News Release

Title

Comparative analyses of copy number variation in autism spectrum disorder and schizophrenia

~Discovery of overlap of genetic risk variants and pathogenesis in the two psychiatric disorders~

Key Points

- We performed large-scale comparative analyses of copy number variation (CNV) in autism spectrum disorder (ASD) and schizophrenia (SCZ) in a Japanese population
- Pathogenic CNVs were identified in around 8% of both patient groups and their overlap was observed between the two disorders.
- Overlap of biological pathways was also confirmed between the two disorders.
- Patients with pathogenic CNVs have a higher prevalence of intellectual disability.
- Disease-relevant genes were identified in well-known ASD/SCZ-associated CNV loci (e.g., 22q11.2 and 3q29) using a bioinformatics approach.

Summary

Prof. Norio Ozaki (Department of Psychiatry) in Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, M.D., Ph.D.) and Itaru Kushima in Nagoya University Institute for Advanced Research (Director: Yoshiyuki Suto) and collaborators performed comparative analyses of copy number variation (CNV) in autism spectrum disorder (ASD) and schizophrenia (SCZ) in a Japanese population and found evidence for overlap of both genetic risk variants and pathogenesis between the two disorders.

In the present diagnostic criteria based on psychiatric symptoms, ASD and SCZ are defined as two distinct disorders. However, recent epidemiological studies suggested that there might be etiological overlap between them. Therefore, we examined CNV in patients with ASD or SCZ and controls (total samples >5500) and found that around 8% of both patient groups had known pathogenic CNVs. CNVs in 29 loci were common to both patient groups, confirming overlap of genetic risk variants. Phenotypic analysis revealed that patients with pathogenic CNVs have a higher prevalence of intellectual disability. Furthermore, we observed overlap of biological pathways involved in pathogenesis of these disorders, including oxidative stress response, genomic integrity, and lipid metabolism. Finally, we identified multiple disease-relevant genes in well-known ASD/SCZ-associated CNV loci (e.g., 22q11.2 and 3q29).

These findings should be useful for development of novel diagnostics and therapeutics, as well as elucidation of pathophysiology of these disorders. In addition, the finding of etiological overlap between ASD and SCZ may influence the diagnostic concept of these disorders. This work was published online in Cell Reports on September 11, 2018.

Research Background

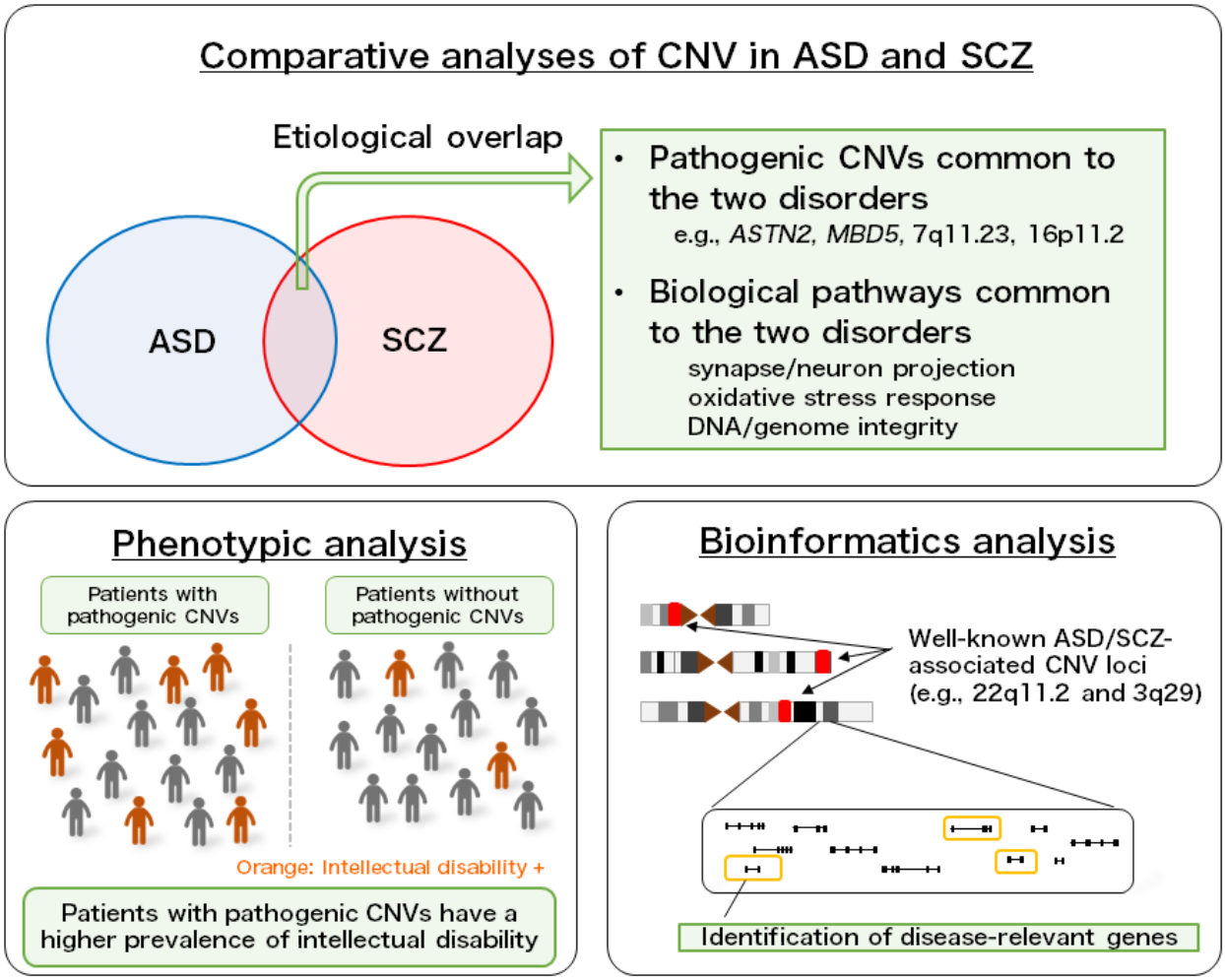
In the present diagnostic criteria (DSM-5) based on psychiatric symptoms, ASD and SCZ are defined as two clinically distinct disorders. However, recent epidemiological studies suggested that there might be etiological overlap between the two disorders. Molecular genetic studies on Caucasian populations also identified multiple pathogenic CNVs associated with the risk for both ASD and SCZ. However, genetic studies on other populations including a Japanese population are lacking, and few studies have directly compared CNVs between ASD and SCZ. Thus, direct comparative analyses of CNVs in a Japanese population are crucial to clarify the relationship of the two disorders and the pathophysiology of these disorders.

Research Results

Using array comparative genomic hybridization, we performed genome-wide analyses of CNVs in Japanese patients with ASD or SCZ and controls (total samples >5500). As a result, we found that around 8% of both patient groups had known pathogenic CNVs associated with the risk for developmental or psychiatric disorders. These CNVs were widely distributed in the human genome and those in 29 loci (*ASTN2*, *MBD,* 7q11.23, 16p11.2) were common to both patient groups, confirming overlap of genetic risk factors. For individual CNVs, we obtained evidence for significant associations between 1) 22q11.2 duplication and ASD, and 2) 22q11.2 deletion, 1q21.1 deletion, 47,XXY/47,XXX and SCZ. We also identified novel pathogenic CNVs in 12 genes. Phenotypic analysis revealed that patients with pathogenic CNVs have a higher prevalence of intellectual disability.

Next, we examined which biological pathways were preferentially affected by patient CNVs. Gene set analysis based on the CNV dataset identified multiple biological pathways relevant to the pathogenesis of each disorder. We found evidence for overlap of pathogenesis between them, such as synapse, small GTPase signaling, gene expression regulation, oxidative stress response, genomic integrity, and lipid metabolism. Finally, we set out to identify disease-relevant genes in eight well-known ASD/SCZ-associated CNVs (e.g., 22q11.2 deletion, 3q29 deletion). These CNVs are large (>500 kb) and include many genes, preventing identification of responsible genes for the disorders. We performed bioinformatics analysis based on the findings of biological pathways, identified multiple disease-relevant genes in these CNVs.

These findings should be useful for development of novel diagnostics and therapeutics, as well as elucidation of pathophysiology of these disorders. In addition, the finding of etiological overlap between ASD and SCZ may influence the diagnostic concept of these disorders.



Research Summary and Future Perspective

The present study suggests etiological overlap of ASD and SCZ and provides novel insights into the pathogenesis of these disorders. The results will be applied to genomic medicine including diagnosis and treatment of patients. In fact, such efforts have already begun in patients with 22q11.2 deletion, the most important genetic factor for SCZ. In the near future, more studies will be conducted using iPSCs derived from patients with pathogenic CNVs. The establishment and analysis of animal model based on pathogenic CNVs will also become more popular. Studies using iPSCs and model animals will contribute to the elucidation of molecular network and neuronal circuit dysfunction relevant to psychiatric disorders. Finally, as how the same CNVs produce different psychiatric disorders remain unknown, more studies on this point are also required.

Publication

Comparative Analyses of Copy Number Variation in Autism Spectrum Disorder and Schizophrenia Reveal Etiological Overlap and Biological Insights
Cell Reports, in press (published online on September 11, 2018)
DOI: 10.1016/j.celrep.2018.08.022

Itaru Kushima M.D.[1,2], Branko Aleksic M.D.[1], Masahiro Nakatochi Ph.D.[3], Teppei Shimamura Ph.D.[4], Takashi Okada M.D.[1], Yota Uno M.D.[1,5], Mako Morikawa M.D.[1], Kanako Ishizuka M.D.[1], Tomoko Shiino Ph.D.[1,45], Hiroki Kimura M.D.[1], Yuko Arioka Ph.D.[1,2,6], Akira Yoshimi Ph.D.[7], Yuto Takasaki M.D.[1], Yanjie Yu M.D.[1], Yukako Nakamura Ph.D.[1], Maeri Yamamoto M.D.[1], Tetsuya Iidaka M.D.[8], Shuji Iritani M.D.[1], Toshiya Inada M.D.[9], Nanayo Ogawa M.A.[1], Emiko Shishido Ph.D.[1], Youta Torii M.D.[1,10], Naoko Kawano Ph.D.[1,11], Yutaka Omura M.D.[12], Toru Yoshikawa M.D.[13], Tokio Uchiyama M.D.[14], Toshimichi Yamamoto Ph.D.[15], Masashi Ikeda M.D.[16], Ryota Hashimoto M.D.[17,18,45], Hidenaga Yamamori M.D.[18], Yuka Yasuda M.D.[18], Toshiyuki Someya M.D.[19], Yuichiro Watanabe M.D.[19], Jun Egawa M.D.[19], Ayako Nunokawa M.D.[19], Masanari Itokawa M.D.[20], Makoto Arai Ph.D.[21], Mitsuhiro Miyashita M.D.[21], Akiko Kobori Ph.D.[21], Michio Suzuki M.D.[22], Tsutomu Takahashi M.D.[22], Masahide Usami M.D.[23], Masaki Kodaira M.D.[23], Kyota Watanabe M.D.[23], Tsukasa Sasaki M.D.[24], Hitoshi Kuwabara M.D.[25], Mamoru Tochigi M.D.[26], Fumichika Nishimura M.D.[27], Hidenori Yamasue M.D.[28], Yosuke Eriguchi M.D.[29], Seico Benner Ph.D.[29], Masaki Kojima M.D.[29], Walid Yassin MMedSc[29], Toshio Munesue M.D.[30], Shigeru Yokoyama M.D.[30], Ryo Kimura M.D.[31], Yasuko Funabiki M.D.[32], Hirotaka Kosaka M.D.[33,34], Makoto Ishitobi M.D.[34,35], Tetsuro Ohmori M.D.[36], Shusuke Numata M.D.[36], Takeo Yoshikawa M.D.[37], Tomoko Toyota M.D.[37], Kazuhiro Yamakawa Ph.D.[38], Toshimitsu Suzuki Ph.D.[38], Yushi Inoue M.D.[39], Kentaro Nakaoka M.D.[12], Yu-ichi Goto M.D.[40], Masumi Inagaki M.D.[41], Naoki Hashimoto M.D.[42], Ichiro Kusumi M.D.[42], Shuraku Son M.D.[43], Toshiya Murai M.D.[43], Tempei Ikegame M.D.[27], Naohiro Okada M.D.[27], Kiyoto Kasai M.D.[27,46], Shohko Kunimoto Ph.D.[1], Daisuke Mori Ph.D.[1,44], Nakao Iwata M.D.[16], Norio Ozaki M.D.[1,47,*]

1. Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Aichi, 466-8550, Japan
2. Institute for Advanced Research, Nagoya University, Nagoya, Aichi, 464−8601, Japan
3. Division of Data Science, Data Coordinating Center, Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Aichi, 466-8560, Japan
4. Division of Systems Biology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, 466-8550, Japan
5. Laboratory for Psychiatric and Molecular Neuroscience, McLean Hospital, Belmont, Massachusetts, 02478, USA
6. Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Aichi, 466-8560, Japan
7. Division of Clinical Sciences and Neuropsychopharmacology, Faculty and Graduate School of Pharmacy, Meijo University, Nagoya, Aichi, 468-8503, Japan
8. Department of Physical and Occupational Therapy, Nagoya University Graduate School of Medicine, Nagoya, Aichi, 461-8673, Japan
9. Department of Psychiatry and Psychobiology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, 466-8550, Japan
10. Center for Postgraduate Clinical Training and Career Development, Nagoya University Hospital, Nagoya, Aichi, 466-8560, Japan
11. Institutes of Innovation for Future Society, Nagoya University, Nagoya, Aichi, 464-8601, Japan
12. Aichi Psychiatric Medical Center, Nagoya, Aichi, 464-0031, Japan
13. Department of Child Psychiatry, Aichi Prefectural Colony Central Hospital, Kasugai, Aichi, 480-0392, Japan
14. Department of Clinical Psychology, Taisho University, Tokyo, 170-8470, Japan
15. Department of Legal Medicine and Bioethics, Nagoya University Graduate School of Medicine, Nagoya, Aichi, 466-8550, Japan
16. Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, 470-1192, Japan
17. Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Suita, Osaka, 565-0871, Japan
18. Department of Psychiatry, Osaka University Graduate School of Medicine, Suita, Osaka, 565-0871, Japan
19. Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Niigata, 951-8510, Japan
20. Center for Medical Cooperation, Tokyo Metropolitan Institute of Medical Science, Tokyo, 156-8506, Japan
21. Department of Psychiatry and Behavioral Sciences, Tokyo Metropolitan Institute of Medical Science, Tokyo, 156-8506, Japan
22. Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, 930-0194, Japan
23. Department of Child and Adolescent Psychiatry, Kohnodai Hospital, National Center for Global Health and Medicine, Ichikawa, Chiba, 272-8516, Japan
24. Department of Physical and Health Education, Graduate School of Education, The University of Tokyo, Tokyo, 113-0033, Japan

25. Research Center for Child Mental Development, Hamamatsu University School of Medicine, Hamamatsu, 431-3192, Japan
26. Department of Neuropsychiatry, Teikyo University School of Medicine, Tokyo, 173-8605, Japan
27. Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, 113-8655, Japan
28. Department of Psychiatry, Hamamatsu University School of Medicine, Hamamatsu, 431-3192, Japan
29. Department of Child Neuropsychiatry, School of Medicine, The University of Tokyo, Tokyo, 113-8655, Japan
30. Research Center for Child Mental Development, Kanazawa University, Kanazawa, Ishikawa, 920-8640, Japan
31. Department of Anatomy and Developmental Biology, Graduate School of Medicine, Kyoto University, Kyoto, 606-8501, Japan
32. Department of Cognitive and Behavioral Science, Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, 606-8501, Japan
33. Research Center for Child Mental Development University of Fukui, Eiheiji, Fukui, 910-1193, Japan
34. Department of Neuropsychiatry, Faculty of Medical Sciences, University of Fukui, Eiheiji, Fukui, 910-1193, Japan
35. Department of Child and Adolescent Mental Health, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, 187-8551, Japan
36. Department of Psychiatry, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, 770-8503, Japan
37. Laboratory for Molecular Psychiatry, RIKEN Center for Brain Science, Wako, Saitama, 351-0198, Japan
38. Laboratory for Neurogenetics, RIKEN Center for Brain Science, Wako, Saitama, 351-0198, Japan
39. National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorder, Shizuoka, 420-8688, Japan
40. Department of Mental Retardation and Birth Defect Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo, 187-8502, Japan
41. Department of Developmental Disorders, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, 187-8553, Japan
42. Department of Psychiatry, Hokkaido University Graduate School of Medicine, Hokkaido, Sapporo, 060-8638, Japan
43. Department of Psychiatry, Graduate School of Medicine, Kyoto University, Kyoto, 606-8507, Japan
44. Brain and Mind Research Center, Nagoya University, Nagoya, Aichi, 466-8550, Japan
45. Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, 187-8553, Japan
46. The International Research Center for Neurointelligence (WPI-IRCN) at The University of Tokyo Institutes for Advanced Study (UTIAS), Tokyo, 113-0033, Japan

Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Cell_R_20180912.pdf