitalization for more than 15 years. Case 2 was also a treatment-resistant SCZ patient with a history of hospitalization for more than 30 years. Case 3, a girl diagnosed with ASD and ADHD, had hypersensitivity, and impulsivity from an early age, and had difficulty in social communication and interactions. Case 4 was also diagnosed with ASD and ADHD, and mild ID at a very young age, but later in her childhood, she developed delusions and manic symptoms.

Thus, psychiatric manifestations of patients with 16p11.2 duplication varied within and across patients. Other genomic variants except for the 16p11.2 duplication may be involved in the variable psychiatric manifestations, so we conducted whole genome sequencing analysis of the four cases, but could not identify any other pathogenic variants associated with ASD. As for two SCZ patients (cases 1 and 2) there was no improvement in symptoms even after high doses of antipsychotics (dopamine receptor inhibitors), suggesting an association between 16p11.2 duplication and treatment resistant SCZ.

Research Summary and Future Perspective

As aCGH was covered by health insurance in October 2021 in Japan, 16p11.2 duplication can now be examined in clinical setting. As a result, the number of reports of psychiatric patients with 16p11.2 duplication is expected to increase in the future, and further accumulation of detailed clinical data such as this case series will help clarify the detailed clinical history of patients with 16p11.2 duplication and establish evidence-based treatment methods.

Publication

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Yu Hayashi[1,¶], Itaru Kushima*[1,2,¶], Branko Aleksic[1], Tetsu Senaha[3], Norio Ozaki[1]

1 Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Japan

2 Medical Genomics Center, Nagoya University Hospital, Nagoya, Japan

3 Department of Psychiatry, KACHI Memorial Hospital, Toyohashi, Japan

¶These authors contributed equally to this work.

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