REVEALING THE BRAIN'S MOLECULAR ARCHITECTURE

By **The PsychENCODE Consortium***

The brain, our most complex organ, is at the root of both the cognitive and behavioral repertoires that make us unique as a species and underlies susceptibility to neuropsychiatric disorders. Healthy brain development and neurological function rely on precise spatiotemporal regulation of the transcriptome, which varies substantially by brain region and cell type. Recent advances in the genetics of neuropsychiatric disorders reveal a highly polygenic risk architecture involving contributions of multiple common variants with small effects and rare variants with a range of effects. Because most of this genetic variation resides in noncoding regions of the genome, establishment of mechanistic links between variants and disease phenotypes is impeded by a lack of a comprehensive understanding of the regulatory and epigenomic landscape of the human brain.

To address this matter, the PsychENCODE Consortium was established in 2015 by the National Institute of Mental Health (NIMH) to characterize the full spectrum of genomic elements active within the human brain and to elucidate their roles in development, evolution, and neuropsychiatric disorders. To reach this objective, a multidisciplinary team of investigators across 15 research institutes has generated an integrative atlas of the human brain by analyzing transcriptomic, epigenomic, and genomic data of postmortem adult and developing human brains at both the tissue and single-cell levels. Samples from more than 2000 individuals were phenotypically characterized as neurotypical or diagnosed with schizophrenia, autism spectrum disorder (ASD), or bipolar disorder.

In *Science*, *Science Translational Medicine*, and *Science Advances*, we present manuscripts that provide insights into the biology of the developing, adult, and diseased human brain. These papers are organized around three flagship articles, the first analyzing human development, the second examining disease transcriptomes, and the third describing integration of tissue and single-cell data with deep-learning approaches.

The consortium's integrative genomic analyses elucidate the mechanisms by which cellular diversity and patterns of gene expression change throughout development and reveal how neuropsychiatric risk genes are concentrated into distinct coexpression modules and cell types. Developmental analysis of macaque and human brains reveals shared and divergent spatiotemporal features and expression of neuropsychiatric risk genes. Another study shows how the transcriptomes of affected and neurotypical brains exhibit differences in gene regulatory networks and mRNA splicing, thus highlighting the importance of isoform-level regulation and cell type specificity in neuropsychiatric disorders. Because we examined a large number of individuals, quantitative trait loci (QTL) identification is improved, and QTLs are found to be associated with variation in cell type proportions in the brain, as well as those affecting chromatin, DNA hydroxymethylation, and gene expression.

Additional investigations highlight the role of noncoding regions, particularly promotors, in ASD, as well as the three-dimensional structure of the genome and specific noncoding RNAs and transcription factors in schizophrenia. For these papers, the consortium developed analytical and biological tools. These include model systems for delineating regulatory networks: human induced pluripotent stem cell–derived cerebral organoids and primary cultured olfactory neuroepithelial cells. Finally, all data and associated analysis products are available from the consortium website (psychencode.org).

Overall, efforts such as the PsychENCODE project address how to link molecules, genes, and their regulatory elements to higher levels of biological complexity, from a single cell to human behavior. However, continued investigations are necessary, and the NIMH and the PsychENCODE Consortium envision future work that will provide additional insights into human brain origin, development, and function in health and disease.

We dedicate this series of papers to Pamela Sklar, one of the chief architects and leaders of the PsychENCODE Consortium. Pamela's vision and ideas resonate throughout our studies.

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RESEARCH ARTICLES

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- *SCI. ADV.* 10.1126/sciadv.aav8550
- NEWS STORY P. 1227

Genetic variants may lead to disease, denoted here by a dimmed letter representing a nucleotide. The PsychENCODE Consortium presents research to link the effects of genetic variation to gene expression in the brain.

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Revealing the brain's molecular architecture

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