Chen Institute Symposium 2025

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Talk title: *You contain multitudes: somatic mutation in human cerebral cortex*

Abstract: Although it was long been assumed that every cell in the brain had an identical genome, we now see the brain as a brilliant mosaic, with each cell having a distinctive genome that marks the prenatal history and postnatal life story of that cell. During brain development, every cell division creates a few somatic mosaic mutations—shared in clones of cells but not all cells of the body. These developmental mutations represent a lineage map of how every cell relates to every other cell. But the big surprise is that neurons, which do not divide or replicate their DNA after birth, continue to accumulate mutations throughout life as fast as many dividing cells.

Developmental somatic mutations that activate the mTOR pathway are found in brain specimens removed for the treatment of intractable focal epilepsy of childhood, which has enabled using mTOR inhibitors to treat these epilepsies. More recently, we discovered somatic mutations activating the PTPN11/RAS/RAF/MAPK pathway in hippocampus specimens removed to treat mesial temporal lobe epilepsy, where seizures start most often in adulthood. Life style events known to influence the postnatal neurogenesis that occurs in the hippocampus after birth have the potential to regulate these mutations and hence influence epilepsy risk. Most recently, we found that a portion of schizophrenia brains (10-12%) studied postmortem show somatic mutations at transcription factor binding sites (TFBS) in recurrent patterns, suggesting the existence of fetal factors that may influence the rates and types of somatic mutation in developing brain. We have also found roles for mutations occurring during this unique, yet error-prone, development that defines each of human brain to create risk for certain degenerative diseases that do not present until even later in life.

Sequencing the genomes of single neurons in brains shows that each neuron accumulates about 20 point mutations per year in remarkably linear, clock-like fashion. This age-related mutational process is accelerated in many human degenerative diseases, in ways that illuminate mechanisms that may influence neuronal degeneration. Supported by the NINDS, NIA, SFARI, the Allen Frontiers Program, and the HHMI.