GENETICS

Predicting brain-disorder risk genes

H-MAGMA leverages chromatin interaction data to interpret GWAS results for brain disorders.

Genome-wide association study (GWAS) has become a standard tool for identifying DNA variation underlying complex diseases and traits. "Thanks to the large consortia such as PGC, iPSYCH and UKBB, we now live in the era of GWAS of almost every human trait you can think of," says Hyejung Won, who studies genetics of neuropsychiatric disorders at the University of North Carolina. Despite its statistical power, careful annotation and interpretation are needed to elucidate the functional roles of GWAS hits. Various methods have been proposed for this purpose, but it remains a challenging endeavor. For example, MAGMA, a widely adopted tool, assigns single nucleotide polymorphisms (SNPs) to genes using a linear genome that lacks biological context, as noted by Won. "It came to the point that we obtained well-powered GWAS for a number of brain disorders. However, it is unclear how to distill biological mechanism from the growing list of genetic variants associated with brain disorders."

To bridge the gap between GWAS findings and biological insights, Won and colleagues developed Hi-C-coupled MAGMA (H-MAGMA), a platform that advances MAGMA by integrating chromatin interaction profiles generated by Hi-C experiments for inferring gene–SNP relationships. Although similar ideas underlie conventional Hi-C mapping, "because this approach only focuses on genome-wide significant loci, we simply miss subthreshold signals that explain a significant proportion of heritability. In addition, this approach has been highly sensitive to the fine-mapping tool," says Won. Instead, H-MAGMA takes a whole-genome approach by using the predicted gene–SNP pairs as input for MAGMA and obtaining gene-level association statistics. This is a particularly appealing strategy for low-powered GWAS where conventional Hi-C mapping might be too stringent.

Won and colleagues applied H-MAGMA to analyze the genetic basis of five psychiatric disorders (attention-deficit/hyperactivity disorder, autism spectrum disorder, schizophrenia, bipolar disorder and major depressive disorder) and four neurodegenerative disorders (amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease and Parkinson's disease), using human Hi-C datasets from the developing cortex and the adult dorsolateral prefrontal cortex. The experimental design led to intriguing observations on the similarities and differences in genetic architecture between brain disorders, as well as their characteristics in different developmental epochs and brain cell types. Further aided by published gene expression data, they found aging-related processes to be associated with multiple degenerative disorders, and genes associated with degenerative disorders gradually increased across a lifespan. "This may provide a reason why our risk of developing these disorders increases upon aging," notes Won. "Another intriguing finding was that amyloid-β and tau, two neurotoxic proteins implicated in Alzheimer's disease, were also associated in other degenerative disorders, suggesting that they may have a broader impact in neurodegeneration." The researchers also identified pleiotropic genes that are associated with multiple brain disorders. Further functional analysis helped to suggest mechanisms for their broad impact.

Won envisions a number of directions worth future exploration. "We would like to extend the frameworks to include more brain cell types (e.g., microglia, oligodendrocytes), given their role in degenerative disorder is emerging. We are also in the process of adding other functional genomic datasets including H3K27ac and ATAC-seq, which may help further refine the gene list." To those who are interested in trying H-MAGMA, "we hope to extend H-MAGMA to other tissue types, so that H-MAGMA can be applied to non-brain GWAS as well."

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