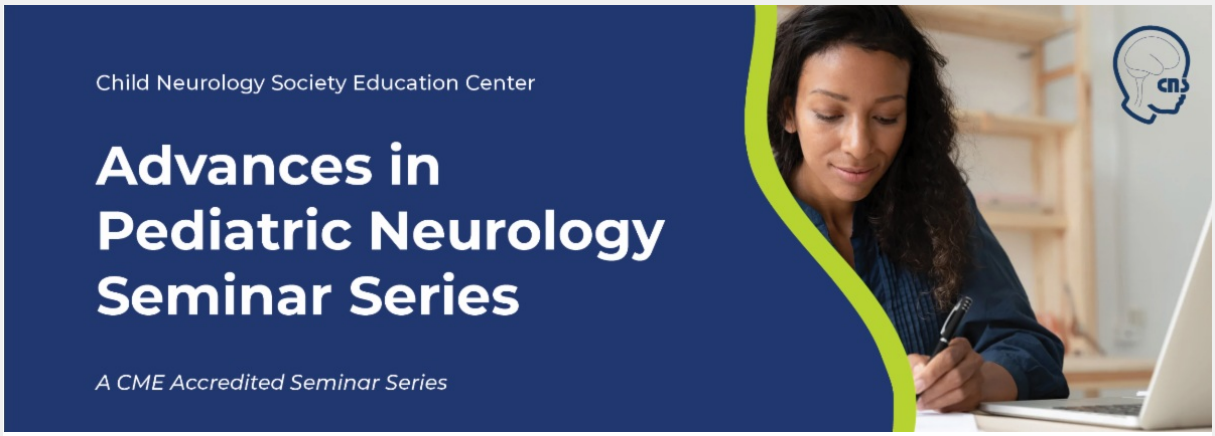

Brain Mosaicism in Neurodevelopmental Disorders and Epilepsy

Tuesday, October 29, 2024
6:00 pm CST
Seminar is live & recorded

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Seminar Description

Despite the revolution of exome sequencing, there are many highly heritable neurodevelopmental disorder without a clear monogenic cause. One unique type of genetic variants – postzygotic somatic variants (mosaicism) - has currently identified in the patients with these disorders. Recent studies have estimated that somatic variants in the probands and in parents transmitted to probands contribute to ASD risk in about 3-5 % of simplex family. Additionally, there is increasing evidence for “brain limited” mosaicism in conditions such as ASD, focal cortical dysplasia (FCD) and hemimegalencephaly (HME). Molecular diagnostics has become more important as the emerging precision medicine (such as pathway-specific inhibitors and genetic therapies) for genetic conditions. In the past decade, deep-sequencing technologies have been developed and widely used to reliably identify single nucleotide variants (SNV) with a low mosaic levels. In the case of HME and FCD2, caused by somatic variants in AKT-PI3K-MOT pathway, identifying the underlying molecular cause has become increasingly important, as selective MTOR, AKT3 and PI3K inhibitors, become more widely available.

When it comes to diagnosing somatic brain disorders, special consideration must be given to the most appropriate genetic tools and tissue type to ensure the detection of somatic variants. Recent research has demonstrated the successful use of deep sequencing with proxies such as SEEG electrodes and CSF for genetic diagnosis, offering a less invasive approach. This method holds promise for more efficient diagnosis, potential targeted resection, and pathway-specific treatment. Lastly, early recognition and treatment are also crucial for optimal care and outcome for children with

epilepsy from neurodevelopmental disorders. Lastly, advances in genetics and neuroimaging techniques such as 7T MRI, FDG-PET, SPECT, and functional MRI continue to enhance our understanding and improve medical and surgical therapies for these conditions.

About the Speakers

Wei-Liang Chen, MD

Wei-Liang Chen, MD, specialized in child neurology and genetics with focus on epilepsy, infantile spasm, brain malformation and other neurodevelopmental disorders. Dr. Chen is in charge of treatment trials in epilepsy. He is the site investigator in a national research consortium, Pediatric Epilepsy Research Consortium (PERC) Infantile Spasm group. He is also the principal investigator for the Epileptic Encephalopathy program at Children's National Hospital and serves as co-investigator in several other research projects focusing on neurogenetic diseases, neurometabolic disorders and functional neuroimaging.

Edward Novotny MD, FAAN, FAES, FACNS

Edward “Rusty” Novotny MD, FAAN, FAES, FACNS is Professor of Neurology and Pediatrics at the University of Washington School of Medicine and the Director of the Epilepsy Program at Seattle Children's Hospital. He has adjunct appointments in Neurosurgery and Radiology and serves as a principal investigator in the Center of Integrative Brain Research at the Seattle Children’s Research Institute. His clinical residency and fellowship training was in: child neurology clinical neurophysiology, and epilepsy at Stanford and Yale. His clinical and basic science postdoctoral training was in advanced neuroimaging at Yale University with support from NIH training grants and fellowships. As a resident, he was the recipient of the S. Weir Mitchell award from the American Academy of Neurology for investigation of a family with a novel mitochondrial disorder. After moving to Seattle Children's Hospital, he became site PI for the NIH funded Epilepsy Phenome/Genome Project. He collaborated with Drs. Heather Mefford, Bill Dobyns and Ghayda Mirzaa to develop an interdisciplinary epilepsy genetics clinic and more recently, a neurotherapeutics clinic to provide precision treatments for neurogenetic epilepsies. As Director of the epilepsy program, he has led development of multimodal imaging and advanced signal processing of neurophysiological data as an interdisciplinary program with involvement of investigators from engineering, computer science, genetics and physics with our clinical neuroscience center. This program focuses on investigations of somatic mosaicism of focal cortical dysplasias and malformations of cortical development to develop targeted surgical and medical treatments.

Christina Lockwood, PhD, DABCC, DABMGG

Christina Lockwood, PhD, DABCC, DABMGG is division head and director of the Genetics and Solid Tumors Laboratory at UW Medical Center and a UW professor of

Laboratory Medicine and Pathology and adjunct professor of Genome Sciences.

Dr. Lockwood is an expert in prenatal screening, genetic disorders and molecular oncology. She strives to create active partnerships with her patients to achieve the best possible outcomes.

Dr. Lockwood earned her PhD at the University of Wisconsin, Madison. She is board certified in both Clinical Molecular Genetics and Clinical Chemistry. Her research focuses on the development and implementation of innovative genomic methods to guide patient care, molecular oncology, pediatric oncology, prenatal screening, genetics, next-generation sequencing, tumor profiling and cell-free DNA.

Charles Jake Sadle, DO

C.J. (Charles Jake) Sadle is a PGY 6 Medical Genetics resident at UC Davis in Sacramento, CA. Before practicing genetics, he previously completed a residency in Child Neurology at University of Louisville, and before that he completed medical school at Michigan State University College of Osteopathic Medicine. CJ's goal is to practice as both a geneticist and neurologist in the service of children with neurodevelopmental disabilities. His academic interests are centered around the pathophysiology of Autism Spectrum Disorder. In 2024, he co-authored with Dr. Andrea Gropman a chapter on "The Epigenetics of Autism Spectrum Disorder" in the 2nd Edition of Epigenetics in Psychiatry. His research focuses on oxytocin, neuroinflammation, and microbiome metabolomics of children with Autism Spectrum Disorder.

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