Allelic imbalance of chromatin openness is linked to neuropsychiatric disorders

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A new study led by NorthShore University HealthSystem (NorthShore) and the University of Chicago took a novel approach to identifying SNPs influencing the risk of neuropsychiatric disorders like schizophrenia,

bipolar and major depressive disorder, the institutions announced today. The findings, published in the current issue of *Science*, significantly advance understanding of the genetics of neuropsychiatric disorders and offer a path to translating genetic discoveries into novel disease biology and better clinical treatments.

Current approaches to genome-wide association studies (GWAS) in neuropsychiatry have advanced the identification of many single-base pair changes in the DNA (single nucleotide polymorphisms, or SNPs) associated with an increased risk of developing a psychiatric condition. However, these studies don't necessarily determine which of these SNPs are linked to functional changes in gene expression, and which might actually play a role in the disease.

In this study, the researchers were interested in identifying SNPs that directly affected how readily available DNA is for gene expression (chromatin accessibility). To find these candidates, they first identified SNPs that were heterozygous in their patient samples—that is, they had one variant of the SNP from their mother and a different copy from their father. SNPs that were differentially accessible were dubbed "allele-specific open chromatin" or ASoC, variants.

The study was led by Jubao Duan, Ph.D., the Charles R. Walgreen Research Chair and director of functional genomics of psychiatry at NorthShore, who is also an associate professor of psychiatry and behavioral neuroscience at the University of Chicago.

"Much like a mixed jar of peanut butter and plain M&M's that look alike but taste very different, functional disease variants in DNA appear similar and novel approaches are required to identify them," said first author Siwei Zhang, Ph.D., a research scientist at NorthShore. "Since we can't taste DNA the way we do M&M's, we had to find other ways to separate the functional SNPs from the non-functional. We reasoned that

the presence of risk alleles might change the local accessibility of chromatin, and they did."

Investigators used human blood samples to create induced pluripotent stem cells (iPSCs) and turned those iPSCs into different kinds of neuronal cells that model developing human brain cells. They then took a look at chromatin accessibility of DNA sequences in the neurons.

Profiling the ASoC variants identified thousands of potentially functional SNPs, a large fraction of which were associated with changes in the expression of nearby genes. The majority of these ASoC SNPs were found in closed chromatin regions of post-mortem brains, thus highlighting the unique value of using iPSC-derived neurons as a neurodevelopmental cellular model to link a functional SNP to psychiatric disease.

Further analysis demonstrated that these ASoC variants are more likely to be causally linked to a range of neuropsychiatric traits, allowing the researchers to prioritize the study of specific SNPs in genomic regions associated with schizophrenia risk.

"Using ASoC to identify functional SNP has some advantages over other, more conventional approaches," said Xin He, Ph.D., an assistant professor of human genetics at the University of Chicago, who co-led the computational analysis in the study. "This is because ASoC SNPs likely affect chromatin accessibility directly, while many traditionally identified SNPs associated with gene expression aren't necessarily functional. Compared with potentially functional SNPs identified with other methods, our ASoC SNPs showed much stronger enrichment for psychiatric disease risk variants."

In a proof-of-principle experiment, the scientists were also able to edit the genome of their iPSCs using CRISPR and determined that editing an

ASoC SNP frequently led to changes in nearby gene expression. This led the researchers to nominate putative causal genes in several schizophrenia disease regions, which can be explored in future studies for their role in causing the neuropsychiatric illness.

"Although schizophrenia and other neuropsychiatric disorders involve multiple risk genes that each have a small effect on disease risk and likely act in gene networks, our findings offer important insights that may advance an area of medicine with tremendous potential," said Dr. Duan. "We hope to continue harnessing multi-dimension genomic datasets and stem cell models to unravel how these devastating disorders are caused by genes and interactions with environmental factors such as stress or infection during early neurodevelopment."

More information: Siwei Zhang et al. Allele-specific open chromatin in human iPSC neurons elucidates functional disease variants, *Science* (2020). DOI: 10.1126/science.aay3983

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