



EPILEPSY GENETICS PROGRAM

BOSTON CHILDREN'S HOSPITAL | SPRING 2020

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A LOOK AHEAD AT 2020

We in the Boston Children's Hospital Epilepsy Genetics Program sincerely hope that 2020 is off to a good start for you. This past year was challenging for our team, but we have not wavered from our mission to help children and families with known or suspected genetic epilepsy syndromes and to advance research in epilepsy genetics. Through a translational approach that combines laboratory research and patient care, we strive not only to better understand the genetic basis of epilepsy, but also to apply that understanding toward the development of better treatments for people with epilepsy. We continue to collaborate with clinicians and researchers around the world, with contributions to groundbreaking scientific research, educational outreach initiatives, and advocacy in the field of epilepsy genetics. We extend our deepest appreciation to all of you who participated in the Epilepsy Genetics Program's research studies.

WALL STREET JOURNAL

In May 2019, the *Wall Street Journal* shared the story of Esme Savoie. The Savoie Family raised funds for the Poduri Laboratory's zebrafish research (see page 3 for more details about how zebrafish are used for genetic research in epilepsy).

THE BOSTON GLOBE

Dr. Poduri's research was featured in a September 2019 Special Issue recognizing scientific breakthroughs at BCH.

**SCIENCE MAGAZINE**

Dr. Poduri represented the research team in an interview for the December 2019 Feature Issue of *Science*. Read "Epilepsy's Next Frontier" for more information regarding our program's focus on gene discovery through mosaicism and its translation to people with epilepsy.

BOSTON'S MOST INFLUENTIAL WOMEN GALA

In January 2020, Dr. Poduri was honored by the Harvard Club of Boston as one of Boston's Most Influential Women.

A LOOK BACK AT 2019

Here are some highlights of conference presentations, publications, and professional/community activities of members of the Poduri Lab.



Annapurna Poduri, MD, MPH is the Director of the Epilepsy Genetics Program as a clinician-scientist. Dr. Poduri had a unique opportunity to spend a 4-month research sabbatical with Dr. Ingrid Scheffer in Melbourne, Australia. Dr. Poduri started her first term as a member of the Epilepsy Foundation's Professional Advisory Board and served as a co-editor of genetics for epilepsy.com. She is PI/co-PI of NIH grants on *PCDH19*, the genetics of Sudden Death in Childhood, and a ClinGen Brain Malformations Gene Curation Expert Panel and Co-Investigator of a grant on the genetics of pediatric brain malformations.



Beth Rosen Sheidley, MS, CGC is the Co-Director of the Epilepsy Genetics Program and a Senior Genetic Counseling Program Manager in the BCH Department of Neurology. In 2019, Beth was a speaker in the American Epilepsy Society's Presidential Symposium. Ms. Sheidley is a member of the Epilepsy Foundation's Professional Advisory Board and is co-editor of genetics for epilepsy.com. Finally, Ms. Sheidley is leading a systematic review of the epilepsy genetics literature on behalf of the National Society of Genetic Counselors.



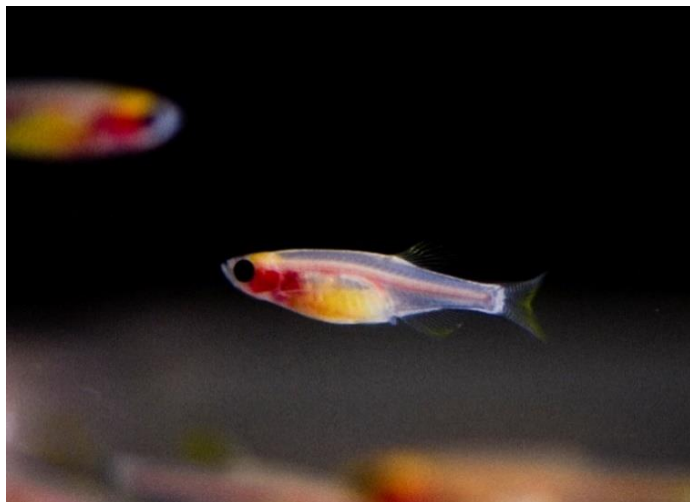
Christopher Yuskaitis, MD, PhD is an Attending Neurologist and Co-Director of the Infantile Spasms Program at BCH. Alongside his work in the Epilepsy Genetics Program, he sees families in the Brain and Developmental Genetics Clinic. Dr. Yuskaitis is conducting research with a K08 award from the NINDS, mentored by our colleague Dr. Mustafa Sahin and co-mentored by Dr. Poduri. He is also a member of the NIH-funded ClinGen Brain Malformations Gene Curation Expert Panel. In 2019, he presented his research regarding the *DEPDC5* gene and the role of animal models in genetic epilepsy at the American Epilepsy Society Annual Meeting.



Heather Olson, MD, MPH is an Attending Neurologist and Epileptologist with the Epilepsy Genetics Program and the Brain Development and Genetics Program. She is conducting research supported by an NIH K23 award. In 2019, Dr. Olson presented a poster at the American Epilepsy Society Annual Meeting regarding her recent work on the *CDKL5* gene, and using visual assessment as a biomarker for disease.



Christelle Moufawad El Achkar, MD is an Attending Neurologist in the Epilepsy Genetics Program and the Division of Epilepsy and Neurophysiology. Dr. Achkar's primary research and clinical interest is the connection between epilepsy and autism spectrum disorder and other comorbidities of epilepsy, particularly in genetic epilepsies.



Laura Turner, DVM is the Poduri Lab Research Supervisor. She joined the Poduri Lab in June 2018. She brings extensive pre-doctoral and post-doctoral zebrafish experience. In addition to her role managing the research laboratory, she also performs electrophysiological recordings on zebrafish.



Mark LaCoursiere, MS has been a member of the Poduri Lab since 2012. As Lead Research Technologist, Mark is responsible for conducting biochemical experiments to find novel genetic etiologies of epilepsy. He is screening large numbers of epilepsy genes in zebrafish models using high-throughput behavioral assessment and automated seizure detection methods. He recently completed his Master's degree, with a thesis on the expression of immediate early genes in zebrafish larvae with seizures.



Barbara Robens, PhD joined the Poduri Laboratory in July 2018 as a Post-Doctoral Fellow. Dr. Robens studies *PCDH19* gene function during early brain development in zebrafish, aiming to better understand the mechanisms underlying *PCDH19*-related epilepsy. She is the recipient of a prestigious research fellowship from Germany.



Ikhianosen Ukhuedoba joined the Poduri Lab as a Research Assistant in May 2019 after graduating with a BS in Biology from Regis College. She is responsible for conducting experiments in zebrafish aimed at investigating the genetic etiologies of epilepsy and schizophrenia.

SPOTLIGHT: ZEBRAFISH

Zebrafish (*Danio rerio*) represent an extremely versatile model system for studying genetic disease and neurodevelopment. Their high genetic homology to humans, ease of genetic manipulation with CRISPR/Cas9 genome editing, rapid generation times, and large clutch sizes are all advantages to using this model. Neural development occurs rapidly and can be readily observed in translucent zebrafish. Observable seizure-like behaviors and electrophysiological responses to pro-convulsant drugs have been recorded in larval zebrafish, making them a particularly useful model for epilepsy. High-throughput screens of known and novel chemical compounds can be readily performed on larval zebrafish to identify molecular targets for further experimental investigation, with the goal of eventually conducting clinical drug trials in people with epilepsy.

The Poduri Laboratory is currently modeling candidate epilepsy genes from the literature as well as our own candidates emerging from sequencing projects in our Epilepsy Genetics Program. Using CRISPR/Cas9, we create knock-out zebrafish models of the most promising candidate genes. Then, we evaluate these transgenic zebrafish lines for spontaneous behavioral seizures as well as increased seizure susceptibility in response to pro-convulsant drugs, hyperthermia, or other triggers.

In addition to pursuing novel epilepsy gene candidates, we are establishing and characterizing zebrafish models of *PCDH19*-related epilepsy. With its unusual X-linked pattern of inheritance in which females are predominantly affected, *PCDH19*-related epilepsy presents a unique challenge for animal modeling. We are currently utilizing both CRISPR/Cas9 and other innovative genetic strategies to create stable, mosaic zebrafish models of *PCDH19*-related epilepsy that reflect the random X-inactivation that occurs in human females. Due to the range of cognitive and psychiatric features in people with *PCDH19*-related epilepsy, in addition to evaluating for seizures and hyperexcitability, we are developing behavioral paradigms to evaluate cognitive abilities and assess for anxiety-like behavior in zebrafish models of this gene.

Not Pictured: Chris McGraw, MD, PhD

CLINICAL RESEARCH HIGHLIGHTS: BCH GENOMIC COHORTS INITIATIVE

The Boston Children's Hospital Genomic Cohorts Initiative offers exome sequencing to several research groups studying different health conditions. The Epilepsy Genetics Program is one of the first pilots in this institutional project, through which we are enrolling 500 people affected with epilepsy, as well as their parents, and conducting genetic sequencing of the exome (all of the coding regions of the DNA) to evaluate for explanatory genetic changes in the children with epilepsy. The goal is to understand how genetic factors contribute to epilepsy and related neurological disorders, such as developmental delay, intellectual disability, and movement disorders, and how genetic diagnoses modify the clinical course for these individuals. With the cooperation and support of physicians, researchers, people with epilepsy, and their families, the program has enrolled over 465 families in 16 months. Poduri Laboratory members Lacey Smith and Dr. Hyunyoung Koh have dedicated their efforts to analyzing participants' data.



Hyunyoung Koh, MD, PhD joined the Poduri Laboratory as a Research Fellow in September 2019 from Daejeon, South Korea. Dr. Koh has clinical and research interests in the neurodevelopmental processes that contribute to a variety of epilepsy phenotypes. Dr. Koh is currently analyzing exome sequencing data in an effort to identify novel genetic causes of epilepsy. He is also actively involved in the genetic analysis of DNA from infants and children who have died suddenly through our work with Robert's Program in Sudden Death in Childhood.



Devon Knight joined the Poduri Laboratory as a Clinical Research Assistant in June 2019 after graduating with a BS in Biology at the University of North Carolina – Chapel Hill. She is responsible for recruiting and enrolling families to participate in research studies aimed toward investigating genetic causes of epilepsy.



Emma Sexton joined the Poduri Laboratory as a Clinical Research Assistant in June 2019 after graduating with a BS in Health & Exercise Science and Anthropology at Wake Forest University. She is currently enrolling families in research studies to better understand the genetic etiologies of epilepsy.

For more information about our clinical research opportunities, please contact our Research Assistants, Devon Knight and Emma Sexton, at (617) 355-5254 or at EpilepsyGenetics@childrens.harvard.edu.

GENE AND VARIANT CURATION FOR BRAIN MALFORMATIONS



Abbe Lai, MS, CGC is a Genetic Counselor for the Brain and Developmental Genetics Clinic. She coordinates the ClinGen Brain Malformation Expert Panel. In 2019, Abbe presented data from gene and variant curation work at the American Society of Human Genetics Annual Meeting.

The ClinGen Brain Malformation Expert Panel is supported by a U24 cooperative grant from the NICHD and represents a collaboration across many institutions and countries to curate genes and variants associated with developmental brain malformations. Somatic mutations arising during embryogenesis and fetal development are increasingly recognized as important causes of human diseases, now extending beyond just cancer into the realm of developmental disorders. Post-zygotic mutations in the mTOR pathway genes (including *MTOR*, *ATK3*, *PIK3CA*, and *PIK3R2*) are known to cause a spectrum of brain overgrowth syndromes ranging from focal cortical dysplasia to dysplastic megalencephaly (PMID: 27159400; PMID: 29281825). Proper interpretation of somatic mutations requires consideration of several

factors not necessarily accounted for in the current 2015 ACMG/AMP Sequence Variant Interpretation variation (PMID: 25741868). Our group has drafted a framework for the curation of somatic mosaic (post-zygotic) variants that addresses many issues unique to somatic variants. Our work provides a useful framework for standardizing the curation of mTOR pathway mutations, and for the interpretation of somatic variants across other clinical settings. A standardized framework for evaluating functional assays is important for curation panels. Mosaic variants represent a significant proportion Guidelines, which focus predominantly on germline of disease-causing variants for certain disorders and it is critically important that such variants are accurately captured in ClinVar.

GENE SPECIFIC PROJECTS



Lacey Smith, MS, CGC joined the Epilepsy Genetics Program as a Genetic Counselor in May of 2014. Last year, she presented work on *PCDH19* at the University of Adelaide in South Australia. In addition to her work on *PCDH19*, Lacey has been instrumental in our Genomics Cohorts Initiative pilot study. In December, she led the Clinical Skills Workshop: Genetics Testing in Epilepsy Patients at the American Epilepsy Society's Annual Meeting. Ms. Smith also serves on the Professional Advisory Board for the Epilepsy Foundation of New England.

◀ PCDH19 ▶

Lacey Smith is working on two ongoing clinical research projects focusing on *PCDH19*-related epilepsy. The first is the *PCDH19*-Related Epilepsy Registry, which launched in 2014 in collaboration with the University of California, San Francisco. The Registry collects clinical and genetic information from individuals with *PCDH19* variants to be used for future research. It also maintains a readily-available database of participants who may be notified for other projects and future clinical trials. We currently have 75 participants, as well as additional genotype-positive family members, enrolled. Additionally, we are conducting a study to better characterize the cognitive and behavioral profile of individuals with *PCDH19*-related epilepsy. Our hope is that our clinical research, combined with our zebrafish work, will ultimately lead to better treatment and outcomes for individuals with *PCDH19*-related epilepsy.

◀ KCNQ2 ▶

Sonal Mahida is currently working on a study focused on *KCNQ2*-related disorders in collaboration with the *KCNQ2* Alliance. Through this study, we are collecting phenotypic information from individuals diagnosed with *KCNQ2*-related disorders through a questionnaire focused on symptoms and outcomes. We hope to use this natural history study as a foundation for larger scale efforts in the search for targeted therapies for this unique population. We have currently enrolled approximately 70 individuals in our natural history study and are working on collecting questionnaire data. We hope to publish our initial findings from this study within the next year.



Sonal Mahida, MGC, CGC joined the Epilepsy Genetics Program in June of 2018 as a Genetic Counselor with an expertise in Neurogenetics. She sees families in the Epilepsy Genetic Clinical Consultation Program and the Neonatal Epilepsy Clinics.

RECENT PUBLICATIONS

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- *Winawer MR, *Griffin NG, Samanamud J, Baugh EH, Rathakrishnan D, Ramalingam S, Zagzag D, Schevon CA, Dugan P, Hegde M, Sheth SA, McKhann GM, Doyle WK, Grant GA, Porter BE, Mikati MA, Muh CR, Malone CD, Bergin AMR, Peters JM, McBrien DK, Pack AM, Akman CI, LaCoursiere CM, Keever KM, Madsen JR, Yang E, Lidov HGW, Shain C, Allen AS, Canoll PD, **Crino PB, **Poduri AH, **Heinzen EL. Somatic *SLC35A2* variants in the brain are associated with intractable neocortical epilepsy. *Ann Neurol.* 2018 Jun;83(6):1133-1146.
- Yuskaitis CJ, Rossitto LA, Gurnani S, Bainbridge E, Poduri A, Sahin M. Chronic mTORC1 inhibition rescues behavioral and biochemical deficits resulting from neuronal *Depdc5* loss in mice. *Hum Mol Genet.* 2019 Sep 1;28(17):2952-2964.

For a comprehensive list of publications by Poduri Lab Team Members, please visit PubMed:
<https://www.ncbi.nlm.nih.gov/pubmed/?term=annapurna+poduri>

A LOOK AHEAD AT 2020

- ◆ Welcome our new Research Program Manager!



Rebecca Pinsky, MSN, RN, CPNP is a Certified Pediatric Nurse Practitioner who re-joined the Epilepsy Genetics Program in January 2020 as Research Program Manager. She initially joined the Epilepsy Genetics Program in 2013 as a research assistant prior to completing her Masters in Nursing Science at Regis College. Rebecca manages the program's research portfolio and ongoing projects, including establishing clinical trials.

- ◆ **COMING SOON:** Epilepsy Genetics Program and Poduri Lab Website – www.podurilab.org
Visit the website to stay up-to-date on research projects, presentations, conferences, and more!

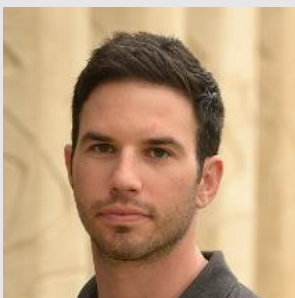
RESPONSE TO COVID-19

We were planning to share a calendar of our upcoming presentations and events in this space. Due to COVID-19, however, all presentations have either been canceled or postponed until further notice. Our participation in future presentations will be updated on our website as conferences and other events are rescheduled. Please visit www.podurilab.org for more information.

Our clinical research protocols have also shifted to remote enrollment of study participants to align with Boston Children's Hospital and Massachusetts state guidelines.

We would like to thank all of our colleagues and collaborators for their continued support and partnership.

IN MEMORIAM



Jeremy Ullmann, PhD

Dr. Ullmann joined the Epilepsy Genetics Program in January of 2016. He was a neuroscientist with extensive experience in imaging and zebrafish models of neurodegenerative disease. Dr. Ullmann received his BSc in Biology from Brandeis University in 2003 and a PhD in neuroscience and bio-imaging at The University of Queensland in Brisbane Australia in 2010. He completed his first post-doctoral fellowship at the Centre for Advanced Imaging (The University of Queensland) under Prof. David Reutens, where he developed high-resolution models of pre-clinical animal models and examined the correlation of febrile seizures and temporal lobe epilepsy later in life. As part of the Epilepsy Genetics Program, he performed high-throughput genetic screens to validate candidate epilepsy genes. Dr. Ullmann tragically passed away unexpectedly on February 10, 2019 in a hiking accident at Mt. Washington. Dr. Ullmann's full obituary can be viewed at: <https://www.demunn.com/obituary/jeremy-p-ullmann>. In memory of our dear friend and colleague, and with support from the Department of Neurology, we have begun the Jeremy Ullmann Annual Lecture in Epilepsy Genetics.