News Release

Title

Treatment-resistant schizophrenia in patients with 3q29 deletion: A case series of four patients

Key Points

- This case series reported the detailed psychiatric phenotypes of four Japanese schizophrenia patients with 3q29 deletion.
- We revealed that treatment-resistant schizophrenia (TRS) was a common characteristic among the four patients with 3q29 deletion and that clozapine, an antipsychotic for TRS, was effective.
- The results of this study are expected to lead to the establishment of a clinical treatment for patients with 3q29 deletion, the elucidation of the pathological mechanism of TRS, and the development of new therapeutic agents.

Summary

Prof. Norio Ozaki, Dr. Itaru Kushima and Dr. Yoshihiro Nawa (Department of Psychiatry, Nagoya University Graduate School of Medicine) and collaborators have retrospectively investigated the longitudinal clinical data of four Japanese schizophrenia (SCZ) patients with 3q29 deletion. As a result, we reported that treatment-resistant schizophrenia (TRS) was a common characteristic among the four patients with 3q29 deletion and that two of them responded to clozapine.

Recent genomic studies have identified several genomic variants that are strongly associated with psychiatric disorders. The 3q29 deletion is one of the strongest known risk factors for SCZ and has an increased risk of other psychiatric disorders including intellectual disability, autism spectrum disorder, and bipolar disorder. On the other hand, few studies have reported psychiatric phenotypes and responsiveness to medication in these patients.

Professor Norio Ozaki and his research group previously performed a genome-wide analysis of copy number variants (CNVs) using the array comparative genomic hybridization (aCGH), and identified 3q29 deletion in four SCZ patients. We retrospectively investigated the longitudinal clinical data of the four patients, and revealed that TRS was a common characteristic among the four patients with 3q29 deletion and that clozapine treatment was effective. The results of this study are expected to lead to the establishment of a clinical treatment for patients with 3q29 deletion and the elucidation of the pathological mechanism of TRS.

Research Background

Genomic copy number variants (CNVs) are one type of genomic variants, and rare CNVs at

several loci are associated with the risk of psychiatric and neurodevelopmental disorders. Among them, the 3q29 deletion is one of the strongest risk factors (odds ratio >40) for schizophrenia (SCZ) and is also associated with other psychiatric disorders including intellectual disability (ID), autism spectrum disorder (ASD), and bipolar disorder (BD). The canonical region affected by the 3q29 deletion contains ~22 genes, including *DLG1*, *PAK2*, and *FBXO45*. These three genes have been proposed as candidates for causing ID and psychiatric disorders, because they play putative roles in synaptic transmission. On the other hand, details of psychiatric manifestations and treatment responses have not been described in these patients.

Research Results

We retrospectively investigated the longitudinal clinical data of four Japanese SCZ patients with 3q29 deletion from medical records. The data included developmental history, family history, past medical history, social history, psychiatric symptoms, age at onset of schizophrenia, number and duration of hospitalizations, doses of antipsychotics, presence of treatment resistance, and results of brain magnetic resonance imaging (MRI), electroencephalography (EEG), intelligence tests and laboratory tests.

As a result, four SCZ patients showed resistance to high doses of antipsychotics (dopamine D2 receptor antagonists), and thus they were diagnosed with treatment-resistant schizophrenia (TRS). Two of them (Patient 3 and 4) were introduced to clozapine treatment, and both patients responded to the treatment. These findings suggest the potential usefulness of early introduction of clozapine for treatment of TRS patients with 3q29 deletion.

Depending on the developmental stage, patients with 3q29 deletion also showed variable psychiatric manifestations including ID, ASD, and BD. Patient 2 showed mild to moderate ID. Patient 2 and 3 showed autistic features, including hyperacusis or restricted, repetitive patterns of behavior and interests. All patients had manic symptoms such as elevated mood, irritability, agitation, or aggression, which required mood stabilizers such as valproate. Moreover, Brain MRI detected structural brain abnormalities such as reduced volume in cerebellum and a caudate nucleus defect in four patients. EEG test detected diffuse spike-and-wave discharges during photic stimulation in Patient 1 and 3.

Research Summary and Future Perspective

As array comparative genomic hybridization (aCGH) was covered by health insurance in October 2021 in Japan, 3q29 deletion can now be examined in clinical setting. As a result, the number of reports of patients with 3q29 deletion 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 3q29 deletion and establish evidence-based treatment methods. Moreover, our findings may suggest a potential link between 3q29 deletion and TRS and that neurobiological studies of 3q29 deletion may provide insight into the mechanism of TRS.

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