When Cranial Axon Growth and Guidance Goes Awry

March 3

Tuesday, 12:30 pm

Billings Building—Rosedale Room

SPEAKER:

Elizabeth C. Engle, M.D.

Director of the F.M. Kirby Center and Program in Neurobiology, Boston Children's Hospital

Professor of Neurology and Ophthalmology, Harvard Medical School

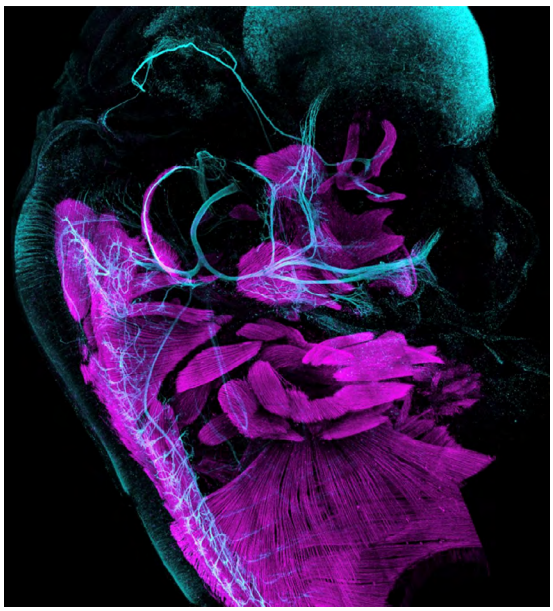
Investigator, Howard Hughes Medical Institute

Associate Member, The Broad Institute of MIT and Harvard

Host: Katherina Rees, Ph.D.

For more information contact
Darlene White
daw9085@med.cornell.edu

Abstract



As a child neurologist trained also in pediatrics and neuropathology, I hypothesized that my patients born with complex eye-movement disorders, once thought to be myogenic, may have defects in cranial motor neuron development. As a physician-scientist, I meticulously phenotyped these patients, including ascertainment of clinical data, MR imaging, and neuropathological studies. This has led to our definition of multiple related human malformation syndromes that extend far beyond eye movements and result from coding and noncoding genetic variation. Consistent with my initial hypothesis, our modeling reveals that these genetic disorders perturb steps in the development of cranial motor neurons or the growth and guidance of their axons; hence, they are now referred to as the congenital cranial dysinnervation disorders (CCDDs). The disorders that alter motor neuron identity have led us to extensive transcriptomic and epigenomic analyses of the embryonic mouse brainstem and cranial motor neurons to better define cranial motor neuron development and to interpret noncoding genetic variation in the context of specific regulatory regions. By contrast, many of the disorders that result from altered axon growth or guidance do so by directly or indirectly perturbing the neuronal cytoskeleton through alterations in cell signaling, motor transport, or microtubule dynamics, potentially converging on a common mechanism of selective vulnerability. Thus, coupling CCDD gene discovery with targeted mechanistic studies provides an opportunity to explore and validate mechanisms underlying these human disorders. This knowledge can be taken back to the clinic with the goal of understanding human development and enhancing patient care.

Publications

1. Tenney AP1, Di Gioia SA1, Webb BD1, Chan WM, de Boer E, Garnai SJ, Barry BJ, Ray T, Kosicki M, Robson CD, Zhang Z, Collins TE, Gelber A, Pratt BM, Fujiwara Y, Varshney A, Lek M, Warburton PE, Van Ryzin C, Lehky TJ, Zalewski C, King KA, Brewer CC, Thurm A, Snow J, Facio FM, Narisu N, Bonnycastle LL, Swift A, Chines PS, Bell JL, Mohan S, Whitman MC, Staffieri SE, Elder JE, Demer JL, Torres A, Rachid E, Al-Haddad C, Boustany RM, Mackey DA, Brady AF, Fenollar-Cortés M, Fradin M, Kleefstra T, Padberg GW, Raskin S, Sato MT, Orkin SH, Parker SCJ, Hadlock TA, Vissers LELM, van Bokhoven H, Jabs EW, Collins FS, Pennacchio LA, Manoli I, Engle EC*. *Noncoding variants alter GATA2 expression in rhombomere 4 motor neurons and cause dominant hereditary congenital facial paresis.* Nat Genet. 2023 Jul;55(7):1149-1163. doi: 10.1038/s41588-023-01424-9. Epub 2023 Jun 29. PMID: 37386251; PMCID: PMC10335940.

2. Jurgens JA, Barry BJ, Chan WM, MacKinnon S, Whitman MC, Matos Ruiz PM, Pratt BM, England EM, Pais L, Lemire G, Groopman E, Glaze C, Russell KA, Singer-Berk M, Di Gioia SA, Lee AS, Andrews C, Shaaban S, Wirth MM, Bekele S, Toffoloni M, Bradford VR, Foster EE, Berube L, Rivera-Quiles C, Mensching FM, Sanchis-Juan A, Fu JM, Wong I, Zhao X, Wilson MW, Weisburd B, Lek M; Ocular CCDD Phenotyping Consortium; Brand H, Talkowski ME, MacArthur DG, O'Donnell-Luria A, Robson CD, Hunter DG, Engle EC*. *Expanding the genetics and phenotypes of ocular congenital cranial dysinnervation disorders.* Genet Med. 2024 Jul 18;27(4):101216. doi: 10.1016/j.gim.2024.101216. PMID: 39033378; PMCID: PMC11739428.

3. Lee AS*, Ayers LJ, Kosicki M, Chan WM, Fozo LN, Pratt BM, Collins TE, Zhao B, Rose MF, Sanchis-Juan A, Fu JM, Wong I, Zhao X, Tenney AP, Lee C, Laricchia KM, Barry BJ, Bradford VR, Jurgens JA, England EM, Lek M, MacArthur DG, Lee EA, Talkowski ME, Brand H, Pennacchio LA, Engle EC*. *A cell type-aware framework for nominating non-coding variants in Mendelian regulatory disorders.* Nat Commun. 2024 Sep 27;15(1):8268. doi: 10.1038/s41467-024-52463-7. PMID: 39333082; PMCID: PMC11436875.