In genetics, context matters

Understanding how to biologically interpret the loci identified in genome-wide association studies is a major goal of current genetics research. To achieve this goal, we need to understand where, when and how relevant genes are expressed in specific contexts, in order to explore the mechanistic links between genetic associations and diseases or complex traits.

Over approximately the past 15 years, the genome-wide association study (GWAS) approach has become a core method in the genetics field for understanding complex traits and diseases. Thousands of such studies have been published, and the list of loci associated with various phenotypes continues to grow. These statistical associations are a good starting point for understanding biological mechanisms. However, identifying causal variants as well as causal genes presents considerable challenges. To reap the maximum benefits from GWAS, an exciting current (and future) direction in genetics research is post-GWAS analyses that resolve genetic associations in terms of cell type, stimulation condition, cell state or developmental timing.

Most GWAS hits are found in non-coding regions, and presumably these variants affect the expression of genes that have biological relevance for the trait of interest. Linking non-coding GWAS SNPs to the correct gene requires the proper regulatory context and gene expression landscape. Two studies published in this issue from the Trynka and Pritchard groups use RNA-seq and/or ATAC-seq to profile different immune cells at various stages of development or stimulation. The authors look for enrichment of chromatin accessibility in different cell contexts to determine activity and then integrate GWAS variants for autoimmune or inflammatory diseases. Analyzing the variants with this greater context specificity and resolution provides insights into disease development and helps to identify critical transitions or functions that might be potential targets for therapy.

Another approach that can be used to link GWAS variants to relevant genes is examining the three-dimensional interactions between chromosomal regions, reflecting potential enhancer–promoter associations. Also in this issue is a study from the Ren group that presents maps of long-range chromatin interactions in 27 human cell types and tissues. The authors analyze almost 19,000 promoter regions and infer target genes for more than 70,000 regulatory elements. Through integration of chromatin interaction information together with genome-wide-significant loci from the GWAS catalog, the authors were able to assign target genes for more than 27,325 GWAS SNPs and provide experimental validation for a few of these variants. Thus, understanding the three-dimensional genomic context of candidate disease loci can help prioritize target genes for further analysis or validation.

Although cell type, cell state and chromatin context clearly influence which genes are assigned as being functionally relevant for a particular trait, genetic context in the classic sense—that is, genetic background or genetic interactions—should also not be overlooked. An interesting study from the Brennand group presents a notable example of non-additive genetic interaction. In this case, the authors use isogenic human induced pluripotent stem cells to analyze schizophrenia-associated variants prioritized on the basis of colocalization with brain expression quantitative trait loci, ultimately focusing on five loci. The authors not only identify cell-type-specific effects of these common variants but also, through combinatorial perturbations, show the existence of synergistic downstream effects on both rare and common risk variant genes. These findings underscore the polygenic nature of schizophrenia and serve as an example of non-additive genetic interactions that have potential implications for understanding disease.

This month, the American Society for Human Genetics will host their annual meeting in Houston, Texas, USA. We hope that there will be some excellent GWAS presented. We also hope that there will be many studies analyzing the GWAS loci that have been identified in comprehensive and context-specific ways, by examining specific cell types in specific chromatin conformations or together with other variants. We believe that, rather than being in the post-GWAS era, genetics is instead right in the middle of an exciting, integrative time when new data, ideas and approaches are being used to enhance mechanistic understanding of what the genetics is telling us about disease. ❐

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