Symposium | Schizophrenia：[Symposium 56] Current status of psychiatric research using genetic medicine and genomic medicineImportance of collaborative research among East Asians

Sat. Sep 27, 2025 9:00 AM - 10:30 AM JST | Sat. Sep 27, 2025 12:00 AM - 1:30 AM UTC Session Room 3 (Large Hall A)

[Symposium 56] Current status of psychiatric research using genetic medicine and genomic medicineImportance of collaborative research among East Asians

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[SY-56-03] Contribution of common and rare variants to schizophrenia risk in East and South Asian ancestries

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Keywords：Schizophrenia、Genetics、Sequencing

Schizophrenia genetic studies have primarily focused on European ancestries, leaving variants in other populations underexplored and potentially increasing health disparities. Here, we report initial findings from the first large-scale schizophrenia sequencing study examining both common and rare variants in East and South Asian populations (EAS and SAS), using the Blended Genome Exome (BGE), a technology combining low-pass whole-genome and deep whole-exome sequencing.

We ascertained 98,739 East Asian (cases: 45,925, controls: 52,814) and 17,697 South Asian individuals (cases: 8,843, controls: 8,854), and conducted genotyping, WES, and BGE. We also incorporated European (EUR) cohorts (cases: 53,386, controls: 77,258), achieving a total sample size of 247,080. In GWAS, we identified 41 schizophrenia-associated loci in EAS—a 5x increase over the largest previous EAS study. In SAS, we found 7 genome-wide significant loci, marking the first large-scale GWAS in this population. We observed high genetic correlations across the three populations: 0.86-1.08. A multi-ancestry meta-analysis across EUR, EAS, and SAS revealed 461 loci significantly associated with schizophrenia, 131 of which are novel, with SNP-based heritability of 23%.

For RVAS, we identified 12 exome-wide significant genes (29 at FDR 5%), including four novel genes. Schizophrenia RVAS signals were significantly enriched in schizophrenia GWAS loci compared to loci for a non-psychiatric trait. By integrating both common and rare variants, we prioritized genes strongly associated with schizophrenia, such as SCAF1, FYN, and KLC1.

This study provides, for the first time, insights into the genetic architecture in the SAS population and the integrative contribution of both common and rare variants to schizophrenia in three major populations. These novel findings will enable future investigations and uncover the pathogenesis of schizophrenia, ultimately contributing to the reduction of its disease across ancestries.