ALLEN INSTITUTE for BRAIN SCIENCE

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COMPREHENSIVE MAP OF PRIMATE BRAIN DEVELOPMENT PUBLISHED IN NATURE

Transcriptional atlas sheds crucial light on what makes human brain development distinct

SEATTLE, WASH. — **July 13, 2016** — Researchers at the Allen Institute for Brain Science have published an in-depth analysis of a comprehensive molecular atlas of brain development in the non-human primate. This analysis uncovers features of the genetic code underlying brain development in our close evolutionary relative, while revealing distinct features of human brain development by comparison. The study is based on the NIH Blueprint Non-Human Primate (NHP) Atlas, a publicly available resource created by the Allen Institute and colleagues at the University of California, Davis and the California National Primate Research Center. This resource enables researchers to understand the underpinnings of both healthy brain development and many neuropsychiatric diseases. Analysis of the atlas is featured this week in the journal *Nature*.

“This is the most complete spatiotemporal map we have for any mammal’s development, and we have it in a model system that provides directly meaningful insight into human brain development, structure, and function,” says Ed Lein, Ph.D., Investigator at the Allen Institute for Brain Science. “This exceptional dataset is useful for exploring precisely where and when genes are active in relation to the events of brain development and the onset of brain disorders.”

“Collaborating with the NIH on this project allowed us to make use of the Allen Institute’s unique capabilities to generate high-quality, large scale data resources that enable the scientific community around the world to make valuable discoveries,” says Allan Jones, Ph.D., CEO of the Allen Institute.

"While we know many of the details of gene expression in the adult brain, mapping gene expression across development has been one of the missing links for understanding the genetics of disorders like autism and schizophrenia,” says Thomas R. Insel, Ph.D., former Director of the National Institute of Mental Health. “This new atlas will be the foundation for the next generation of studies linking the genetics of neurodevelopmental disorders to the development of specific brain pathways."

The goal of the NHP atlas was to marry the techniques of modern transcriptomics with the rich history of anatomical developmental studies by measuring gene activity at a series of ten important stages in prenatal and postnatal brain development. At each stage a technique called laser microdissection was used to precisely isolate fine layers and nuclei of cortical and subcortical brain regions associated with human psychiatric disease, thereby creating a high resolution time series of the generation and maturation of these brain regions and their underlying cell types. The gene expression data are complemented by neuroimaging and histological and cellular resolution gene expression reference data.

“This time series reveals how genes code for the enormous complexity of the human brain,” says Trygve Bakken, M.D., Ph.D., Scientist II at the Allen Institute for Brain Science. “Prenatal development is a time of exceptionally rapid change reflected in gene usage, yet many of the molecular characteristics of the mature brain are not achieved until surprisingly late in postnatal development when brain development can be affected by physical activity and social interaction.”

Because the atlas targeted areas of the brain associated with human disease, the authors collaborated with colleagues at the Baylor College of Medicine to use this molecular map to pinpoint when and where candidate genes for diseases like autism and schizophrenia become active. Genes associated with autism are particularly active in the prenatal neocortex in newly generated neurons, consistent with other studies and the early onset of autistic pathology. In contrast, genes for schizophrenia become active much later in development, also in neurons in the neocortex, which correlates with the disease's later onset.

"This tremendous resource is freely available to the research community and will guide important research into the etiology of many developmental disorders for years to come', says Michelle Freund, Ph.D., program officer at the National Institute of Mental Health.

Finally, by comparing these data to similar human and rat gene expression data, the researchers demonstrate that many genes show different developmental trajectories in primates compared to rodents, with many fewer differences between monkey and human. Human brain development is uniquely characterized by an unusually protracted period of developmental plasticity, referred to as neoteny. "We found evidence for genes showing regulation consistent with neoteny, but with a twist," says Lein. A set of human genes showed two patterns, a sharp change in expression earlier than other species, followed by a prolonged increase lasting longer than monkeys. "These findings show the value of closely related non-human primates to study shared characteristics of close evolutionary relatives and to identify unique features of the human brain related to our cognitive abilities and susceptibility to certain diseases."

The data for the NIH Blueprint Non-Human Primate Atlas are publicly accessible through blueprintnhpatlas.org and with the suite of Allen Institute resources at brain-map.org.

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About the Allen Institute for Brain Science

The Allen Institute for Brain Science is a division of the Allen Institute (alleninstitute.org), an independent, 501(c)(3) nonprofit medical research organization, and is dedicated to accelerating the understanding of how the human brain works in health and disease. Using a big science approach, the Allen Institute generates useful public resources used by researchers and organizations around the globe, drives technological and analytical advances, and discovers fundamental brain properties through integration of experiments, modeling and theory. Launched in 2003 with a seed contribution from founder and philanthropist Paul G. Allen, the Allen Institute is supported by a diversity of government, foundation and private funds to enable its projects. Given the Institute's achievements, Mr. Allen committed an additional $300 million in 2012 for the first four years of a ten-year plan to further propel and expand the Institute's scientific programs, bringing his total commitment to date to $500 million. The Allen Institute for Brain Science's data and tools are publicly available online at brain-map.org.

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