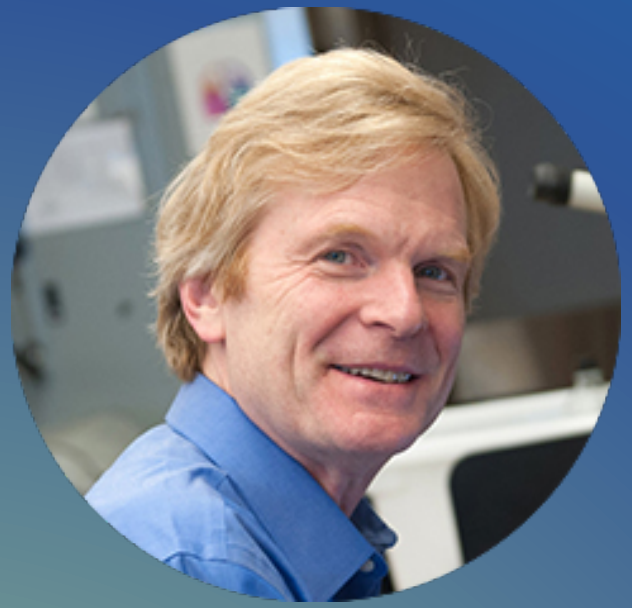
"Cell lineage in the human cerebral cortex using somatic mutations and RNA analysis"

Abstract: The cerebral cortex undergoes massive expansion in the primate lineage, especially in humans, but very little information is available on patterns of cell proliferation and lineage outside of rodents. Direct knowledge of cell lineage in human brain is especially important because of the role of somatic mutations in brain cancer and in an increasingly wide array of other neurological diseases including epilepsy and autism spectrum disorders. We have shown that newborn neurons in human cerebral cortex already show hundreds of somatic single nucleotide variants (SNV) relative to the germline, in addition to clonal retrotransposon insertions, microsatellite mutations, and copy number variants (CNV). Somatic SNV occur frequently with each cell division, 2-3 SNV/genome/cell division, providing in principle enough information to provide a permanent, systematic, forensic lineage map of the brain of any species. Recent work combines single-cell DNA sequencing and bulk sequencing to identify clonal somatic mutations, and then adds RNA analysis to assess neuronal and glial cell types.

Patterns of lineage in human cerebral cortex show some similarities to rodent, with early divergence of excitatory and inhibitory lineages, and widespread dispersion of interneuron clones. Somatic SNV also allow the demonstration that excitatory neurons in deep cortical layers become postmitotic before upper layer neurons. But human cell lineage shows marked widespread dispersion and intermingling of clonally related neurons even in the excitatory lineage at low levels of mosaicism. Each cortical unit is composed of neurons derived from multiple progenitors distinct from early stages, and functionally cortical borders are only respected by clones that make up <3% of cells. These results have important consequences for clonal patterns of distribution of disease-associated mutations that confer risk to neuropsychiatric disease. Supported by the NIMH, NINDS, The Paul G. Allen Frontiers Group, and HHMI.



Christopher A. Walsh is Bullard Professor of Pediatrics and Neurology at Harvard Medical School, Chief of the Division of Genetics and Genomics at Boston Children's Hospital, and an Investigator of the Howard Hughes Medical Institute. Dr. Walsh completed his MD and PhD degrees at the University of Chicago, neurology residency and chief residency at Massachusetts General Hospital, and postdoctoral training in Genetics at Harvard Medical School with Dr. Connie Cepko. In 1993 he became Assistant Professor of Neurology at Harvard and Beth Israel Deaconess Medical Center. From 2003-2007 he served as Director of the Harvard-MIT Combined MD-PhD training program.

He moved to Boston Children's Hospital in 2006, becoming Chief of Genetics. Dr. Walsh's research has focused on the development, function, and evolution and of the human cerebral cortex, pioneering the analysis of genetic diseases that affect the developing brain, and has discovered that some of these disease genes were important targets of the evolutionary processes that shaped the human brain. In 2017 he inaugurated the Allen Discovery Center for Human Brain Evolution at Boston Children's Hospital and Harvard Medical School, bringing together brain science with evolutionary genetics to search for the key changes in the genome that endow humans with their unique abilities for language, art, culture, and science. Dr. Walsh is an elected member of the American Association of Physicians, the American Association for the Advancement of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences, and the National Academy of Sciences.