News Release

Title

Comprehensive analysis of a novel mouse model of the 22q11.2 deletion syndrome: A model with the most common 3.0-Mb deletion at the human 22q11.2 locus

Key Points

- We generated a genetically modified mouse that reproduces the 3.0-Mb (megabase) deletion seen in most patients with 22q11.2 deletion syndrome associated with the onset of various psychiatric disorders including schizophrenia.

- In the mice that replicated the 3.0-Mb deletion, some phenotypes associated with schizophrenia were observed, including reduced prepulse inhibition and abnormal visual evoked potentials.

- This model mouse is expected to be a useful model for elucidating the pathogenesis of psychiatric disorders associated with 22q11.2 deletion syndrome, such as schizophrenia.

Summary

Schizophrenia is a psychiatric disorder that develops from puberty to adolescence and has positive symptoms (e.g., delusions and hallucinations) and negative symptoms (e.g., flattening of emotions and decreased motivation). In addition, cognitive dysfunctions such as intelligence, memory, attention, and executive function are also occurred, which impairs daily life. Schizophrenia is a psychiatric disorder that frequently affects about 1 in 100 people, but the cause and mechanism involved in its onset have not yet been elucidated, and no treatment or diagnosis based on it has been established. Therefore, there is a need to generate a useful animal model that can be applied to elucidation of the onset mechanism and research on therapeutic development.

Here, Prof. Atsushi Aiba, Ryo Saito (Animal Resources Division, Center for Diseases and Biotechnology, Graduate School of Medicine, The University of Tokyo), Prof. Norio Ozaki (Psychiatry, Nagoya University), Itaru Kushima (Medical Genomics Center, Nagoya University Hospital) , Daisuke Mori (Brain and Mind Research Center, Nagoya University), Prof. Kiyofumi Yamada and Taku Nagai (Neuropsychopharmacology and Hospital Pharmacy, Nagoya University) were focused on 22q11.2 deletion syndrome, which is known to be strongly associated with psychiatric disorders including schizophrenia. Using genome editing

technology, we succeeded in generating the chromosome deletion [3.0-Mb (megabase) 22q11.2 deletion] that caused this syndrome in mice. A detailed analysis of this genetically modified mouse revealed a phenotype that was also observed in the patients, such as impaired prepulse inhibition and abnormal visual evoked potentials. This study has established a new schizophrenia model mouse that mimics the human chromosome microdeletion of 22q11.2. Further analysis of this model mouse would be expected to contribute to understanding the pathogenesis of schizophrenia and to developing therapeutic methods.

Research Background

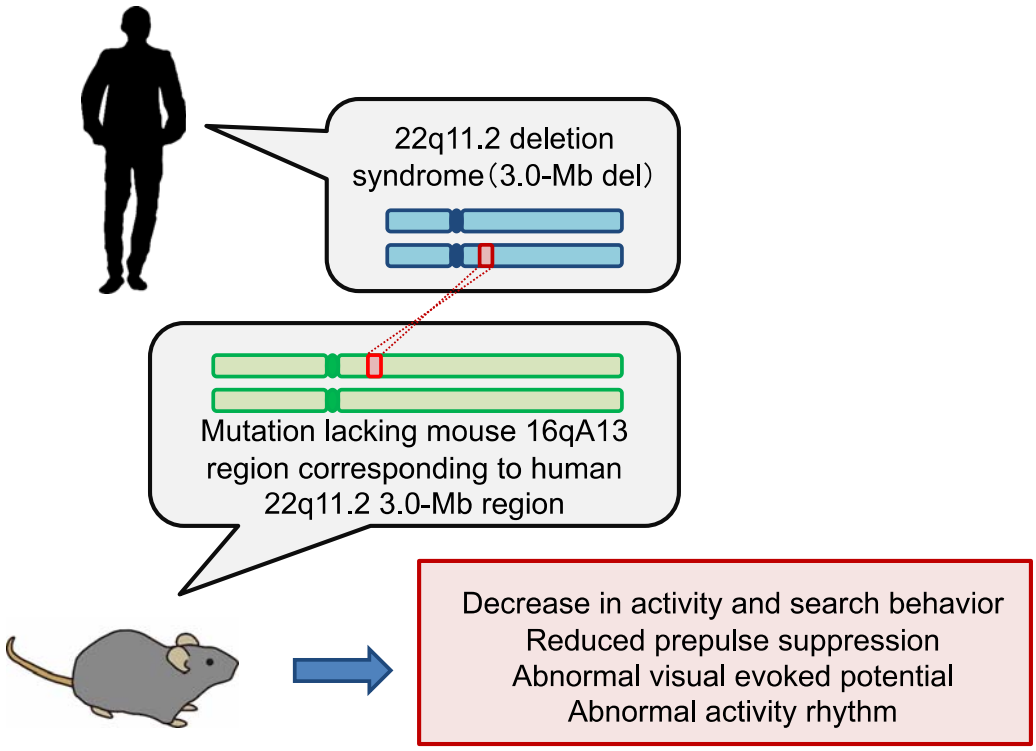
Schizophrenia is a psychiatric disorder that develops from puberty to adolescence and has positive symptoms (e.g., delusion and hallucination) and negative symptoms (e.g., flattening of emotions and decreased motivation). In addition, cognitive dysfunctions such as intelligence, memory, attention, and executive function are also recognized, which impairs social functions and daily life. The etiology and pathology of schizophrenia are still largely unknown, and treatments and diagnostics based on them have not been developed. Since schizophrenia patients are accumulated in the family and the heritability is as high as about 80%, the discovery of its genetic basis is thought to be important for elucidating the etiology and pathology of schizophrenia. In recent years, with the progress of genome analysis technology, a large number of genomic variants strongly associated with onset have been reported.

The 22q11.2 deletion syndrome is attracting attention as a genomic variant involved in the development of various psychiatric disorders, because patients frequently develop psychiatric disorders such as schizophrenia and intellectual disability. In particular, the risk of schizophrenia is the highest among single genetic risk factors known so far (odds ratio: 16.3–44.2), and is important in elucidating the mechanism of schizophrenia. In the 22q11.2 deletion syndrome, approximately 90% of patients have a specific 3.0-Mb (megabase = 1 million base pairs) deletion. In this region, there are 46 protein-coding genes, and these genes are conserved in the long arm A13 region of chromosome 16 in mice while maintaining a similar group. Therefore, it is possible to reproduce the deletion seen in the 22q11.2 deletion syndrome in mice, and several model mice have been generated by different research groups. However, the model mice generated so far could reproduce only the partial deletion of the 3.0-Mb region, and did not fully reproduce the patient's genetic predisposition.

Research Results

In this study, we performed genome editing using the CRISPR / Cas9 system to reproduce the deletion of the 3.0-Mb region in the 22q11.2 deletion syndrome in mice. As a result, we succeeded in producing and breeding mice that lack the target genomic region.
The genetically modified mice showed a high mortality rate, with 70.6% of the offspring dying within three weeks of birth.

Histological analysis was performed using embryos at 18.5 days to investigate the cause of the increase in mortality. Aortic arch transection (13.3%), right subclavian artery abnormalities (6.7%), thymic low A phenotype observed in patients with the 22q11.2 deletion syndrome, formation (46.7%), was observed. Next, we analyzed the behavior of mice that reproduced the 3.0-Mb deletion. As a result, in the open field test and the Y-shaped maze test, activity and exploratory behavior decreased. These results seemed to reflect negative symptoms in schizophrenia. In addition, a decrease in contact time with the novel mouse in the social interaction test and a decrease in memory ability in the fear conditioning memory learning test were observed. In addition, mice that replicated the 3.0-Mb deletion exhibited a schizophrenia-like phenotype with reduced prepulse inhibition and reduced visual evoked potential. Next, the circadian rhythm was measured to examine its association with sleep disorders, which are important clinical symptoms in various mental disorders. Analysis of daily activity rhythms in a constant dark environment showed that mice that reproduced the 3.0-Mb deletion showed different activity rhythms than wild-type mice. This suggested that the mice that reproduced the 3.0-Mb deletion may have an abnormal endogenous activity rhythm. In addition, we conducted a jet lag experiment to check whether the phase adjustment of the biological clock is performed normally. After breeding mice in a 12-hour light / dark cycle with a 12-hour light / dark cycle, the light-dark cycle was shifted by 8 hours to give a time difference, and it was measured how many days it took to eliminate jet lag. As a result, mice that reproduced the 3.0-Mb deletion resolved Jet-lag faster than wild-type mice when the 8-hour light-dark cycle was advanced.



Research Summary and Future Perspective

This genetically modified mice created in this study replicate the deletion of the most significant type of the 3.0-Mb region in the 22q11.2 deletion syndrome. The establishment of novel model mouse that more similar reproduces the genetic predisposition of human patients than previous model mice has elucidated the mechanism of the onset of mental disorders associated with 22q11.2 deletion syndrome, including schizophrenia. It is expected to lead to the development of treatment methods.

Publication

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