Neuropsychopharmacology

HOT TOPICS

Chromatin architecture provides a roadmap to improve our understanding of psychiatric disorders

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Neuropsychopharmacology (2021) 46:234–235; https://doi.org/10.1038/s41386-020-00822-5

Genome-wide association studies (GWAS) successfully identified hundreds of genomic risk loci that are associated with psychiatric disorders, whereas translating these genetic findings to interpretable biological principles has been a significant challenge. For example, because GWAS-identified common variants are often co-inherited with the nearby variants due to the structure called linkage disequilibrium (LD), GWAS do not provide a single causal variant, but a genomic region that contains up to several hundred variants. Moreover, roughly 90% of genetic risk factors identified by GWAS reside in the non-coding genome [1]. While the common practice is to link these risk factors to nearest genes, accumulating evidence points to the fact that these risk factors can regulate distal genes via distal enhancer–promoter interactions [2, 3]. Therefore, an imperative goal is to establish a computational framework that functionally annotates GWAS risk variants based on (distal) gene regulatory interactions while controlling for LD.

Multi-marker Analysis of GenoMic Annotation (MAGMA) is one of the most widely used tools that convert SNP associations into gene-level associations while taking LD into account [4]. However, it annotates SNPs to the nearest genes and ignores pivotal gene regulatory landscape. Given that disease risk variants can regulate distal genes via tissue-specific enhancer–promoter interaction, we developed Hi-C coupled MAGMA (H-MAGMA) that assigns non-coding SNPs to their regulatory targets based on chromatin interaction profiles from the human brain tissue [5].

We applied H-MAGMA to psychiatric disorder GWAS to identify genes and pathways involved in schizophrenia, major depression, bipolar disorder, autism spectrum disorder, and attention-deficit/hyperactivity disorder [5]. Genes associated with psychiatric disorders showed molecular, cellular, and developmental convergence: they were involved in transcriptional regulation and neural differentiation, enriched in glutamatergic neurons, and highly expressed during early brain development. Genetic risk factors associated with pleiotropic effects of psychiatric disorders further confirmed molecular convergence during neurodevelopment [6]. Notably, pleiotropic genes reveal a distinct feature of the shared neurobiological basis of psychiatric disorders which is not apparent in individual disorders. Pleiotropic genes, but not genes associated with individual disorders, showed selective enrichment in supragranular layer neurons, a key component of human cortical expansion and higher-order cognition [5]. These findings suggest that the neurobiological underpinning of psychiatric disorders is multifactorial: different mechanisms may underlie different modalities of psychiatric disorders.

While H-MAGMA sheds light onto disease biology, it is of note that genetic risk factors can exert their effects through a multitude of gene regulatory mechanisms that H-MAGMA may not fully capture. For example, while the majority of studies focus on regulatory variation engaged in enhancer–promoter interactions, SNPs may have a broader impact in gene regulation via affecting global chromatin architecture by disrupting CCCTC-binding factor (CTCF) binding sites. Moreover, some SNPs are associated with posttranscriptional regulation such as alternative splicing and alternative polyadenylation. Therefore, systematic delineation of gene regulatory mechanisms that encompass chromatin architecture, pre-mRNA processing, and post-transcriptional modification will be essential to provide mechanistic insights into how SNPs affect gene regulation and advance our understanding of psychiatric disorder etiology.

FUNDING AND DISCLOSURE

HW is supported by NARSAD Young Investigator Award, NIMH grants (DP2MH122403, R00MH113823), and a NIDA grant (R21DA051921). The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

HW and BH co-wrote this paper.

ADDITIONAL INFORMATION

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Published online: 28 August 2020

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