Novel Schizophrenia Susceptibility Loci Uncovered Through Genome-Wide Association Study

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NEW YORK (GenomeWeb) – Researchers have uncovered 30 novel susceptibility loci for schizophrenia in an analysis of genome-wide association studies of cohorts of Chinese and European individuals.

Some 110 loci have previously been linked to schizophrenia risk, but those studies were conducted primarily using people of European descent and whether these loci also conferred disease risk in other populations hasn't been clear.

Researchers led by Yongyong Shi from Qingdao University in China conducted a GWAS that drew upon nearly 36,180 people of Chinese ancestry to search for disease risk loci. As they reported today in *Nature Genetics*, they also conducted transancestry meta-analyses using data collected by the Psychiatry Genomics Consortium to uncover more than two dozen novel schizophrenia susceptibility loci. They also found that a portion of the risk loci, though not all, were common to both cohorts, and homed in on candidate genes.

"[O]ur comprehensive analyses provide further biological insights into the etiology of schizophrenia, thus potentially facilitating further mechanistic studies to assess the pathogenesis of this complex disorder," the authors wrote in their paper.

Shi and his colleagues performed a GWAS using 7,699 schizophrenia cases and 18,327 controls of Chinese ancestry. The individuals had been genotyped using either Affymetrix or Illumina arrays that were imputed to 1000 Genomes Project data. In this dataset, they examined more than 5.1 million genetic variants.

They combined this Chinese dataset with 35,476 schizophrenia cases and 46,839 controls from the PGC2 dataset. In their combined analysis, they found 5,618 SNPs that mapped to 104 loci that were associated with schizophrenia.

The researchers then conducted meta-analyses using a replication cohort of 4,384 schizophrenia cases and 5,770 controls of Chinese ancestry. When they combined the Chinese GWAS and replication datasets, they found seven loci with genome-wide significance for association with schizophrenia, four of which were novel.

Likewise, in a meta-analysis of the Chinese GWAS and replication datasets and the PGC2 dataset, the researchers uncovered 109 loci of genome-wide significance, 26 of which were novel.

All together, the SNPs the researchers uncovered mapped to 113 distinct loci. Of these, four loci only reached genome-wide significance in the Chinese population, 106 in the transancestry analysis, and three in both analyses.

Some loci that were significant among the PGC2 dataset were overrepresented in the Chinese dataset. This indicated to the researchers that schizophrenia susceptibility loci uncovered in a European population could be applicable to a Chinese population.

The researchers also fine-mapped and functionally analyzed the susceptibility loci to home in on candidate genes. They focused in on genes previously linked to schizophrenia like FYN and MAGI2, but also new ones like EMX1 and BNIP3L that had multiple lines of evidence — such as being in high linkage disequilibrium with the index SNP and containing a missense mutation or being a *cis*-eQTL for the index SNP — supporting their possible role in schizophrenia.

Pathway analyses further indicated roles for known contributors to schizophrenia pathogenesis like the voltage-gated calcium-channel pathway and postsynaptic density and a novel pathway, regulation of insulin secretion by glucagon-like peptide 1. While that pathway hasn't before been linked to schizophrenia, the researchers noted that other studies have found a possible tie between insulin signaling and schizophrenia and that people with schizophrenia have a higher prevalence of metabolic syndrome.

"Our results provide several lines of evidence supporting candidate genes at many loci and highlight some pathways for further research," the researchers wrote. "Together, our findings provide novel insight into the genetic architecture and biological etiology of schizophrenia."

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