**Illuminating the molecular architecture of the human brain**

The brain, our most complex organ, is at the root of both the cognitive and behavioral repertoire that makes 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. Since most of this genetic variation resides in non-coding regions of the genome, establishing mechanistic links between variants and disease phenotypes is impeded by the lack of a comprehensive understanding of the regulatory and epigenomic landscape of the human brain.

To address this, 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 multi-disciplinary team of investigators across 15 research institutes has generated an integrative atlas of the human brain by analyzing transcriptomic, epigenomic, and genomic data of post-mortem adult and developing human brains both at the tissue and single cell levels. Samples from over 2,000 individuals were phenotypically characterized as either 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 new insights into the biology of the developing, adult, and diseased human brain. These papers are organized around 3 flagship articles, the first analyzing human development, the second studying disease transcriptomes, and the third integrating tissue and single-cell data with deep-learning approaches.

The consortium's integrative genomic analyses show how cellular diversity and patterns of gene expression change throughout development and reveal how neuropsychiatric risk genes are concentrated into distinct co-expression modules and cell types. Developmental analysis of macaque monkeys reveals shared and divergent spatiotemporal features with human brain development and the expression of neuropsychiatric risk genes. Another study shows how the transcriptomes of affected and neurotypical brains reveals differences in gene regulatory networks and mRNA splicing; highlighting the importance of isoform-level regulation and cell-type specificity in neuropsychiatric disorders. Because we examine large numbers of individuals, quantitative trait loci (QTL) identification is improved and we find QTLs 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 non-coding regions, particularly promotors, in ASD, as well as the 3D structure of the genome and specific non-coding 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 (iPSC)-derived cerebral organoids and primary cultured olfactory neuroepithelial cells. Finally, all the data and associated analysis products are available from the consortium website (psychencode.org).

Overall, efforts, such as PsychENCODE, 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 efforts are necessary, and the NIMH and the PsychENCODE Consortium envision future work that will provide further insights into how the human brain arose, develops and functions 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.