Cracking the code of brain development

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With a unique, multi-faceted approach, researchers at the Lieber Institute for Brain Development (LIBD) have quantified the effect of previously unidentified anomalies in genetic expression that determine how the human brain develops from its earliest stages. Their work, published online December 15th in *Nature Neuroscience*, offers a novel technique for identifying biological markers in brain development that associate with risk for neurodevelopmental disorders such as schizophrenia and autism spectrum disorder (ASD).

Using state-of-the-art sequencing technology to examine postmortem brain samples from among their vast collection, the research team identified many thousands of differences in gene expression (differentially expression regions or DERs) in the dorsolateral prefrontal cortex (DLPFC) region of the brain across life stages. They examined brains from six distinct life stages—fetal, infant, child, teen, adult and late life—and focused on the DLPFC because of its known association with schizophrenia and ASD. The team used a sophisticated statistical approach called "derfinder" to identify the regions.

"By searching the entire genome for association with the 'derfinder' technique, we were able to identify many segments of the genome that were previously thought to not play an active role in brain development," explains Andrew E. Jaffe, Ph.D., Investigator at LIBD and lead author of the paper.

Following their analysis of 72 human brain samples, the researchers accessed open-source databases to map their identified DERs onto the

human genome and to examine expression in 16 different brain regions, in the developing mouse cortex and with human tissue samples and stem cells. They found that genes containing DERs most highly expressed from infancy through adulthood were most associated with important brain signaling and communication mechanisms. The vast majority of DERs were found to be crucial to the maturation process of neurons during fetal development, offering new evidence of how neurodevelopmental disorders may first begin.

"We find that the transition from fetal to postnatal life is the primary driver of differential expression, and the differences appear to represent a 'signature' found in cells from the earliest stages of development," says Dr. Jaffe. The team found the patterns to be similarly expressed across the 16 brain regions, suggesting that the genes containing these DERs function as developmental switches for the brain, regardless of where they are located.

There is significant overlap between these "signatures" of early brain development and regions of genetic risk for schizophrenia identified in the latest international genome-wide association study (GWAS), as well as genes previously associated with ASD and Intellectual Disability, the team reports. Interestingly, the DERs most expressed in the late life stages significantly overlapped other regions of genetic risk for disorders such as Alzheimer's disease and Parkinson's disease.

Daniel R. Weinberger, M.D., Director and CEO of LIBD says that "by linking developmental brain disorders like schizophrenia and autism to specific molecular signatures in early brain development, we are much closer to finding new treatments based on how a brain first gets ill rather than only on how it behaves ill."

The LIBD team concludes that many of the DERs important for brain development—and the developmental "signatures"—contain anomalies

not measurable with earlier technologies and approaches, and suggests that the transcriptome, which reflects genes that are actively expressed at any given time, of the human genome accessed in public databases is currently incomplete.

All of the team's data is openly accessible for further analyses in the new Track Hub of the UCSC Genome Browser "LIBD Human DLPFC Development" and through databases maintained by the National Center for Biotechnology Information.

More information: Jaffe A.E., Shin J., Collado-Torres L., Leek J.T., Tao R., Li C., Gao Y., Jia Y., Maher B.J., Hyde T.M., Kleinman J.E., and Weinberger D.R. Developmental regulation of human cortex transcription and its clinical relevance at single base resolution. *Nature Neuroscience*, 2014, Dec 15. DOI: 10.1038/nn.3898

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