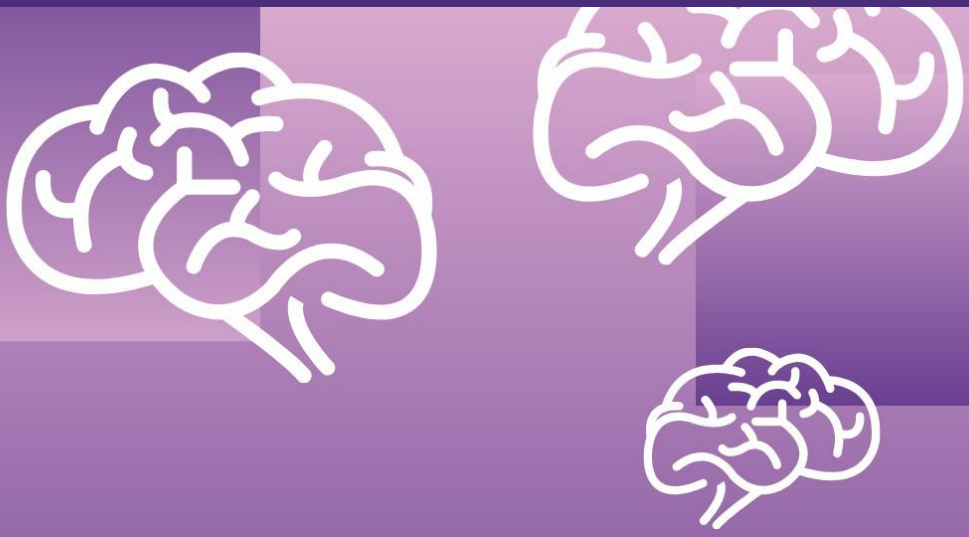

DRAVET® SYNDROME FOUNDATION

Raising hope & changing lives through research

Raising Hope through Research

10 Years of Research, 10 Years of Hope

WELCOME

The Dravet Syndrome Foundation (DSF) was founded in 2009 with the goal of funding research into Dravet syndrome and associated epilepsies. We are proud to commemorate the 10th anniversary of our Research Grant Program with this booklet showcasing the researchers and projects we have supported over the years.

It's a very exciting time for us at DSF. After a decade of steady progress, we are fortunate to have new treatments now available for our patient community, with several more potential treatments on the horizon. We are proud to have been able to help drive vital progress in the field of Dravet syndrome by supporting the work and focused commitment of our research community. Without their dedication and shared vision, we know we simply would not be where we are today.

At DSF, we have embraced our role to become a catalyst for change. And while we are inspired and invigorated by the decade of good work behind us, we recognize that there are still challenges that lay ahead, and that our work isn't done.

We thank each of our community stakeholders - researchers, medical professionals, industry partners, patient families and supporters - for the role you have played, and continue to play, in our success. You have helped to bring about great change in the field of Dravet syndrome. We are honored to work alongside each of you, and thanks to you, DSF has been able to *Raise Hope Through Research*.

Sincerely,

Mary Anne Meskis

Mary Anne Meskis
Executive Director
Dravet Syndrome Foundation

DSF GRANT PROGRAMS

DSF is dedicated to funding the highest caliber research on Dravet syndrome and associated epilepsies. We place a high priority on funding research that has a clear pathway to genetic understanding, clinical application, and/or therapeutic development.

DSF has awarded over $4.5M in research grant awards since 2009.

Research Grants

This 2-year, $150,000, 2-year award is intended for established, experienced, independent investigators affiliated with a research or academic institution whose proposed projects investigate hypotheses directly related to Dravet syndrome.

Postdoctoral Fellowships

This program develops academic physicians and scientists committed to research related to Dravet syndrome and associated disorders. This $50,000, 1-year award is designed to support early-career researchers under the mentorship of an independent investigator.

Clinician-Researcher Awards

This $150,000, 2-year award supports hypothesis-driven clinical research projects that have significant potential to advance our understanding of DS; slow or halt the progression of the disease, characteristics, or comorbidities of the disease; and/or reduce mortality.

Clinical Research Grant Awards

Beginning in 2020, this new $150,000, 2-year award will support projects that help us better understand all areas of Dravet syndrome, from basic mechanisms to actual intervention in seizures, disease progression, and a host of comorbidities by supporting clinicians, their research assistants, and the institutional staff/materials required in clinical studies.

Request For Applications

DSF occasionally issues RFAs for areas of interest. These notices include research objectives and project scope. Join our email list and follow us on social media to receive notice of RFAs.

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Mayo Clinic

Danielle Andrade, MD

Multi-modal assessment of adults with Dravet syndrome

Dr. Andrade plans to better characterize the adult patient with Dravet syndrome. She will study balance, gait, posture, memory, ability to perform day-to-day activities, and genome in a cohort of adults with Dravet syndrome to test the hypothesis that there may be premature brain ageing in adult patients. They also plan to explore whether previous use of contraindicated medications influence adult outcome.

Jennifer Kearney, PhD

MicroRNA-mediated modification of Dravet syndrome

Dr. Kearney plans to investigate microRNAs (small RNA molecules that regulate expression of gene products) and their modulation of Nav1.1. They have identified two miRNAs that are elevated following seizures and can reduce SCN1A expression and hypothesize that this may contribute to disease progression. She will study this relationship further and evaluate this pathway as a therapeutic target for Dravet syndrome.

Vania Broccoli, PhD

Gene therapy for Dravet Syndrome by CRISPR/dCas9 mediated activation of SCN1A

Dr. Broccoli is seeking to stimulate the expression of healthy *SCN1A* by a novel technology named activatory CRISPR/dCas9. dCas9 activator is a powerful tool that can be specifically targeted to the *SCN1A* gene and enhance protein production to a level that can possibly restore correct function of GABAergic inhibitory INs. Dr. Broccoli aims to improve the technology to make it more suitable for future delivery in DS patients.

John M Schreiber, MD

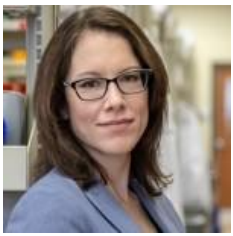
Subclinical myocardial damage in Dravet syndrome, other refractory convulsive epilepsy, and convulsive status epilepticus

Dr. Schreiber is currently studying whether subtle changes in heart function can be seen in children with Dravet syndrome, other forms of severe refractory epilepsy, and prolonged seizures (status epilepticus). Speckle tracking echocardiography is a non-invasive ultrasound technique that measures certain aspects of heart function (strain) that correlate with heart injury. They hypothesize that acute and/or repeated damage to the heart in childhood – related to seizures, and/or direct effects of *SCN1A* mutations on the heart muscle – may lead to subtle injury, evident on speckle tracking echocardiography, which increases the risk for sudden unexpected death in epilepsy (SUDEP).

Gemma Carvill, PhD

Pathogenic splicing mechanisms of an SCN1A poison exon in Dravet syndrome

Dr. Carvill and her team discovered that inclusion of a poison exon in *SCN1A* results in a truncated non-functional protein and identified patients with mutations that cause the erroneous inclusion of this exon. In this project, she aimed to identify the proteins that control its inclusion and to test the inclusion of the exon on production of *SCN1A* protein and neuron function, addressing a basic fundamental question involving *SCN1A* expression that had yet to be addressed: What are the RNA-binding proteins that control splicing of this *SCN1A* poison exon? This is the same exon that is targeted by Stoke Therapeutics's ASO therapy, expected in clinic in the next 1-2 years. Dr. Carvill and Dr. Mefford presented findings at the American Society of Human Genetics Annual Meeting in October 2019 in a standing room-only session on poison exons in neurodevelopmental disorders, and they (along with Dr. Isom) will be moderating an Investigators Workshop on poison exons at AES on Sun. Dec. 8th from 1:30-3:00 pm.



Sharon Swanger, PhD

Balancing thalamic excitation and inhibition in a Dravet syndrome mouse model

Patients with Dravet syndrome have altered neural activity in the thalamus, a brain region involved in the generation and spread of seizures. Dr. Swanger's work utilizes a Dravet syndrome mouse model to test if novel small molecules that modulate a subpopulation of glutamate receptors can correct neural activity in the thalamus. This new therapeutic approach for Dravet syndrome has great potential impact as glutamate receptors mediate excitatory brain activity involved in all seizures. Results of this study will advance our knowledge of mechanisms underlying disrupted brain activity in Dravet syndrome and, if successful, will provide a new strategy for correcting brain activity and reducing seizures.

Rajeswari Banerji, PhD

Identifying a novel metabolic target for improving disease outcomes in Dravet syndrome

Using the zebrafish model of DS, Dr. Banerji's team recently uncovered metabolic deficits as a characteristic feature for the disease model. A deeper understanding is required to identify specific metabolic drug targets, to develop novel therapies to treat DS, and other genetic epilepsies in general. Her preliminary work identified a novel drug that could improve metabolic defects, particularly glucose metabolism, seizures and/or behavioral alterations in this disease model. The goal of the current project is to validate a metabolic gene as a therapeutic target for DS. She is testing the anti-epileptic potential of the drug and validating its therapeutic target that improves the disease outcomes for DS. This work will help to understand the role of energy metabolism, particularly defects in glucose metabolism as the primary mechanism explaining DS etiology.

Jessica Chancey, PhD

Mechanisms of altered neuronal excitability and synaptic integration in a mouse model of Dravet syndrome

Dr. Chancey's project explores neurophysiological changes in mice genetically engineered to lack the *SCN1B* gene. These mice show many of the same symptoms as DS patients. She studies how loss of b1 alters the activity of and communication between brain cells, with a goal of linking the genetic changes caused by loss of b1 with the complex pathophysiology of DS, potentially identifying new therapeutic targets.

David R. Hampson, PhD

Exploring gene therapy to treat sudden unexpected death and other pathological features of Dravet syndrome

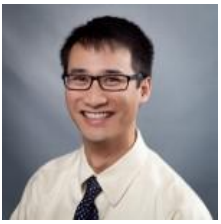
Adeno-associated virus (AAV) is currently being tested in many human clinical trials covering a wide range of diseases and disorders, including neurological disorders. They appear to be a safe and effective vector for gene therapy. However, the *SCN1A* gene is too large to fit in most known AAV. Dr. Hampson is creating and testing viral vectors containing various segments of DNA, including sodium channel subunits, in a mouse model of DS. Dr. Hampson has extensive experience with AAV with other disorders and we look forward to learning what this 2-year project yielded in the coming year.

Daniel Mulkey, PhD

Disordered breathing contributes to SUDEP in a mouse model of Dravet syndrome

Dr. Mulkey sought to characterize respiratory behavior at the cellular, neural network, and whole animal levels in a mouse model of Dravet syndrome. Using a conditional mouse that can have an *Scn1a* mutation turned on or off in various populations of cells, Dr. Mulkey's team induced inhibitory neurons to express the mutation and studied its effects on breathing. Despite having the mutation only expressed in this group of cells, the mice were phenotypically similar to mice with global *Scn1a* mutations, but were quicker to suffer from heat-induced seizures and death. The mice hypoventilated, had more apneas, and diminished response to carbon dioxide by two weeks of age, which corresponded to increased mortality. There were cellular differences in chemosensitive neurons as well, suggesting *Scn1a* dysfunction disrupts respiratory control at several levels in the mouse.

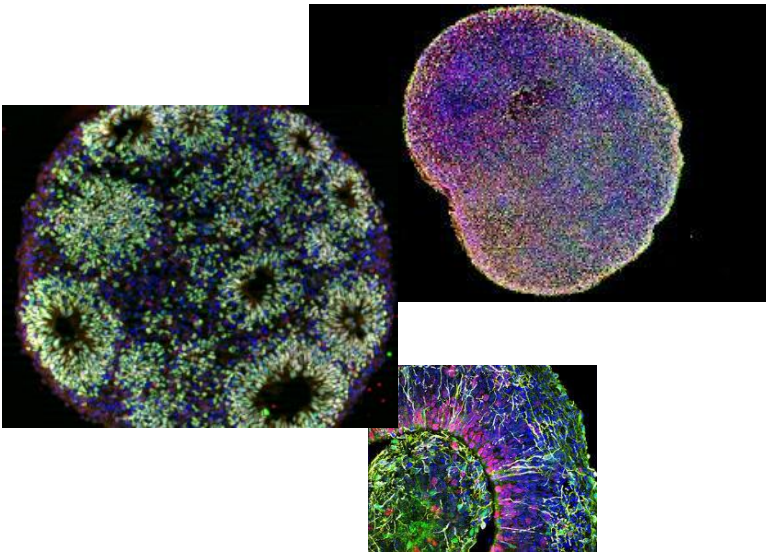
Kuo FS, Cleary CM, LoTurco JJ, Chen X, Mulkey DK. Disordered breathing in a mouse model of Dravet syndrome. Elife. 2019 Apr 26;8. doi: 10.7554/eLife.43387.



Louis Dang, MD, PhD

Using human stem cell-derived neurons and cerebral organoids to model pathogenesis in Dravet syndrome

Dr. Dang took Dravet syndrome patient skin cells and reprogrammed them into stem cells, then differentiated them into “mini brains,” 3D structures that resemble the developing human brain, to study the properties of excitatory and inhibitory neurons as they mature together. Understanding that excitatory Dravet syndrome neurons are hyperactive, possibly from overcompensation in *SCN8A*, they attempted to restore the normal activity in Dravet syndrome patient-derived excitatory neurons by decreasing *SCN8A* function. Since this project, Dr. Dang has continued his work with iPSCs and Dravet syndrome, expanding to the use of ASOs to target upstream open reading frames to increase *SCN1A* expression in neurons and has presented his recent research at professional conferences and our 2019 Day of Dravet community event.



Evangelos Kiskinis, PhD

Using patient specific iPSC-derived neurons to identify molecular biomarkers of drug treatment responsiveness in Dravet syndrome

Using Dravet patient-derived iPSCs, Dr. Kiskinis and his lab compared brain cells of patients who had good seizure control to patients who had poor seizure control after treatment, as well as those who've been completely refractory to treatment. By studying the electrical patterns, the molecular properties and the responses to drugs of these brain cells grown in a dish they aimed to: a) understand what makes brain cells respond well to drugs, and b) determine whether we can predict what drug would work best for each patient simply by studying their cells. Dr. Kiskinis has published several papers on iPSC models in various diseases, outlining the benefits of this approach as well as the challenges.

Simkin D, Kiskinis E. Modeling Pediatric Epilepsy Through iPSC-Based Technologies. Epilepsy Curr. 2018 Jul-Aug;18(4):240-245. doi: 10.5698/1535-7597.18.4.240.

Dennis Lal, PhD

A Novel System to evaluate SCN1A Pathogenicity

Dr. Lal and his group developed novel methods to computationally distinguish pathogenic *SCN1A* variants from benign variants and related genes in patients with Dravet syndrome (DS) and related epilepsies. In their analyses, they incorporated chemical, biological and other factors to identify differences between patients and controls. Dr. Lal has presented his characterization of *SCN1A* variants along with several other epilepsy-related genes at many recent conferences and continues to work on the "big data" side of genetics and Dravet syndrome.

Lal D, Reinthaler EM, Dejanovic B, May P, Thiele H, Lehesjoki AE, Schwarz G, Riesch E, Ikram MA, van Duijn CM, Uitterlinden AG, Hofman A, Steinböck H, Gruber-Sedlmayr U, Neophytou B, Zara F, Hahn A, Gormley P, Becker F, Weber YG, Cilio MR, Kunz WS, Krause R, Zimprich F, Lemke JR, Nürnberg P, Sander T, Lerche H, Neubauer BA. Evaluation of Presumably Disease Causing SCN1A Variants in a Cohort of Common Epilepsy Syndromes. PLoS One. 2016;11(3):e0150426. doi: 10.1371/journal.pone.0150426. eCollection 2016.

Ruth Westenbroek, PhD

Understanding the mechanisms and efficacy of cannabidiol (CBD)

Dr. Westenbroek tested the hypothesis that CBD attenuates or completely eliminates thermally evoked seizures, spontaneous seizures and/or sudden unexpected deaths using a mouse model of Dravet syndrome. She and her team found that a high dose of CBD (100 mg/kg) was needed to protect against seizures, while a low dose (10-20 mg/kg) improved social behaviors, and the improvement was lost at higher doses. They also found that antagonism of the lipid activated G protein coupled receptor (GPR55) may mediate the increased inhibition.

Kaplan JS, Stella N, Catterall WA, Westenbroek RE. Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A. 2017 Oct 17;114(42):11229-11234. doi: 10.1073/pnas.1711351114.

Orrin Devinsky, MD

Ataluren Trial

Dr. Devinsky led a small clinical trial of ataluren (Translarna™, formerly PTC 124) in 8 patients with Dravet syndrome and 8 patients with CDKL5. Ataluren has shown some promise in reading through premature termination codons in other genetic disorders, although its efficiency and efficacy has been a topic of concern. Because a significant number of patients with DS have premature termination codons, it was important to investigate on the community's behalf, and results of this double-blind placebo controlled cross-over study may be available soon. Dr. Devinsky continues to advocate for better treatments for patients with Dravet syndrome and has been involved in several clinical trials and research studies.

Jeffrey Calhoun, PhD

Target validation of thalamic T-type calcium channels in a mouse model of Dravet syndrome

Researchers previously identified a modifier gene, *Cacna1g*, that influences seizure susceptibility in a mouse model of Dravet syndrome. Dr. Calhoun sought to determine whether *Cacna1g* and related gene *Cacna1h* are potential molecular targets for therapy using genetic and pharmacological tools in a mouse model of Dravet syndrome, and to map the neuronal circuits activated during seizure initiation and propagation. Since this project, he has further investigated the source of phenotypic variability in Dravet syndrome using QTL mapping and RNA-seq analysis on the genetic background of the two most common strains in research. He found that age-related and seizure-related differences in genetic expression yielded the most prominent disparities (compared to genotype and strain), suggesting potential differences in developmental trajectory during disease onset.

Hawkins NA, Calhoun JD, Huffman AM, Kearney JA. Gene expression profiling in a mouse model of Dravet syndrome. Exp Neurol. 2019 Jan;311:247-256. doi: 10.1016/

Aliesha Griffin, PhD

Optimization of clemizole as a novel treatment for Dravet syndrome

In previous work, Dr. Baraban's lab showed that clemizole (an antihistamine), trazodone, lorcaserin, and fenfluramine were able to significantly reduce these seizure-like episodes in a zebrafish model of Dravet syndrome. Because of the focus of serotonin-modulators in DS and the fact that antihistamines can lower seizure threshold, Dr. Griffin and her team designed 28 analogs of clemizole and tested them in the zebrafish. They found three clemizole analogs with serotonergic properties that also had strong anti-seizure properties, and conducted further mechanistic studies to determine which HT receptors were involved. All three reduced high-velocity (seizure-like) swim behavior in the zebrafish and also suppressed electrographic seizure activity, and they are now in preclinical development by Epygenix.

Griffin AL, Jaishankar P, Grandjean JM, Olson SH, Renslo AR, Baraban SC. Zebrafish studies identify serotonin receptors mediating antiepileptic activity in Dravet syndrome. Brain Commun. 2019;1(1):fcz008. doi: 10.1093/braincomms/fcz008

Alex Nord, PhD

Regulation of SCN1A expression as pathogenic mechanism in Dravet Syndrome

Dr. Nord's work focused on characterizing the regulatory element(s) that likely contribute to *SCN1A* dysfunction and the varied clinical picture of DS patients by creating a mouse model that harbored a deletion of a specific non-coding regulatory element sequence. They found that homozygous deletion of the regulatory element was lethal after post-natal day 28, and both the heterozygous and homozygous mice had a significant reduction in *Scn1a* transcript levels. They also worked on characterization of neurodevelopmental and behavioral phenotypes of this alternate DS mouse model.

Stradleigh TW, et al. (2016) The role of Scn1a-associated non-coding DNA regulatory elements in expression of Nav1.1: a novel alternative mouse model for Dravet syndrome. AES 2016 Annual Meeting Abstract Database. AESnet.org

John C. Oakley, MD, PhD

Understanding the relationship between gene mutation, seizures, and cognitive impairment in Dravet syndrome

Dr. Oakley worked with a DS mouse model to determine whether a reduction in *Scn1a* expression beginning in adulthood, in the absence of prior seizures, is sufficient for seizure susceptibility and cognitive impairment. At the heart of gene therapy is the assumption that restoring healthy *SCN1A* expression will improve the outcome for patients already diagnosed with Dravet syndrome, and Dr. Oakley's studies hoped to provide initial data to support this assumption. Therefore, Dr. Oakley and his team also sought the converse of their first goal: To determine whether, under optimal conditions, restoring *Scn1a* expression in adulthood improves cognition and seizures. Since this project, Dr. Oakley's publications have focused on further characterization of interneuron inhibition, sleep impairment, and sharp wave ripples in Dravet syndrome.

Samir Das, PhD

Structure and function of the sodium channel Beta 1 subunit: a target for Dravet syndrome mutations

Dr. Das used high resolution crystallography to determine the structure of the beta 1 subunit, positioning each atom in the protein. He then sought to determine several mutations' effects on the protein's ability to fold, function, and remain stable under thermal pressure. Since this project, Dr. Das has continued his work in identifying crystal structure of several sodium channel subunits.

Das S, Gilchrist J, Bosmans F, Van Petegem F. Binary architecture of the $Na_v1.2$-ß2 signaling complex. eLife 2016;5:e10960. DOI: 10.7554/eLife.10960

Alison Muir, PhD

Dravet Syndrome – Where are the missing mutations?

Dr. Muir and collaborators looked for the "missing" mutations in the small portion of patients diagnosed with Dravet syndrome in whom no genetic mutation has been found. Certain types of mutations are missed by conventional testing and may be present in patients without a genetic diagnosis. Dr. Muir looked at mosaic mutations of *SCN1A* found in only a subset of cells and tissues and regulatory mutations that cause changes to how much protein is made. Several projects and publications have resulted from this initial funding and the work of her collaborators, including the discovery of a patient with a low level of mosaicism (8.3% and 6.9%) for two separate variants at the same *SCN1A* nucleotide position.

Muir AM, King C, Schneider AL, Buttar AS, Scheffer IE, Sadleir LG, Mefford HC. Double somatic mosaicism in a child with Dravet syndrome. Neurol Genet. 2019 Jun;5(3):e333. doi: 10.1212/NXG.0000000000000333.

Theodore R. Cummins, PhD

Targeting resurgent sodium currents for treatment of Dravet syndrome

Dr. Cummins studied effects of several compounds including cannabidiol and anandamine on human sodium channels $Na_v1.1$ and $Na_v1.6$, focusing on peak transient and resurgent sodium currents from wild-type and mutant channels. The team found that cannabidiol inhibited resurgent current, suggesting its anticonvulsant effects could be through its actions on voltage-gated sodium channels.

Patel RR, Barbosa C, Brustovetsky T, Brustovetsky N, Cummins TR. Aberrant epilepsy-associated mutant Nav1.6 sodium channel activity can be targeted with cannabidiol. Brain. 2016 Aug;139(Pt 8):2164-81. doi: 10.1093/brain/aww129.

Alfred L. George, Jr., MD

Novel Pharmacological Therapy for Dravet Syndrome

Dr. George, along with collaborators Dr. Jennifer Kearney and Dr. Christopher Thompson, investigated the mechanisms underlying a serendipitous observation that GS967 prevented premature death in a mouse model of Dravet syndrome. During their research, they discovered that GS967, a known sodium channel blocker, improved survival of *Scn1a*$^{+/-}$ mice and suppressed spontaneous seizures, which they attribute to their findings that it does not appear to affect action potential in the interneurons, but suppresses firing in pyramidal neurons. Since then, Dr. George has pursued further study and development of GS967 as a treatment for gain-of-function *SCN8A* mutations and potential indirect treatment for loss of function *SCN1A* mutations. Dr. George continues to be a leader in research for Dravet syndrome.

Anderson LL, Hawkins NA, Thompson CH, Kearney JA, George AL Jr. Unexpected Efficacy of a Novel Sodium Channel Modulator in Dravet Syndrome. Sci Rep. 2017 May 10;7(1):1682. doi: 10.1038/s41598-017-01851-9.

Elaine C. Wirrell, MD

Dravet Syndrome North American Consensus Project

(Funding provided through an unrestricted grant from GW Pharmaceuticals)

In this unprecedented project, a group of expert physicians in Dravet syndrome in North America worked together with parents of patients with Dravet syndrome to evaluate the level of consensus in diagnosis, evaluation, management, and treatment of Dravet syndrome. The panel reached strong consensus on clinical presentation, the need for early genetic testing, first and second line treatments, rescue therapies, comorbidity screening, and several other areas. This paper has been used as the standard of care for patients with Dravet syndrome in North America and formed the basis for DSF's physician and family brochures, which are used to educate non-experts in Dravet syndrome.

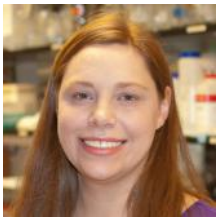
Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, Miller I, Sullivan J, Welborn M, Berg AT. Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel. Pediatr Neurol. 2017 Mar;68:18-34.e3. doi: 10.1016/j.pediatrneurol.2017.01.025.

MacKenzie Howard, PhD

Neural progenitor cell transplantation for the study and treatment of Dravet syndrome

Dr. Howard tested the effectiveness of transplanting non-DS cells into the hippocampus of DS mice, where they might develop into inhibitory interneurons. Successful transplantation revealed that exogenous cells develop rapidly and send and receive signals according to their cell type, potentially increasing inhibitory control. Since this postdoctoral fellowship, Dr. Howard has continued to work on neuronal cell transplantation and electrographic measurement in mouse models of epilepsy, published prolifically, and become Assistant Professor at UT Austin with his own lab focused on cellular and neural circuit changes that affect cognition in neurological disease mutations.

Howard MA, Baraban SC. Synaptic integration of transplanted interneuron progenitor cells into native cortical networks. J. Neurophysiology. 2016. 116:2, 472-478. doi: 10.1152/jn.00321.2016.



Jacy Wagnon, PhD

Brain transcriptomes in SCN1A and SCN8A related epileptic encephalopathies

Dr. Wagnon analyzed gene expression in Scn1a and Scn8A mouse models to identify common, shared pathological pathways that may provide new targets for treatment and prevention of seizures and SUDEP. While most *SCN1A* mutations result in loss of function of the sodium channel $Na_v1.1$, most *SCN8A* mutations actually result in gain of function of the sodium channel $Na_v1.6$. Since completing this project, Dr. Wagnon has conducted in-depth investigation of gene expression in *SCN8A* mouse models, analyzing RNA-seq data and has identified increased abundance of certain transcripts after seizures, supporting the theory that *SCN8A* mutations lead to changes in the brain that contribute to encephalopathy.

Wagnon JL, Barker BS, Hounshell JA, Haaxma CA, Shealy A, Moss T, Parikh S, Messer RD, Patel MK, Meisler MH. Pathogenic mechanism of recurrent mutations of SCN8A in epileptic encephalopathy. Ann Clin Transl Neurol. 2016 Feb;3(2):114-23. doi: 10.1002/acn3.276.

Michael Hammer, PhD

Identifying modifier genes in patients with SCN1A haploinsufficiency using whole exome sequencing

To answer the common question from parents, "What does my child's mutation type mean for future outcome?" Dr. Hammer explored the role that other "modifier" genes play in causing clinical variation among patients with *SCN1A* truncation mutations. This project spawned several other projects, and led Dr. Hammer and colleagues to look at the genetic background of mild phenotypic cases of *SCN1A* haploinsufficiency compared to the severe phenotypic cases. Their work suggests a cumulative effect of rare variants which do not affect phenotype unless present in conjunction with truncation mutations of *SCN1A,* rather than any discrete modifying genes.

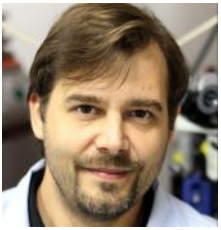
Hammer MF, Ishii A, Johnstone L, Tchourbanov A, Lau B, Sprissler R, Hallmark B, Zhang M, Zhou J, Watkins J, Hirose S. Rare variants of small effect size in neuronal excitability genes influence clinical outcome in Japanese cases of SCN1A truncation-positive Dravet syndrome. PLoS One. 2017;12(7):e0180485. doi: 10.1371/journal.pone.0180485.

Yvonne Wu, MD, MPH

Incidence and predictors of DS: A population based study

Dr. Wu studied a large birth cohort of over 120,000 infants born in the Kaiser Permanente Medical Care Program in Northern California. She and her team reviewed all inpatient and outpatient medical records to determine the incidence of Dravet syndrome based on established clinical criteria, then performed genetic testing on the patients diagnosed with DS. They found that 1:15,700 births between 2007 and 2010 qualified for a clinical diagnosis of DS, and 6/8 of those cases (1:20,900) also had a de novo *SCN1A* mutation. This meant that Dravet syndrome is likely nearly twice as common in the US as was previously thought.

Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, Kuzniewicz MW. Incidence of Dravet Syndrome in a US Population. Pediatrics. 2015 Nov;136(5):e1310-5. doi: 10.1542/peds.2015-1807.



Jokūbas Žiburkus, PhD

Adenosine A1 agonist control of seizure activity in Dravet syndrome

Adenosine is an inhibitory modulator of neuronal activity, and during seizures adenosine levels increase in the brain and suppress seizure activity. Too much activation of adenosine receptors in the brain stem, however, can induce severe respiratory depression. Dr. Žiburkus, in collaboration with Dr. Jeffrey Noebels, tested an adenosine A1 agonist in hippocampal slices and found it can impart seizure resistance to temperature induced seizures.

Gu F, Hazra A, Aulakh A, Žiburkus J. Purinergic control of hippocampal circuit hyperexcitability in Dravet syndrome. Epilepsia. 2014 Feb;55(2):245-55. doi: 10.1111/epi.12487.

Se Hee Kim, MD and Linda Laux, MD

Predictive factors for long-term cognitive outcome in Dravet syndrome

Dr. Laux and Dr. Kim sought to identify predictive factors for favorable cognitive outcome in a cohort of 135 Dravet syndrome patients followed from 2008 to 2013 at the Ann & Robert H. Lurie Children's Hospital Northwestern University. It is believed that early detection and early appropriate management will lead to a better long-term cognitive outcome in Dravet syndrome patients, but cognitive outcomes have proven difficult to study. Dr. Laux and Dr. Kim presented a poster at the 2014 AES meeting outlining their results from analyzing ABAS testing in patients with DS. ABAS scores decreased with age with a rapid drop until approximately 9 years of age, at which point scores may have leveled off, though the ABAS scoring is less accurate at lower levels. Patients with Dravet had higher social skill and lower practical skill. In general, higher IQ was associated with higher General Adaptive Score.

S.H. Kim et al. (2014) Adaptive Function in Dravet Syndrome. AES 2014 Annual Meeting Abstract Database. AESnet.org

Jingqiong "Katty" Kang, MD, PhD

Probing synaptic changes in a novel mouse model of severe epilepsy with nanoparticle-enabled 3D super-resolution imaging

Dr. Kang's project focused on understanding the role of GABAA receptors (GABR) in the etiology of epilepsies, including Dravet syndrome. GABR are a family of genes encoding 19 protein subunits which, in different combinations, mediate the majority of brain inhibition. While some mutations in GABR genes result in mild epilepsies, others result in severe neurodevelopmental defects. Dr. Kang's team will try to understand the mechanisms underlying each. As a result of this project, Dr. Kang also studied a GABRG2 knockout mouse model and found impaired GABAergic transmission and neuronal dysfunction in these brainstem nuclei are involved in the cardiorespiratory collapse in SUDEP. She continues to look at GABR genes in Dravet syndrome, including their treatment with various DS-associated drugs.

Xia G, P Pourali S, Warner TA, Zhang CQ, L Macdonald R, Kang JQ. Altered GABAA receptor expression in brainstem nuclei and SUDEP in Gabrg2(+/Q390X) mice associated with epileptic encephalopathy. Epilepsy Res. 2016 Jul;123:50-4. doi: 10.1016/j.eplepsyres.2016.04.002.

Annapurna Poduri, MD, MPH

Genetics of severe early onset epilepsies

Dr. Poduri used her experience with genetics and several early onset epileptic encephalopathy syndromes (including Dravet, infantile spasms, Ohtahara, and others) to further clarify the relationship between genotype and phenotype. They examined EEG, MRI, and seizure presentation of a cohort of patients with early myoclonic encephalopathy, and searched the whole exome for patients who did not have a previously identified epilepsy associated mutation. Dr. Poduri has continued to excel in genetics of early epilepsy syndromes, including Dravet syndrome, and this is just one of several publications:

Olson HE, Kelly M, LaCoursiere CM, Pinsky R, Tambunan D, Shain C, Ramgopal S, Takeoka M, Libenson MH, Julich K, Loddenkemper T, Marsh ED, Segal D, Koh S, Salman MS, Paciorkowski AR, Yang E, Bergin AM, Sheidley BR, Poduri A. Genetics and genotype-phenotype correlations in early onset epileptic encephalopathy with burst suppression. Ann Neurol. 2017 Mar;81(3):419-429. doi: 10.1002/ana.24883.

Jack Parent, MD

Read-through treatment of Dravet syndrome caused by nonsense SCN1A mutations

Dr. Parent and collaborators Dr. Lori Isom and Dr. Miriam Meisler examined the effects of ataluren (Translarna™, formerly Premature Termination Codon (PTC 124)) on iPSC neurons and a mouse model of Dravet syndrome with a premature termination codon. Ataluren, a compound that is reported to help the cell read through premature stop codons, is currently in development for other genetic disorders with varied success and failure. They also tested gentamicin, an aminoglycoside with mRNA read-through properties. No publications resulted from this project, but all three collaborators have continued to devote their time to Dravet syndrome, publishing many papers and receiving substantial NIH funding.

Scott Baraban, PhD

Gene profiling and high-throughput drug screening in a zebrafish model of Dravet syndrome and drug discovery in a zebrafish model of Dravet syndrome

Dr. Baraban sought to shift research in the epilepsy field by utilizing an immature zebrafish models designed to mimic the *SCN1A* gene mutation in children with Dravet syndrome. Characterization of the zebrafish larvae revealed a phenotype similar to haploinsufficiency found in humans: The fish exhibit spontaneous seizure-like activity, abnormal swim behavior, and respond similarly to drugs known to be effective in humans with Dravet syndrome. They have proven to be an excellent model for high-throughput drug screening and mechanism of action studies. Dr. Baraban has continued to receive NIH funding for this program and found several drug candidates including clemizole (and derivatives), lorcaserin, and trazodone, all of which are in development for Dravet syndrome by Epygenix. Dr. Baraban and his team have published several papers as a result of this initial funding, including the one below that describes how the zebrafish model can and has moved drugs from the lab to the clinic:

Griffin A, Hamling KR, Knupp K, Hong S, Lee LP, Baraban SC. Clemizole and modulators of serotonin signaling suppress seizures in Dravet syndrome. Brain. 2017 Mar 1;140(3):669-683. doi: 10.1093/brain/aww342.

Sooky Koh, MD, PhD

Novel therapies to block epileptogenesis in Dravet syndrome mice

Using a mouse model of Dravet syndrome, Dr. Koh and her colleagues investigated three novel strategies to treat Dravet syndrome and understand epileptogenesis, the process by which the developing brain evolves to produce repeated seizures. They utilized anti-inflammatory therapy, dietary intervention, and investigated the use of an enriched environment on the impact and outcome of seizures. Dr. Koh has continued her research on the relationship between brain inflammation and epileptogenesis, exploring several feedback mechanisms and pro-inflammatory pathways that may contribute to epileptogenesis in Dravet syndrome and serves on DSF's Scientific Advisory Board.

Sebastian Maier, MD, PhD and Massimo Mantegazza, PhD

Cardiac arrhythmias and SUDEP in SMEI and other Nav1.1 (SCN1A) related epilepsies

Drs. Maier and Mantegazza studied the role of the sodium channel in the heart of a mouse model of Dravet syndrome in order to investigate the occurrence and mechanism of arrhythmias and their possible involvement in SUDEP. Since this project, several other researchers have looked at the effects of *SCN1A* mutations on cardiac tissue in DS mice and iPSCs (including patient-derived iPSCs and their edited controls) and have found distinct differences in sodium current. The role of *SCN1A* mutations in cardiac arrhythmias and SUDEP continues to be a topic of great interest to DSF.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