The human brain is at the root of both the cognitive and behavioral repertoire that makes us unique as a species, as well as our susceptibility to neuropsychiatric disease. As the most complex biological tissue, it is comprised of a myriad of molecularly, morphologically, and functionally distinct regions and cell types, with numerous molecular and cellular processes transpiring over a prolonged course of development and adulthood. These processes are reliant on the diversity and precise spatiotemporal regulation of the transcriptome, which is highly specific with respect to tissue and cell type. The importance of understanding these gene regulatory processes is emphasized by recent advances in genetics and genomics, which identify neuropsychiatric disorders as polygenic, with most common genetic risk variants for disease in non-coding, regulatory regions of the genome. Unfortunately, elucidating the mechanistic links between variants and disease phenotypes has been slow, in no small part due to the dearth of comprehensive analyses of the transcriptomic, regulatory, and epigenomic landscape of the human brain in the healthy and disease states.

The PsychENCODE Consortium was established in 2015 and arose from the recognition by the National Institute of Mental Health (NIMH) that neuropsychiatric disorders, an endemic and growing public health issue, require joint large scale and multidimensional studies to identify mechanistic links between variants and disease phenotypes. Consequently, the NIMH developed a multi-disciplinary team of investigators across 15 research institutes to work in concert to generate an integrative atlas of the human brain by analyzing multi-omics (i.e., transcriptomic, epigenomic, and genomic) data at homogenate tissue and single cell levels from over 2,000 phenotypically well-characterized, high-quality human neurotypical and disease-affected (i.e., schizophrenia, autism spectrum disorder, and bipolar disorder) post-mortem adult and developing brains as well as human cellular model systems, including induced pluripotent stem cell (iPSC)-derived organoids, which can recapitulate early brain development. The goal of PsychENCODE consortium is to characterize the full spectrum of genomic elements active in the human brain and to elucidate their roles in development, evolution and neuropsychiatric disorders.

We present the first set of manuscripts developed by the PsychENCODE Consortium to provide new insights into the biology of the developing, adult, and diseased human brain. These papers are organized around 3 core manuscripts, the first analyzing human development (Li et al), the second analyzing disease transcriptomes (Gandal et al), and the third carrying out multi-level analyses integrating tissue and single-cell data with deep-learning approaches (Wang et al). Integrative genomic analysis of human brain development at tissue and single-cell levels identified a cup-shaped pattern of spatiotemporal transcriptome, and a convergence of neuropsychiatric risk genes into distinct co-expression modules and cell types (Li et al); while a complementary analysis (Zhu et al) of macaque, a closely related non-human primate, revealed shared and divergent spatiotemporal features of human brain development. The cross-disorder transcriptome analyses, including gene regulatory networks and isoform level analysis highlight the importance of isoform level regulation and cell type specificity in neuropsychiatric disease (Gandal et al.). In Wang et al, the large sample size permitted a substantial improvement in quantitative trait loci (QTL) identification, including QTLs associated with cell-type proportions, as well as with gene expression and chromatin marks. Another study of the adult brain showed a unique association between DNA hydroxymethylation and gene expression in inhibitory

neurons that differed significantly from other brain cell types (Kozlenkov et al). The reorganization of chromosomal contacts was also associated with the coordinated expression of genes directing synaptic function, and risk for schizophrenia (Rajarajan et al). These global analyses are complemented by studies functionally validating individual genes associated with disease risk; *DGCR5*, a lncRNA in a 22q11 deletion (Meng et al), and *POU3F2*, a transcription factor (Chen et al), were both experimentally validated as hub regulators modulating expression of other genes implicated in schizophrenia. Other studies develop and characterize biological tools, including human iPSC-derived cerebral organoids (Amiri et al.) and primary cultured neuronal cells derived from the olfactory neuroepithelium (Rhie et al.), as suitable model systems by delineating gene regulatory networks. More importantly, the data and associated analysis products developed by PsychENCODE consortium are available from the consortium website (psychencode.org).

Efforts such as the PsychENCODE consortium that focus on human neuronal gene regulation are an important step in the path of solving one of the "hard problems" of neuropsychiatry: the causal linking of genes and their regulatory elements to different levels of biological complexity spanning from the single cell on the way to the apex of human behavior. However, we are just beginning this endeavor. Continued efforts are necessary for deeper characterization of human brain molecular mechanisms at the single-cell level across brain regions and critical developmental time periods as well as the development of novel theoretical frameworks, machine learning and computational approaches to capitalize on rapidly growing high-dimensional multi-omics datasets through convergence of perspectives from orthogonal disciplines. The PsychENCODE Consortium will continue to build these resources and frameworks, developing new insights into the spatiotemporal dynamics of the human brain and the dysregulation of these dynamics in neuropsychiatric disease.

We would like to dedicate this series of papers to Dr. Pamela Sklar, who was one of the chief architects and leaders of this consortium. Pamela's vision and ideas resonate throughout our PsychENCODE studies.