A critical window into the developing human brain profiled

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FOLR1, a receptor utilized for proper folate transport in cortex, is most highly expressed in brain areas of new neuron generation during prenatal development. Credit: Allen Institute for Brain Science

Researchers at the Allen Institute for Brain Science have generated a high-resolution blueprint for how to build a human brain, with a detailed map of where different genes are turned on and off during mid-pregnancy at unprecedented anatomical resolution. This first major report using data from the BrainSpan Atlas of the Developing Human Brain is published in the journal *Nature* this week. The data provide exceptional insight into diseases like autism that are linked to early brain development, and to the origins of human uniqueness. The rich data set is publicly available to everyone via the Allen Brain Atlas data portal.

"Knowing where a gene is expressed in the brain can provide powerful clues about what its role is," says Ed Lein, Investigator at the Allen Institute for Brain Science. "This atlas gives a comprehensive view of which genes are on and off in which specific nuclei and cell types while the brain is developing during pregnancy. This means that we have a blueprint for human development: an understanding of the crucial pieces necessary for the brain to form in a normal, healthy way, and a powerful way to investigate what goes wrong in disease."

This paper represents the first major report to make use of data collected for the BrainSpan Atlas of the Developing Human Brain, a big science consortium initiative which seeks to create a map of the transcriptome across the entire course of human development. "Coming on the first anniversary of the BRAIN Initiative, this is a terrific example of the potential for public-private partnerships to accelerate progress in neuroscience," says Lein.

Thomas R. Insel, Director of the National Institute of Mental Health, praises the BrainSpan Atlas as an already invaluable tool to researchers. "While we have had previous reports of molecular and cellular changes during human brain growth, the BrainSpan Atlas is the first comprehensive map of the dramatic trajectory of gene expression across prenatal and postnatal development," he says. "This atlas is already transforming the way scientists approach human brain development and neurodevelopmental disorders like autism and schizophrenia. Although the many genes associated with autism and schizophrenia don't show a clear relationship to each other in the adult brain, the BrainSpan Atlas reveals how these diverse genes are connected in the prenatal brain."

Spotlight on Autism

Though virtually all developmental diseases and disorders can benefit from increased knowledge about how genes are expressed in the developing brain, the researchers pointed to autism as a disorder with particularly pertinent links to early brain development. The research team used the BrainSpan Atlas to examine a number of genes linked to autism in prior scientific studies during development.

"We used the maps we created to find a hub of genetic action that could be linked to autism—and we found one," says Lein. "These genes were associated with the newly generated excitatory neurons in the cortex, the area of the brain that is responsible for many of the cognitive features affected in autism such as social behavior. This discovery is an exciting example of the ability of the BrainSpan Atlas to generate meaningful hypotheses about the origins of brain developmental disorders."

What Makes Humans Unique?

Understanding what makes humans unique involves deciphering a

complex puzzle—one that begins during the earliest phases of development. The richness of the BrainSpan Atlas gives scientists a new set of tools to assess how the human brain develops compared to other species.

"We know that some important regions of the genome show striking sequence differences in humans compared to other species. Since where a gene is expressed in the brain can give insight into its function, we can use our map to begin to figure out the roles of those genes in making humans distinct," says Lein. "Our analysis of the data showed that these genes are enriched in the frontal cortex, as well as in several specific specialized cell types including inhibitory GABAergic interneurons and neurons of the transient subplate zone that serves as a scaffold during early circuit formation. These features are all known to be expanded or show developmental differences in humans compared to other species, so our data gives unprecedented clues about the molecular underpinnings of what makes human neocortex unique."

A Precious Resource Freely Available

As with all the resources produced at the Allen Institute for Brain Science, sharing the data with the public was a fundamental goal from the very beginning. The BrainSpan Atlas enables researchers around the world to conduct research and ask questions about the early human brain that many would not be able to do otherwise, due to the highly limited availability of prenatal tissues.

"The work behind creating this atlas could not have been done anywhere else," says Allan Jones, Chief Executive Officer at the Allen Institute for Brain Science. "The scope of the project, and the level of detail in the data we collected, could only be accomplished thanks to the highly collaborative and interdisciplinary project-based approach of the Allen Institute team. And now, since the data are publicly available, the entire

scientific community can take advantage of our efforts to drive their own investigations forward and in exciting new directions."

More information: The Allen Institute's data and tools are publicly available online at www.brain-map.org

Paper: Miller JA, et al. Transcriptional landscape of the prenatal human brain. *Nature*, April 10, 2014. DOI: 10.1038/nature13185

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