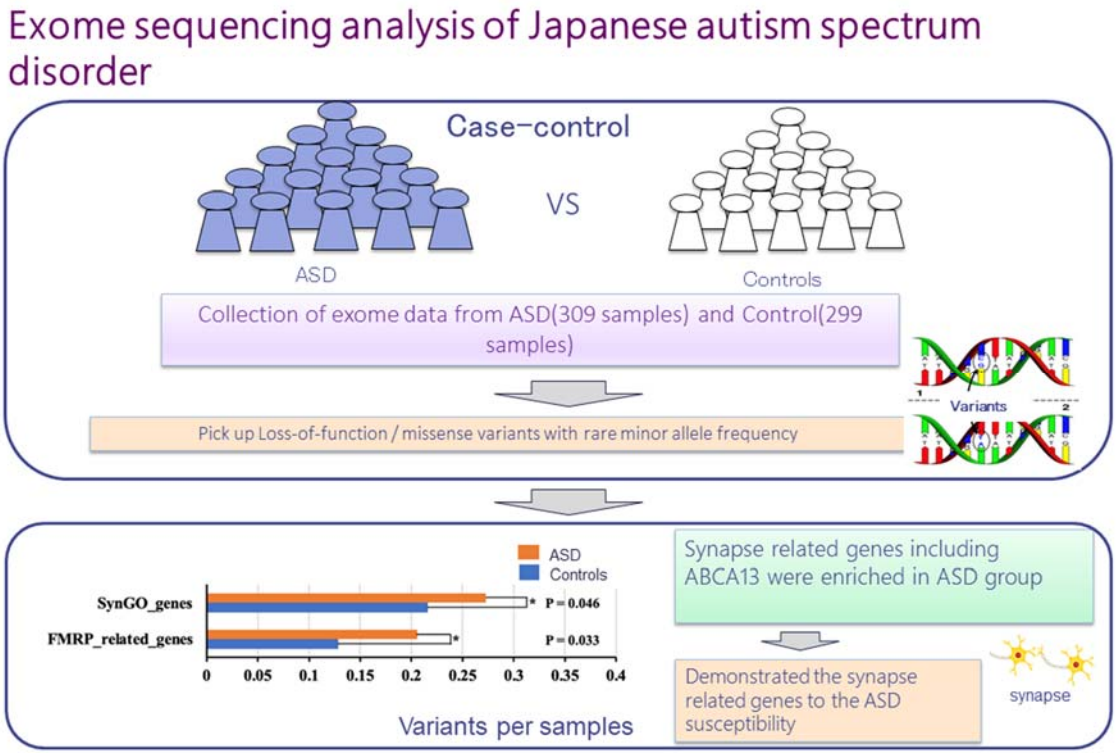
News Release

Title: Exome sequencing analysis of Japanese autism spectrum disorder case-control sample supports an increased burden of synaptic function–related genes



Key Points

- In whole exomes from a Japanese ASD sample of 309 cases and 299 controls, rare variants were associated with ASD within genes involved in synaptic function, with the strongest enrichment in trans-synaptic signaling.
- We strengthen the evidence regarding the role of *ABCA13*, a synaptic function–related gene, in Japanese ASD and ADHD.
- This study demonstrated the clinical utility of exome sequencing analysis for patients with ASD.

Summary:

Prof. Norio Ozaki and Dr. Hiroki Kimura (Department of Psychiatry, Nagoya University Graduate School of Medicine) and collaborators have reported the result of exome sequencing analysis with Japanese Autism spectrum disorder (ASD) samples.

ASD is a highly heritable, complex disorder in which rare variants contribute significantly to disease risk. Although many genes have been associated with ASD, there have been few genetic studies of ASD in the Japanese population. In whole exomes from a Japanese ASD sample of 309 cases and 299 controls, rare variants were associated with ASD within specific neurodevelopmental gene sets, including highly constrained genes, fragile X mental retardation protein target genes, and genes involved in synaptic function, with the strongest enrichment in trans-synaptic signaling ($p = 4.4 \times 10^{-4}$, Q-value = 0.06). In particular, we strengthen the evidence regarding the role of *ABCA13*, a synaptic function–related gene, in Japanese ASD. The overall results of this case-control exome study showed that rare variants related to synaptic function are associated with ASD susceptibility in the Japanese population.

Research Background:

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interactions and repetitive behaviors manifesting in early childhood. ASD is highly heterogeneous, with an estimated heritability as high as 80%. Recent large-scale genetic analyses have revealed that rare (minor allele frequency < 1%) variants in which the major contributors are rare single-nucleotide variants (SNVs) that disrupt gene function or rare copy number variations (CNVs) detected by whole-genome/-exome sequencing (WGS/WES) could have large effect sizes. Much of the gene discovery in ASD research in sequencing studies has focused on *de novo* variants and rare inherited variants discovered through family analyses. However, one of the limitations of family studies is the small sample size resulting from limited access to family samples. Therefore, more recent research has also focused on case-control studies with larger sample sizes than family studies, and these analyses have demonstrated that rare variants prioritized by effect on protein function and frequency in public databases are enriched in various neurodevelopmental disorders. However, these findings have primarily been derived from samples of European ancestry. There are no ASD case-control WES analyses focusing on the Japanese ASD population. By performing a case-control study, we could capture a broader range of rare variants, including rare inherited variants and *de novo* rare variants, compared with a previous study of rare *de novo* variants in trios. Therefore, in this study, we performed a Japanese ASD case-control WES analysis to identify genes or genes sets associated with Japanese ASD pathobiology to facilitate the identification of novel drug targets.

Research Results:

After filtering WES data based on sample and genotype quality, we performed a rare variant burden analysis with prioritized rare variants from 301 ASD patients and 296 HCs. LoF variants in genes with a pLI score > 0.5 were significantly enriched in ASD patients (P-value = 0.0023). LoF variants in genes with pLI > 0.9 (P-value = 0.07), D-Mis variants (P-value = 0.068), and D-Mis + LGD variants (P-value = 0.056) were not significant, but the same tendency as the LoF variants in genes with pLI > 0.5. In addition to comparing the overall number of LoF and D-Mis variants, we performed a gene set burden analysis to elucidate the pathophysiology of ASD with four publicly available sets of genes that have been implicated in ASD susceptibility. We demonstrated that LoF variants in FMRP target genes and genes registered in SynGO were significantly enriched in the ASD samples. Furthermore, LoF + D-Mis variants in genes registered in SynGO were also enriched in the ASD. Additionally, we performed a genome-wide gene-based burden test with LoF and D-Mis variants to identify genes potentially related to susceptibility in ASD patients. Genes showing a nominally significant association are described in Tables S4 and S5. Although no genes reached statistical significance following multiple testing correction, we found a nominally significant association (P = 0.043) with ASD for LoF variants in *ABCA13*, which is known to be related to synaptic vesicle endocytosis and reported as an ASD candidate gene in the SFARI database.

Research Summary and Future Perspective:

This study, involving the largest case-control WES analysis of Japanese ASD patients, demonstrated that ASD candidate rare variants are primarily involved in synaptic function. In particular, we strengthen the evidence regarding the role of *ABCA13*, a synaptic function–related gene, in Japanese ASD pathobiology. In future studies, it would be useful to expand the sample size by aggregating WGS/WES data through collaborations within Japan to characterize Japanese ASD–specific pathophysiology. Furthermore, combined analyses also involving non-Japanese samples would be useful as a means of evaluating the trans-ethnic generalizability of our results.

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