Jeffrey L. Noebels, M.D., Ph.D.

- Professor of Neurology, Neuroscience, and Molecular and Human Genetics
- Cullen Trust for Health Care Endowed Chair in Neurogenetics
- Director, Blue Bird Circle Developmental Neurogenetics Laboratory

Board Certification

American Board of Psychiatry and Neurology, Neurology

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Neurology, Massachusetts General Hospital, Boston, Mass.

Clinical Interests

Epilepsy and inherited neurological disease

Research Interests

The principal research strategy in the Developmental Neurogenetics Laboratory is to apply mutational analysis to learn how genes regulate neuronal excitability and network synchronization within the mammalian central nervous system. Spontaneous and transgenic mutations that express neurological phenotypes in the mouse provide a valuable opportunity to identify excitability genes and examine their role in synaptic plasticity in the developing brain. Brain wave (EEG) phenotypes emerge from altered neuronal signaling properties, and are of special interest. Six mouse mutants causing spike-wave synchronization of the neocortex have been discovered in our laboratory, and four (tottering, lethargic, ducky, and stargazer) are linked to mutations of subunits of neuronal voltage-gated calcium ion channels. Study of these mice have led to the identification of novel members of the gene family, and a new understanding of how related molecules rescue function and determine selective vulnerability within thalamocortical pathways. Other new mouse models for human epilepsy syndromes involving mutant ion channel, receptor, and synaptic vesicle proteins are being analyzed to pinpoint the neural network and specific electrophysiological abnormalities characteristic of the human disorder. We also explore the presynaptic release process and activity-induced changes of downstream gene expression in epileptic brain to identify regulatory pathways that are critical mechanisms of disease progression.

At present, mutant mouse models of inherited disorders in neuronal excitability are under investigation using in vitro cell physiology and optical fluorescence measurements of ion channel activity and exocytosis in presynaptic terminals of mouse brain slices, as well as molecular anatomical techniques including laser-capture microspcopy and realtime quantitative PCR, in situ hybridization and immunohistochemistry, and microarray analysis of seizure-activated mRNAs. These studies form the basis for development of strategies to selectively correct the tissue expression of neuronal gene errors early in development.

In collaboration with the Baylor Human Genome Sequencing Center, a large-scale translational genomic research study examining variants in human ion channel genes is currently in progress. The Human Channelopathy Project will evaluate the contribution of SNP profiles in several hundred ion channel subunit genes to the complex inheritance of neurological excitability disorders such as epilepsy.

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Journal Publications

1. Chen TT, Klassen TL, Goldman AM, Marini C, Guerrini R, Noebels JL. Novel brain expression of ClC-1 chloride channels and enrichment of CLCN1 variants in epilepsy. Neurology. 2013;80(12):1078-85. [View journal article]
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