Poster

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Poster 33

[P-33-05] Investigation on Genetic Differences under Clinical Subtypes of Schizophrenia

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Clinical heterogeneity in schizophrenia (SZ) poses a significant challenge to genetic research, as varying symptoms may be linked to different genetic susceptibilities. This study aims to investigate the genetic heterogeneity underlying clinically defined SZ subtypes. We first classified 2899 SZ patients into three stable clinical subtypes using unsupervised cluster analysis based on their symptom profiles: Cluster-L (low symptom severity), Cluster-S (severe symptom severity), and Cluster-N (predominant negative symptoms). The reproducibility of the classification was also confirmed in another datasets. The network comparison test identified significant differences in symptom structures among three subtypes. Then, subtypes-based genome-wide association studies (GWAS) were applied to identify subtypes-specific risk loci. Notably, a risk locus, rs3767295, within the *CNTN2* gene, which reached genome-wide significance specifically in Cluster-N (P_{meta}=1.5x10^{-08}, OR=0.65). Gene-based analysis further revealed several risk genes unique to individual subtypes. Additionally, we observed subtype-specific patterns in pathway-specific polygenic risk scores (pPRS) and cell type-specific PRS (ctPRS). For instance, the pPRS for ‘regulation of neuron differentiation’ and ctPRS for ‘Oligodendrocyte precursor cells’ were significantly elevated only in Cluster-N when compared to healthy controls. Our results highlight the utility of patient stratification in enhancing statistical power to uncover subtype-specific risk loci and demonstrate that SZ patients with distinct symptom profiles display varying genetic liability involving different biological pathway and cell types.