December 4 - 8 ■ Philadelphia, PA
69TH ANNUAL MEETING

Scientific Symposium
Personalized Medicine in Epilepsy: A Brave New World

Symposium Co-Chairs:
Daniel Lowenstein, M.D.

and

Scott Baraban, Ph.D.

Friday, December 4, 2015
Convention Center – Room 204 AB

8:45 – 10:45 a.m.

GENERAL INFORMATION

Accreditation

The American Epilepsy Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation

Physicians

The American Epilepsy Society designates this live activity for a maximum of 30.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistant

AAPA accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 30.75 hours of Category 1 credit for completing this program.

Jointly provided by AKH Inc., Advancing Knowledge in Healthcare and the American Epilepsy Society.

Nursing

AKH Inc., Advancing Knowledge in Healthcare is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is awarded 30.75 contact hours.

Nurse Practitioners

AKH Inc., Advancing Knowledge in Healthcare is accredited by the American Association of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider Number: 030803. This program is accredited for 30.75 contact hours which includes 8 hours of pharmacology. Program ID #21547

This program was planned in accordance with AANP CE Standards and Policies and AANP Commercial Support Standards.

Pharmacy

AKH Inc., Advancing Knowledge in Healthcare is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Select portions of this Annual Meeting are approved for pharmacy CE credit. Specific hours of credit for approved presentations and Universal Activity Numbers assigned to those presentations are found in the educational schedules. Criteria for success: nursing and pharmacy credit is based on program attendance and online completion of a program evaluation/assessment.

If you have any questions about this CE activity, please contact AKH Inc. at service@akhcme.com.

International Credits

The American Medical Association has determined that non-U.S. licensed physicians who participate in this CME activity are eligible for *AMA PRA Category 1 Credits*™.

CME/CE Certificates

For those attendees who wish to claim CME or CE, there is an additional fee. Registrants can pay this fee as part of the registration process. Those who do not pre-purchase the credit will also have the ability to pay this fee at the time they attempt to claim credit. Fees for CME increase after January 16 and are a one-time charge per annual meeting.

The evaluation system will remain open through Friday, February 26, 2016. Evaluations must be completed by this date in order to record and receive your CME/CE certificate.

Member Fees:	$50 through January 15, 2016 $75 January 16 – February 26, 2016
Non-member Fees:	$75 through January 15, 2016 $100 January 16 – February 26, 2016

Attendance Certificate/International Attendees

A meeting attendance certificate will be available at the registration desk for international meeting attendees on Tuesday, December 8.

Policy on Commercial Support and Conflict of Interest

The AES maintains a policy on the use of commercial support, which assures that all educational activities sponsored by the AES provide in-depth presentations that are fair, balanced, independent and scientifically rigorous. All faculty, planning committee members, moderators, panel members, editors, and other individuals who are in a position to control content are required to disclose relevant relationships with commercial interests whose products relate to the content of the educational activity. All educational materials are reviewed for fair balance, scientific objectivity and levels of evidence. Disclosure of these relationships to the learners will be made through syllabus materials and the meeting app.

Disclosure of Unlabeled/Unapproved Uses

This educational program may include references to the use of products for indications not approved by the FDA. Faculty have been instructed to disclose to the learners when discussing the off-label, experimental or investigational use of a product. Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the AES.

OVERVIEW
Tremendous advances in our understanding of the genetic mutations that underlie different types of epilepsy have left the epilepsy research and clinical world reeling. How to take this knowledge to the next level so that treatments can be identified for these patients in, some of whom exist in only small numbers, is being wrestled with at many levels. At the same time President Obama's recent Precision Medicine Initiative represents a bold new research effort to revolutionize how we improve health and treat disease. This symposium will address these issues, from mutation to bedside in a precision medicine fashion.

LEARNING OBJECTIVES
Following participation in this symposium, learners should be able to:

- Recognize identified genetic causes of epilepsy and is familiar with the literature on emerging genetic causes of epilepsy
- Counsel families regarding prognosis and treatment using a personalized medicine approach
- Participate in counseling families regarding genetic epilepsies
- Assist in treating genetic epilepsies through a better understanding of emerging personalized medicine findings
- Recognize the neuropsychological and developmental impact of genetic epilepsies

TARGET AUDIENCE
Basic: Those new to epilepsy treatment or whose background in the specialty is limited, e.g., students, residents, general physicians, general neurologists and neurosurgeons, other professionals in epilepsy care, administrators.

Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, and other providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Advanced: Address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques or advanced treatment modalities, including surgery.)

Agenda
Co-Chairs: Scott Baraban, Ph.D. and Daniel Lowenstein, Ph.D.

Introduction
Daniel Lowenstein, M.D.

Defining the Target: mutation Discovery in Human Epilepsy
Heather Mefford, M.D., Ph.D.

Precision medicine in Zebrafish: A Primer Using SCN1 mutants
Scott C. Baraban, Ph.D.

Patient-derived IPS Cells to Understand Epileptic Encephalopathy and SUDEP
Lori Isom, Ph.D.

Application of Precision medicine in Patients with a KCNT1 mutation
Ethan Goldberg, M.D., Ph.D.

Conclusions
Daniel Lowenstein, M.D.

Education Credit
2.0 CME Credits

Nurses may claim up to 2.0contact hours for this session.

Nurse Practitioners may claim 2.0 hours of pharmacology for this session.

Pharmacy Credit
AKH Inc., Advancing Knowledge in Healthcare approves this knowledge-based activity for 2.0 contact hours (0.2 CEUs). UAN 0077-9999-15-036-L01-P. Initial Release Date: 12/8/2015.

The American Board of Psychiatry and Neurology has reviewed the Personalized Medicine in Epilepsy: A Brave New World Symposium and has approved this program as part of a comprehensive program, which is mandated by the ABMS as a necessary component of maintenance of certification.

FACULTY/PLANNER DISCLOSURES
It is the policy of the AES to make disclosures of financial relationships of faculty, planners and staff involved in the development of educational content transparent to learners. All faculty participating in continuing medical education activities are expected to disclose to the program audience (1) any real or apparent conflict(s) of interest related to the content of their presentation and (2) discussions of unlabeled or unapproved uses of drugs or medical devices. AES carefully reviews reported conflicts of interest (COI) and resolves those conflicts by having an independent reviewer from the Council on Education validate the content of all presentations for fair balance, scientific objectivity, and the absence of commercial bias. The American Epilepsy Society adheres to the ACCME's Essential Areas and Elements regarding industry support of continuing medical education; disclosure by faculty of commercial relationships, if any, and discussions of unlabeled or unapproved uses will be made.

FACULTY / PLANNER BIO AND DISCLOSURES
Daniel Lowenstein, M.D. (Co-Chair)
Daniel H. Lowenstein, M.D. is the Executive Vice Chancellor and Provost, and the Robert B. and Ellinor Aird Professor and Vice-Chairman of Neurology, at the University of California, San Francisco. He received his BA in Mathematics from the University of Colorado and MD from Harvard Medical School, and completed neurology residency training at UCSF. Dr. Lowenstein is a clinician-scientist and educator who has studied both basic science and clinical aspects of epilepsy. He has been actively involved in advancing the cause of epilepsy at the national and international level, and has held leadership posts in numerous organizations, including AESD< ILAE, and NINDS.

Dr. Lowebstein has indicated he has no financial relationships with commercial interests to disclose.

Dr. Lowenstein does intend to reference unlabeled/unapproved uses of drugs or producs - Quinidine Memantine Ritigabine

Scott Baraban, Ph.D. (Co-Chair)
Scott C. Baraban, PhD is a Professor and William K. Bowes Jr. Endowed Chair in Neuroscience Research at the University of California, San Francisco. Dr. Baraban's lab studies the cellular and molecular basis of epilepsy with a focus on translational work. Publications from the Baraban laboratory have appeared in Science, Nature Neuroscience, Journal of Neuroscience, Proceedings of the National Academy of Sciences, and Neuron. He is the recipient of awards from the Esther and Joseph Klingenstein Fund, the Sandler Family Supporting Foundation, the UCSF Innovation in Basic Science Award, a EUREKA grant and Javits Neuroscience Award from the NIH.

Dr. Baraban discloses receiving support for Royaltiesfrom Springer, annual book royalties.

Ethan Goldberg, M.D., Ph.D.
Ethan M. Goldberg, M.D., Ph.D., is Assistant Professor of Neurology and Neuroscience in the Division of Neurology, The Children's Hospital of Philadelphia, and Departments of Neurology and Neuroscience at The Perelman School of Medicine at The University of Pennsylvania, in Philadelphia, PA, U.S.A. Dr. Goldberg is a member of the Neurogenetics Program in the Division of Neurology at CHOP. His laboratory studies basic mechanisms of epilepsy in experimental models using electrophysiology, optogenetics, and multiphoton calcium imaging.

Dr. Goldberg has indicated he has no financial relationships with commercial interests to disclose.

Lori Isom, Ph.D.
Dr. Isom is Professor and Chair of Pharmacology, Professor of Molecular and Integrative Physiology, and Professor of Neurology at the University of Michigan. She received her PhD in Pharmacology at Vanderbilt University and completed a postdoctoral fellowship in the Catterall laboratory at the University of Washington. Dr. Isom’s research program focuses on voltage-gated sodium channel structure, function, and role in inherited disease. She reported the first mutation in SCN1B linked to Dravet Syndrome in 2009 and is collaborating with Dr. Jack Parent and Dr. Miriam Meisler to investigate SCN1A- and SCN1B-linked Dravet Syndrome mutations and SCN8A-linked EIEE13 in human induced pluripotent stem cell neurons and cardiac myocytes.

Dr. Isom discloses receiving support for Consulting from Zogenix, consultant for education on Dravet Syndrome mechanisms; for Honoraria from giving seminars at universities, including UPenn, Cold Spring Harbor, Xiangya Medical School.

Heather Mefford, M.D., Ph.D.
Heather C. Mefford, MD, PhD, is an Associate Professor of Pediatrics at the University of Washington in the Division of Genetic Medicine. Dr. Mefford’s research laboratory is devoted to the discovery of novel genetic and genomic causes of pediatric disease. A major focus of their current work is to identify causes of pediatric epilepsy. They employ state-of-the-art technologies including whole exome sequencing, gene panel sequencing and custom array CGH. The Mefford lab has discovered numerous novel epilepsy genes and copy number variants that are important for epilepsy.

Dr. Mefford discloses receiving support for Service from Professional Advisory Board, Lennox Gastaut Foundation Scientific Advisory Board, Simons Foundation Powering Autism Research for Knowledge (SPARK) Medical Advisory Board, Supporting Families with KdVS Syndrome Foundation.

CME Reviewer
Kevin Graber, M.D.
Kevin Graber is associate professor of neurology and neurological sciences at Stanford University. I addition to care of patients with epilepsy, he also has research interests in posttraumatic epilepsy and vagus nerve stimulation.

Dr. Graber discloses receiving support for Contract Research from LVIS Corporation; No salary support or indirect payments.

Paul Levisohn, M.D. (Medical Content Specialist, AES)
Dr. Levisohn is a member of the faculty of the section of Pediatric Neurology at The University of Colorado School of Medicine and Children's Hospital Colorado Neuroscience Institute, having joined the faculty over 15 years ago following a similar period of time in the private practice of pediatric

neurology. His academic career has focused on clinical care for children with epilepsy with particular interest in clinical trials and on the psychosocial impact of epilepsy. Dr. Levisohn is currently a consultant on medical content for CME activities to staff of AES. He is a member of the national Advisory Board of EF and has been chair of the advisory committee for the National Center of Project Access through EF.

Dr. Levisohn has indicated he has no financial relationships with commercial interests to disclose.

AKH STAFF / REVIEWERS
Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

Bernadette Marie Makar, MSN, NP-C, APRN-C (Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

John P. Duffy, RPh, B.S. Pharmacy (Pharmacy Reviewer) has indicated he has no financial relationships with commercial interests to disclose.

AKH staff and planners have nothing to disclose.

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How to Claim CME Credit
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Questions?
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NURSING & PHARMACY

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The National Association of Boards of Pharmacy (NABP) requires that all pharmacists and pharmacy technicians seeking CE credit have an ID number issued by NABP. Pharmacy CE providers, such as AKH Inc., Advancing Knowledge in Healthcare, are required to submit participant completion information directly to NABP with your ID number and birth information to include month and date (not year) as a validation to this ID number. If you do not have an ID number (this is not your license #), go to: www.MyCPEmonitor.net

Nursing and Pharmacy credit (per session) is based on attendance as well as completion of an online evaluation form available at:

WWW.AKHCME.COM/2015AES

THIS MUST BE DONE BY JANUARY 15, 2016 TO RECEIVE YOUR CE CREDIT.
We cannot submit credit to NABP after this date.

If you have any questions, please contact AKH at service@akhcme.com.

DISCLAIMER

Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the American Epilepsy Society or any manufacturers of pharmaceuticals.

Personalized Medicine in Epilepsy – A Brave New World

Dan Lowenstein, M.D.
University of California, San Francisco

December 8, 2015

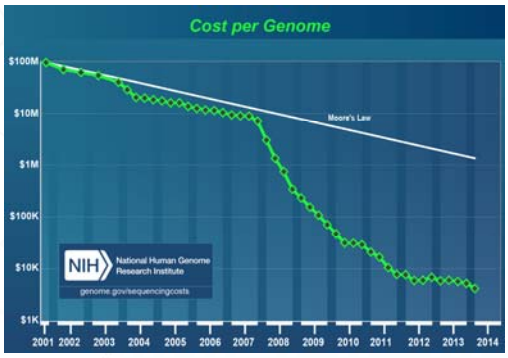
AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

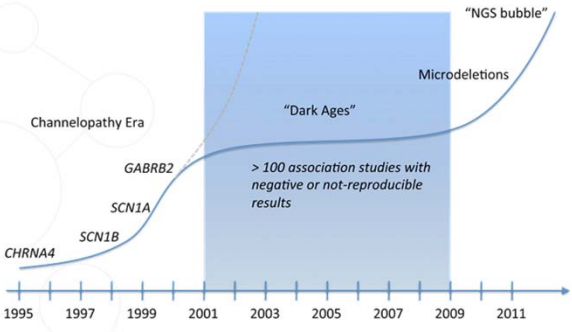
None

Jude Rouslin - *Grey Abstract*

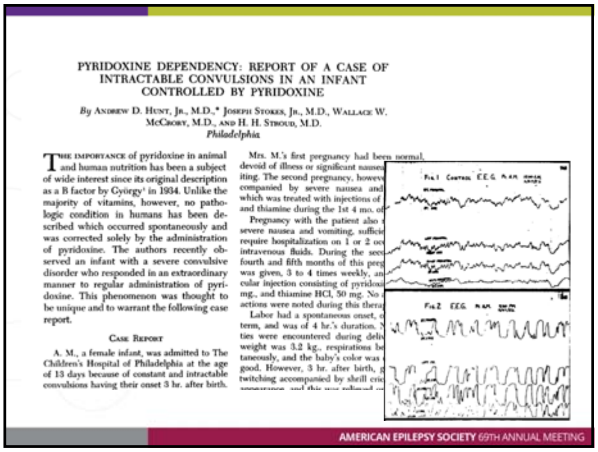
The Sequencing Revolution



Progress in Epilepsy Genetics



Helbig and Lowenstein, Current Opin Neurol. 2013; 26:179-185.



PYRIDOXINE DEPENDENCY: REPORT OF A CASE OF INTRACTABLE CONVULSIONS IN AN INFANT CONTROLLED BY PYRIDOXINE

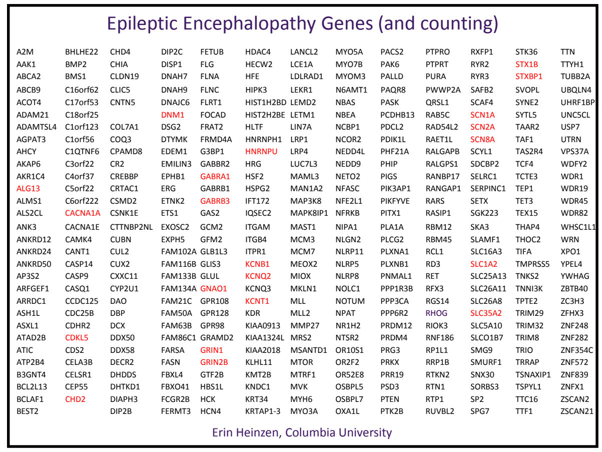
By Andrew D. Hunt, Jr., M.D.,* Joseph Stokes, Jr., M.D., Wallace W. McCrory, M.D., and H. H. Stroud, M.D.
Philadelphia

The importance of pyridoxine in animal and human nutrition has been a subject of wide interest since its original description as a B factor by György[1] in 1934. Unlike the majority of vitamins, however, no pathologic condition in humans has been described which occurred spontaneously and was corrected solely by the administration of pyridoxine. The authors recently observed an infant with a severe convulsive disorder who responded in an extraordinary manner to regular administration of pyridoxine. This phenomenon was thought to be unique and to warrant the following case report.

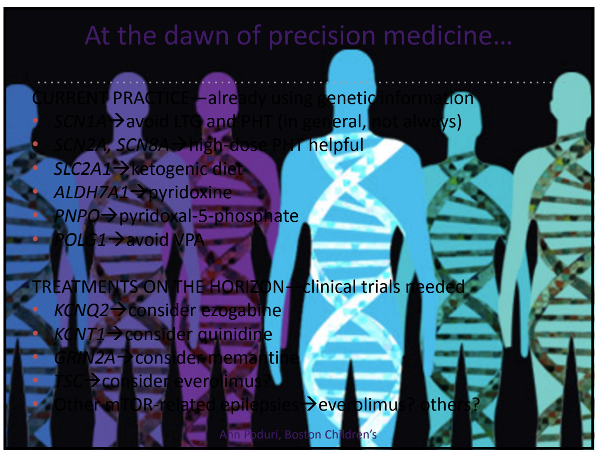
Case Report

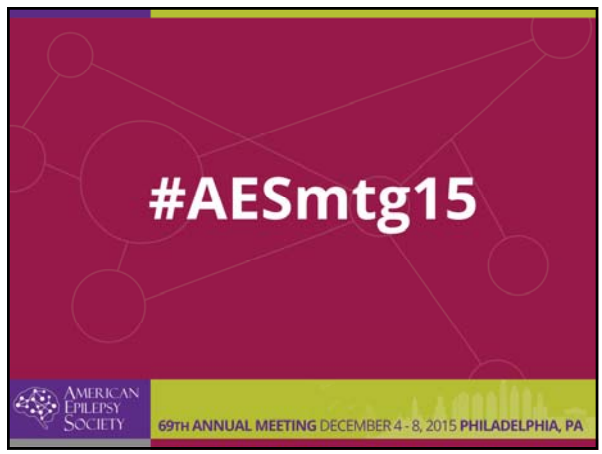
A. M., a female infant, was admitted to The Children's Hospital of Philadelphia at the age of 13 days because of constant and intractable convulsions having their onset 3 hr. after birth.

Mrs. M.'s first pregnancy had been normal,



A2M	BHLHE22	CHD4	DIP2C	FETUB	HDAC4	LANCL2	MYO5A	PACS2	PTPRO	RXFP1	STK36	TTN
AAK1	BMP2	CHIA	DISP1	FLG	HECW2	LCE1A	MYO7B	PAK6	PTPRT	RYR2	STX1B	TTYH1
ABCA2	BMS1	CLDN19	DNAH7	FLNA	HFE	LDLRAD1	MYOM3	PALLD	PURA	RYR3	STXBP1	TUBB2A
ABCB9	C16orf62	CLIC5	DNAH9	FLNC	HIPK3	LEKR1	N6AMT1	PAQR8	PWWP2A	SAFB2	SVOPL	UBQLN4
ACOT4	C17orf53	CNTN5	DNAJC6	FLRT1	HIST1H2BD	LEMD2	NBAS	PASK	QRSL1	SCAF4	SYNE2	UHRF1BP
ADAM21	C18orf25		DNM1	FOCAD	HIST2H2BE	LETM1	NBEA	PCDHB13	RAB5C	SCN1A	SYTL5	UNC5CL
ADAMTSL4	C1orf123	COL7A1	DSG2	FRAT2	HLTF	LIN7A	NCBP1	PDCL2	RAD54L2	SCN2A	TAAR2	USP7
AGPAT3	C1orf56	COQ3	DTYMK	FRMD4A	HNRNPH1	LRP1	NCOR2	PDIK1L	RAET1L	SCN8A	TAF1	UTRN
AHCY	C1QTNF6	CPAMD8	EDEM1	G3BP1	HNRNPU	LRP4	NEDD4L	PHF21A	RALGAPB	SCYL1	TAS2R4	VPS37A
AKAP6	C3orf22	CR2	EMILIN3	GABBR2	HRG	LUC7L3	NEDD9	PHIP	RALGPS1	SDCBP2	TCF4	WDFY2
AKR1C4	C4orf37	CREBBP	EPHB1	GABRA1	HSF2	MAML3	NETO2	PIGS	RANBP17	SELRC1	TCTE3	WDR1
ALG13	C5orf22	CRTAC1	ERG	GABRB1	HSPG2	MAN1A2	NFASC	PIK3AP1	RANGAP1	SERPINC1	TEP1	WDR19
ALMS1	C6orf222	CSMD2	ETNK2	GABRB3	IFT172	MAP3K8	NFE2L1	PIKFYVE	RARS	SETX	TET3	WDR45
ALS2CL	CACNA1A	CSNK1E	ETS1	GAS2	IQSEC2	MAPK8IP1	NFRKB	PITX1	RASIP1	SGK223	TEX15	WDR82
ANK3	CACNA1E	CTTNBP2NL	EXOSC2	GCM2	ITGAM	MAST1	NIPA1	PLA1A	RBM12	SKA3	THAP4	WHSC1L1
ANKRD12	CAMK4	CUBN	EXPH5	GFM2	ITGB4	MCM3	NLGN2	PLCG2	RBM45	SLAMF1	THOC2	WRN
ANKRD24	CANT1	CUL2	FAM102A	GLB1L3	ITPR1	MCM7	NLRP11	PLXNA1	RCL1	SLC16A3	TIFA	XPO1
ANKRD50	CASP14	CUX2	FAM116B	GLIS3	KCNB1	MEOX2	NLRP5	PLXNB1	RD3	SLC1A2	TMPRSS5	YPEL4
AP3S2	CASP9	CXXC11	FAM133B	GLUL	KCNQ2	MIOX	NLRP8	PNMAL1	RET	SLC25A13	TNKS2	YWHAG
ARFGEF1	CASQ1	CYP2U1	FAM134A	GNAO1	KCNQ3	MKLN1	NOLC1	PPP1R3B	RFX3	SLC26A11	TNNI3K	ZBTB40
ARRDC1	CCDC125	DAO	FAM21C	GPR108	KCNT1	MLL	NOTUM	PPP3CA	RGS14	SLC26A8	TPTE2	ZC3H3
ASH1L	CDC25B	DBP	FAM50A	GPR128	KDR	MLL2	NPAT	PPP6R2	RHOG	SLC35A2	TRIM29	ZFHX3
ASXL1	CDHR2	DCX	FAM63B	GPR98	KIAA0913	MMP27	NR1H2	PRDM12	RIOK3	SLC5A10	TRIM32	ZNF248
ATAD2B	CDKL5	DDX50	FAM86C1	GRAMD2	KIAA1324L	MRS2	NTSR2	PRDM4	RNF186	SLCO1B7	TRIM8	ZNF282
ATIC	CDS2	DDX58	FARSA	GRIN1	KIAA2018	MSANTD1	OR10S1	PRG3	RP1L1	SMG9	TRIO	ZNF354C
ATP2B4	CELA3B	DECR2	FASN	GRIN2B	KLHL11	MTOR	OR2F2	PRKX	RRP1B	SMURF1	TRRAP	ZNF572
B3GNT4	CELSR1	DHDDS	FBXL4	GTF2B	KMT2B	MTRF1	OR52E8	PRR19	RTKN2	SNX30	TSNAXIP1	ZNF839
BCL2L13	CEP55	DHTKD1	FBXO41	HBS1L	KNDC1	MVK	OSBPL5	PSD3	RTN1	SORBS3	TSPYL1	ZNFX1
BCLAF1	CHD2	DIAPH3	FCGR2B	HCK	KRT34	MYH6	OSBPL7	PTEN	RTP1	SP2	TTC16	ZSCAN2
BEST2		DIP2B	FERMT3	HCN4	KRTAP1-3	MYO3A	OXA1L	PTK2B	RUVBL2	SPG7	TTF1	ZSCAN21





Defining the target: Mutation discovery in human epilepsy

Heather C. Mefford, MD, PhD
University of Washington
Department of Pediatrics
Division of Genetic Medicine

December 8, 2015

American Epilepsy Society 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

None

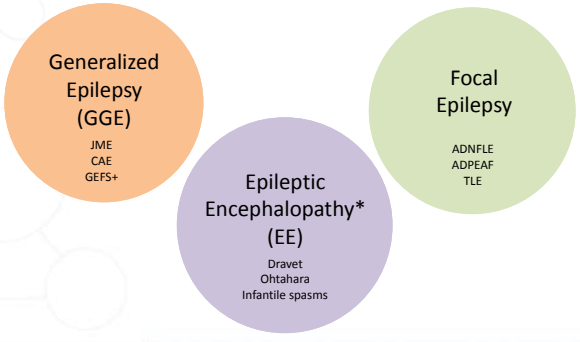
Learning Objectives

- Review types of epilepsy-associated genetic variants
- Define the role of whole exome sequencing in gene discovery
- Introduce examples of potential precision therapies

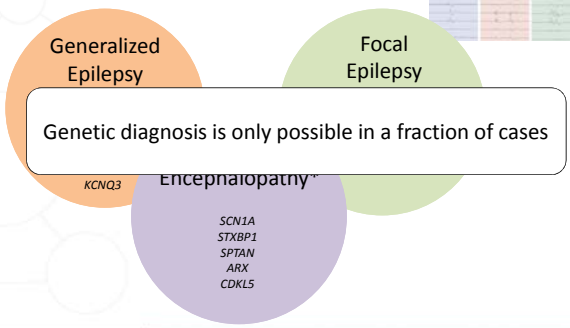
Impact on Clinical Care and Practice

- Providing "Precision Therapy" requires having a precise diagnosis
- Clinical whole exome sequencing provides a genetic diagnosis in a subset of affected individuals, which…
  - Improves prognosis and recurrence risk counseling
  - Connects patients to a community
  - Affects medical management

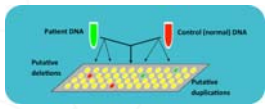
Epilepsy Classification

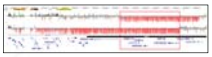


Epilepsy Genetics



Genomics & Epilepsy





ACTTCGGATGACCG

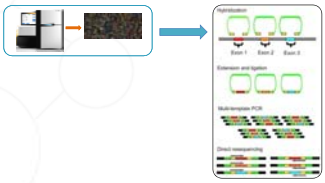
>3% GGE

5-10% EE

? Focal

NOVEL EPILEPSY GENES
*epileptic encephalopathy

Targeted sequencing in EE



>400 genes + ~1000 patients

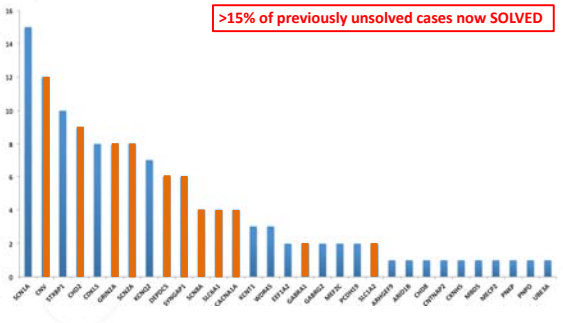
EE Cohort

Syndrome	Unsolved	Solved
Dravet	24	14
Epilepsy aphasia	46	10
Eyelid myoclonus	9	1
Early myoclonic	3	2
Early onset EE	32	11
Infantile spasms	89	8
Lennox Gastaut	41	4
Myoclonic astatic	88	8
Migrating focal sz of infancy	14	1
Ohtahara	2	2
ID+GGE	47	3
FE+ID	32	9
Other	253	47
TOTAL	**679**	**120**

Scheffer, Mefford, unpublished

Genetic heterogeneity in EE

>15% of previously unsolved cases now SOLVED

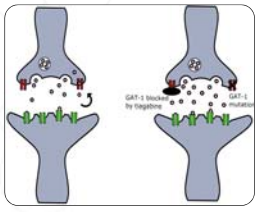


Carvill et al., 2013, Nat Genet & unpublished

SLC6A1: GABA transporter

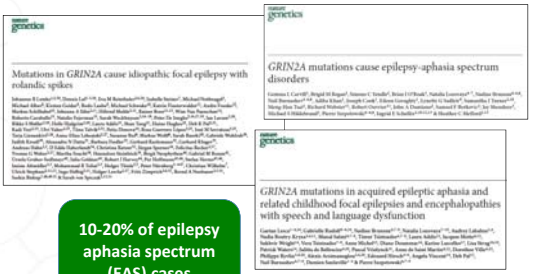
Mutations in the GABA Transporter *SLC6A1* Cause Epilepsy with Myoclonic-Atonic Seizures

Gemma L. Carvill,[1] Jacinta M. McMahon,[1] Amy Schneider,[2] Matthew Zemel,[1] Candace T. Myers,[1] Julia Saykally,[1] John Nguyen,[1] Angela Robbiano,[3] Federico Zara,[4] Nicola Specchio,[5] Oriano Mecarelli,[3] Robert L. Smith,[6] Richard J. Leventer,[7,8,9] Rikke S. Møller,[10,11] Marina Nikanorova,[10] Petia Dimova,[12] Albena Jordanova,[13,14,15] Steven Petrou,[16] EuroEPINOMICS Rare Epilepsy Syndrome Myoclonic-Astatic Epilepsy & Dravet working group, Ingo Helbig,[17,18] Pasquale Striano,[19] Sarah Weckhuysen,[13,14,20] Samuel F. Berkovic,[1] Ingrid E. Scheffer,[1,7,14,21,*] and Heather C. Mefford[2,22,*]



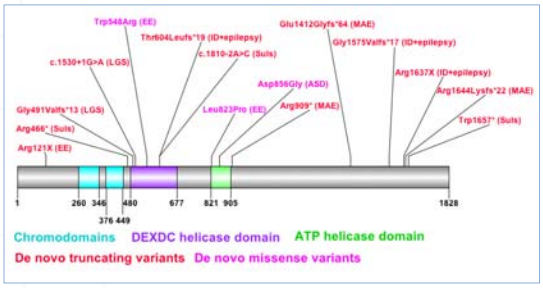
4% of myoclonic atonic epilepsy (MAE)

GRIN2A: glutamate receptor subunit



10-20% of epilepsy aphasia spectrum (EAS) cases

CHD2: chromatin remodeler



Carvill et al., 2012, Nat Genet
Thomas et al., 2015, Neurology

Epi4K: Trio sequencing in EE

INFANTILE SPASMS (IS)
- Onset in first year of life
- Characteristic EEG: hypsarrhythmia
- Often evolves to LGS

LENNOX GASTAUT SYNDROME (LGS)
- Onset before 4 years
- Multiple, refractory seizure types
- Moderate to severe ID

356 Trios analyzed: 429 de novo variants in >400 genes

~15% solved

Trio analysis

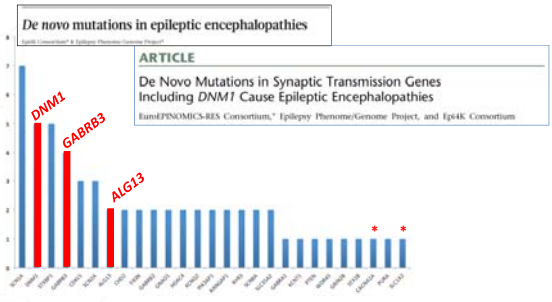
Sequence mom + dad + child

Look for *de novo* change in child

Severe, *de novo* disorders

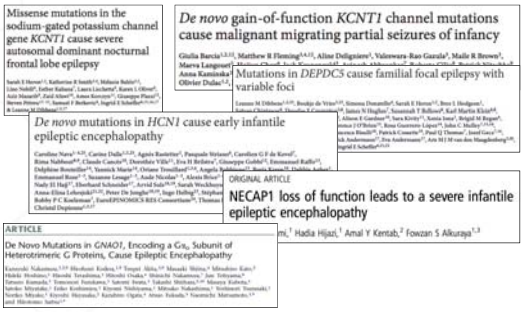
Collected by Epilepsy Phenome/Genome Project & EuroEPINOMICS Consortium

Epi4K: Trio sequencing in EE



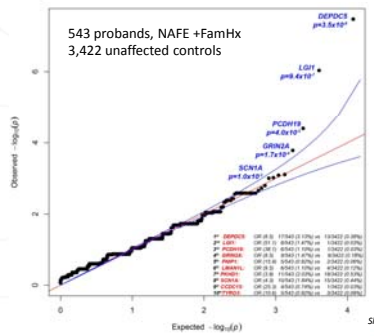
Follow-up targeted sequencing in candidates ongoing

Exome sequencing: Many successes



Exome analysis in focal epilepsy

543 probands, NAFE +FamHx
3,422 unaffected controls



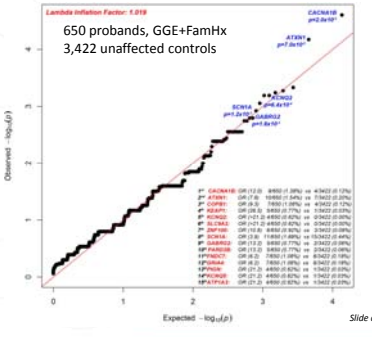
Qualifying variant:
- *LoF/damaging*
- *MAF <0.05%*
- *MAF <0.001% EVS and ExAC*

Likelihood of seeing top 4/18K ranks occupied by 4/43 *bona fide* dominant epilepsy genes
Hypergeometric p = 2.7x10^{-11}

Slide courtesy of Slave Petrovski, Epi4K (unpublished)

Exome analysis in generalized epilepsy

650 probands, GGE+FamHx
3,422 unaffected controls



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Slide courtesy of Slave Petrovski, Epi4K (unpublished)

Precision Medicine in Epilepsy

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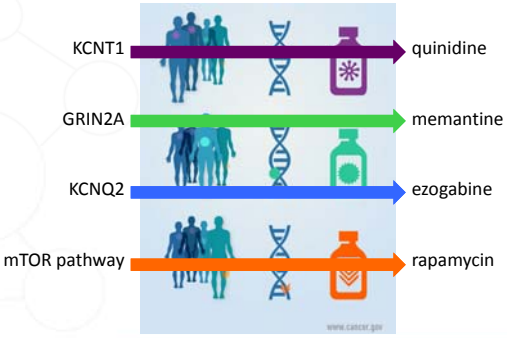
Precision Medicine in Epilepsy



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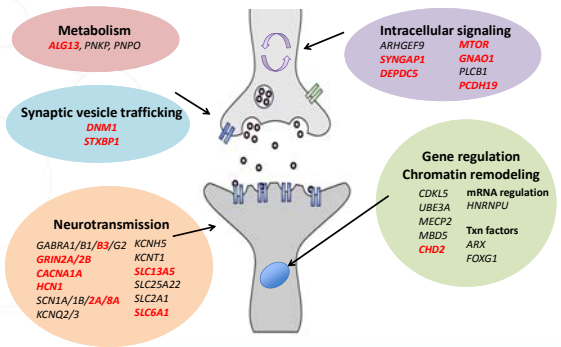
Diverse biological mechanisms



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How do we solve the rest?

- **Epilepsy Genetics Initiative (EGI)**
  - Repository for exome data
  - Regular re-analysis of data
  - CURE Foundation + NINDS
- **Epi25**
  - International effort to combine available cohorts
  - >30,000 available epilepsy samples identified
  - Whole genome sequencing

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How do we solve the rest?

- **Noncoding variation**
  - Do regulatory variants play a role?
  - Whole genomes + RNA-seq
- **Epigenetics**
  - Which assays? How to validate?
- **Somatic mosaic mutations**
  - Tissue type and access
  - Sensitive techniques

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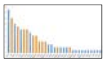
Summary

- Accelerated gene discovery in EE

- Significant genetic heterogeneity



- Genetics teaching us about biology

- Precision medicine in epilepsy looks promising

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Acknowledgments

Mefford Lab
Gemma Carvill
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Ann Poduri
Elliott Sherr
Dennis Dlugos
Slave Petrovski
Erin Heinzen
epi4k.org

NINDS 2R01NS069605
NINDS 1U01NS077303
NINDS 1U01NS077364

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#AESmtg15

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Precision Medicine in Zebrafish: A Primer Using SCN1 Mutants

Scott C. Baraban, PhD
University of California, San Francisco
@BarabanLab

December 8, 2015

American Epilepsy Society
69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

Name of Commercial Interest	Nothing to disclose

Learning Objectives

- To understand the value of zebrafish as a simple vertebrate model for genetic epilepsies and precision medicine
- To examine the research tools available in zebrafish
- To characterize scn1 mutant zebrafish
- To explore the potential for HTS in scn1 mutants

Precision medicine in epilepsy

- **Problem:** How to rapidly identify new and effective drugs for rare, genetic, and catastrophic childhood epilepsies?
- **Solution:** A strategy using genetically engineered zebrafish

Dravet syndrome (*scn1, scn8, gabra1, hcn1*)

Classical Lissencephaly (*lis1*)

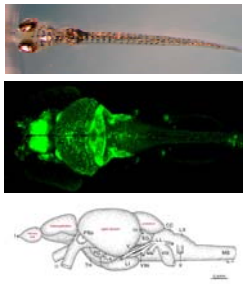
Epileptic encephalopathy (*stxbp1, dnm1, depdc5, grin2b*)

Lennox-Gastaut syndrome (*gabrb3, chd2, cdkl5*)

PCDH19 female epilepsy (*pcdh19*)

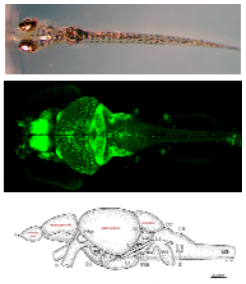
An introduction to zebrafish (*Danio rerio*)

- Vertebrate
- Transparent
- 100s offspring
- Genetic tractable
- Rapid development
- Permeable to drugs



Tools available in zebrafish

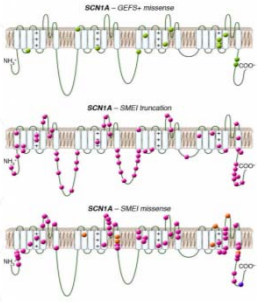
- **CRISPR/Cas9 gene editing**
- **Whole-brain imaging**
  - **GCaMP expressing zebrafish**
- **High-throughput electrophysiology**
  - **integrated Zebrafish Activity Platform**
- **Metabolic function assays**
- **Cardiac function assays**
- **Sleep-wake patterns**
- **Kaplan-Meir survival**



Precision medicine in zebrafish – scn1

- Dravet syndrome
- *scn1* mutant zebrafish
- Screening commercially available libraries
- Lead compound identification

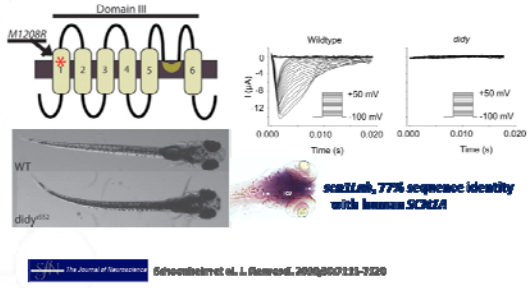
Dravet syndrome – *SCN1* mutation



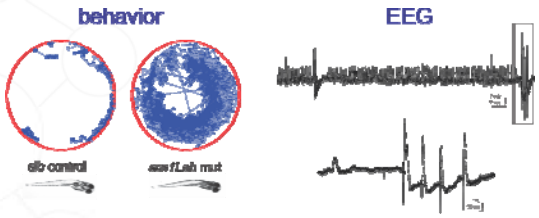
Meisler and Kearney 2005

- Developmental delay
- Early onset (< 1 y.o.)
- Balance issues
- Delayed language
- Cognitive problems
- Autonomic problems
- Sleep disturbance
- Drug-resistant
- Reduced lifespan

Dravet syndrome - *scn1* mutant zebrafish



Epilepsy phenotype in *scn1* mutants



Summary of progress to date

- **Generated 6 new zebrafish mutant lines**
- **Screened >1600 compounds**
- **Identified 72 hits (~4%) in first-pass locomotion assays**
- **Classified >200 compounds (~13%) as toxic**
- **Identified 5 antiepileptic lead compounds (including clemizole) with subsequent retests and electrophysiology**

Impact on Clinical Care and Practice

- **Zebrafish can be used to model specific human genetic forms of epilepsy**
  - Dravet Syndrome zebrafish mutant
  - CRISPR/Cas9 gene editing
  - Multiple behavioral and functional read-outs
- **Drugs identified in scn1 zebrafish screens**
  - Fenfluramine, dimethadione, ketogenic diet, etc.
  - Clemizole

Patient-derived iPS Cells to Understand Epileptic Encephalopathy and SUDEP

Lori L. Isom, Ph.D.
Professor and Chair of Pharmacology
University of Michigan

December 8, 2015

69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

None

Learning Objectives

To understand the mechanism of epileptic encephalopathy:

- Model choice is critical.
- Mice are not small humans.
- Genetic background is important.
- No single model is sufficient – the truth lies at the intersection of models.

Impact on Clinical Care and Practice

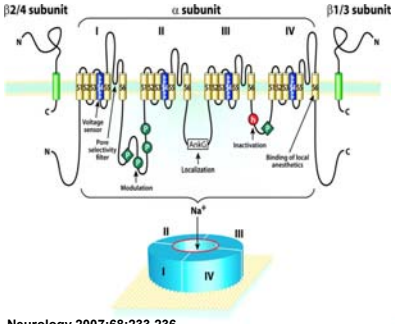
- Patient-derived iPSC cardiac myocytes may provide novel biomarkers for SUDEP risk.
- Patient-derived iPSC neurons and cardiac myocytes may be valuable platforms for drug discovery.

Our translational team

Lori Isom, PhD Jack Parent, MD Miriam Meisler, PhD Jose Jalife, MD

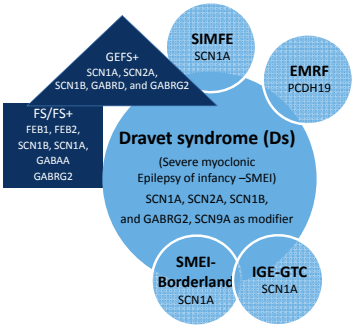



Na+ channels are essential for firing of nerve and heart cells



Benarroch, E. E. Neurology 2007;68:233-236

Sodium channel *SCN1A* is an important gene linked to genetic epilep



http://www.ice-epilepsy.org/ice-informational-brochure.html

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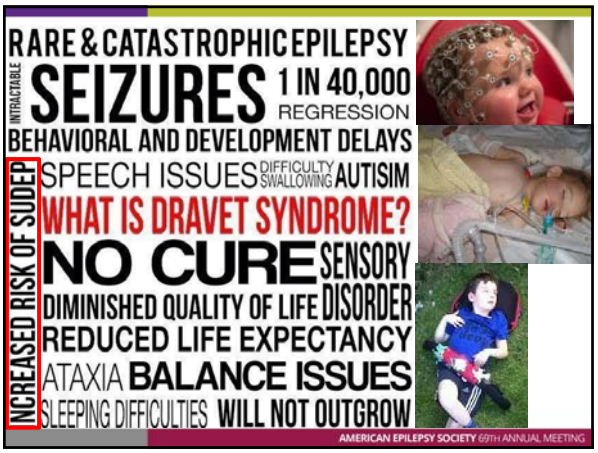

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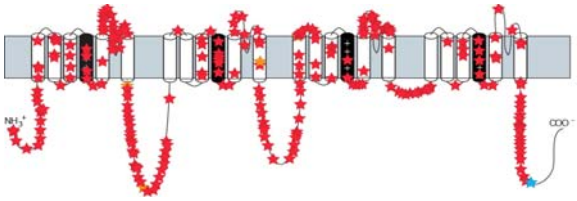
SCN1A and Dravet Syndrome

- Majority of DS cases are caused by *de novo* mutations in the sodium channel gene encoding Nav1.1, *SCN1A*, resulting in haploinsufficiency.
- 50% *SCN1A* is insufficient for normal neuronal function



Kearney and Meisler, 2010

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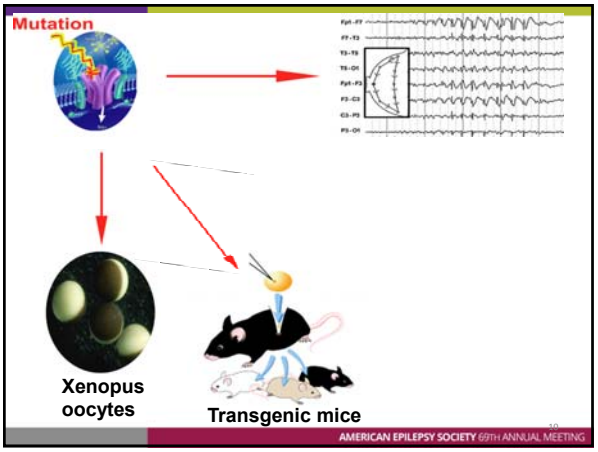

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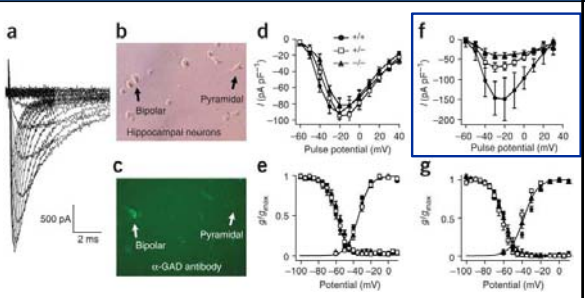
Scn1a$^{+/-}$ mice have reduced Na^+ current in acutely isolated hippocampal GABAergic neurons



Yu et al., *Nature Neuroscience*, 2006

Disinhibition?

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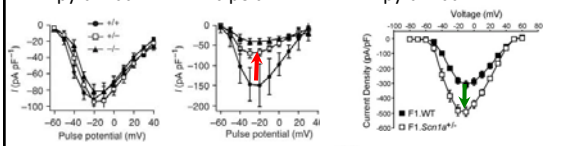
The Plot Thickens!

P14
pyramidal bipolar

P21-24
pyramidal



Yu et al., *Nature Neuroscience*, 2006

Decreased Na+ current in bipolar neurons. No change in pyramidals.

F1.*Scn1a*$^{+/-}$

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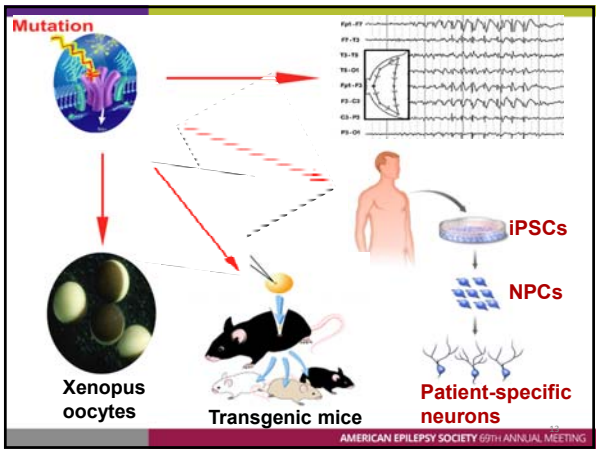
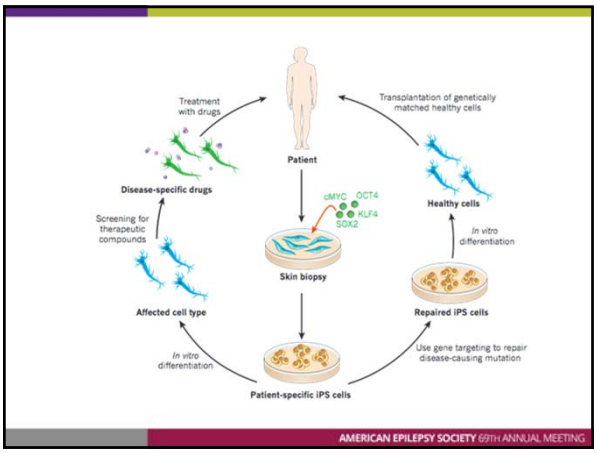
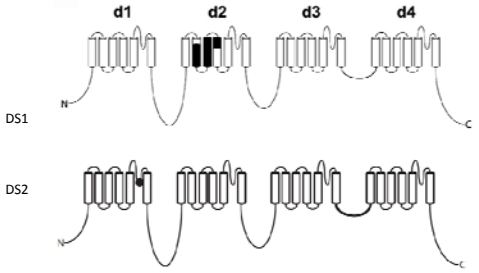




Why use iPSCs to model human genetic epilepsy?

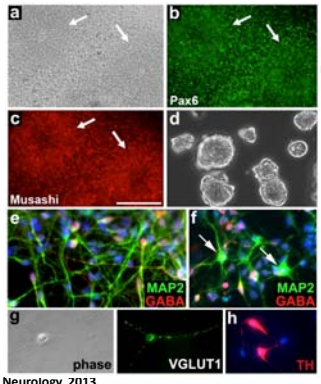
- Genetic background is key
- Mice are not small humans
  - 20% of CNS genes show distinct cortical expression patterns between human and rodent
  - Human and mouse brain development are different:
  - Germinal zone of the developing cerebral mantle is proportionately larger in humans - especially the human outer subventricular zone which contains many outer radial glia (oRG) that are rare in mice
  - The expanded outer SVZ and oRG seen in the human embryonic dorsal forebrain appear to be present in human iPSCs cultured as organoids

iPSC neurons were generated from 2 *SCN1A*-linked DS patients and 3 non-epileptic controls



Liu et al., Annals of Neurology, 2013

Neuronal differentiation of patient iPSCs



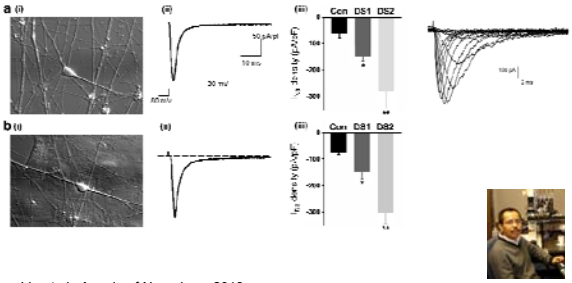
Differentiated neural rosettes expressed NPC markers.

Neuronal differentiation: 90% GABAergic 10% Glutamatergic rare TH+

Yu Liu, PhD

Liu et al., Annals of Neurology, 2013

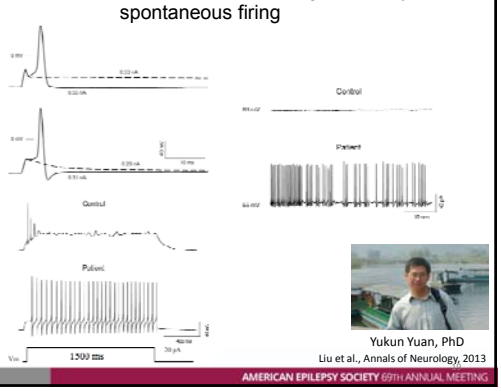
Na+ current density is increased in iPSC pyramidal and bipolar neurons derived from DS1 and DS2 patients at 3 weeks post differentiation.



Liu et al., Annals of Neurology, 2013

Luis Lopez-Santiago, PhD

DS patient-derived bipolar and pyramidal neurons have reduced thresholds for AP initiation, increased firing frequency, and spontaneous firing



Yukun Yuan, PhD

Liu et al., Annals of Neurology, 2013

What is the mechanism:

Slide not available

Will Brackenbury, PhD and Heather O'Malley, PhD

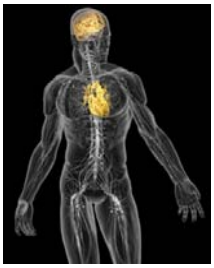
SCN8A-shRNA normalizes sodium current and AP firing properties in DS iPSC neurons

Slide not available

Yu Liu, PhD, Luis Lopez-Santiago, PhD, Yukun Yuan, PhD

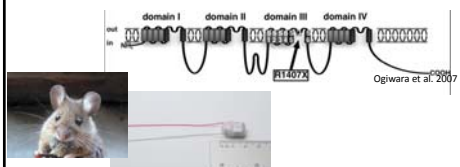
Proposed mechanism of SUDEP in Dravet Syndrome:

Mutant *SCN1A* expressed in brain and heart.

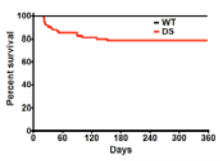


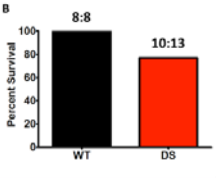
http://persondevelopment.wordpress.com/2013/02/14/heart-brain-connection/

Do DS mice have a cardiac phenotype?



Ogiwara et al. 2007

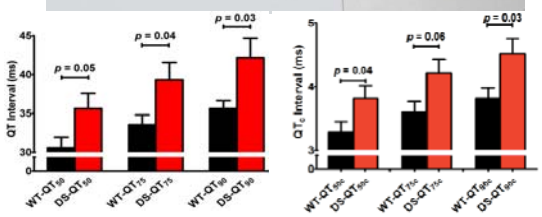




David Auerbach, Ph.D.

PLoS One. 2013 Oct 14;8(10):e77843.

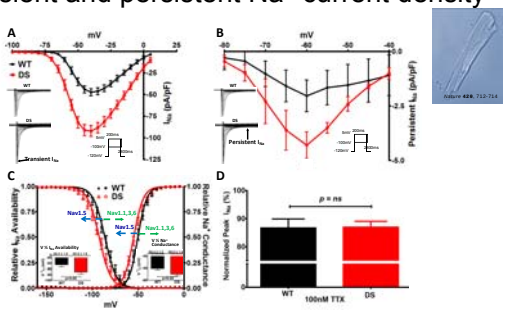
DS mice have prolonged QT intervals



PLoS One. 2013 Oct 14;8(10):e77843.

David Auerbach, Ph.D.

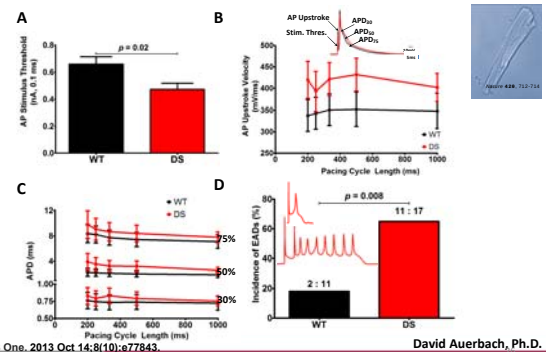
DS mouse myocytes have increased transient and persistent Na^+ current density



PLoS One. 2013 Oct 14;8(10):e77843.

David Auerbach, Ph.D.

DS mouse myocytes exhibit increased excitability and incidence of early after depolarizations



PLoS One. 2013 Oct 14;8(10):e77843.

David Auerbach, Ph.D.

What happens in DS patient iPSC cardiac myocytes?

Helen Zhang and Chad Frasier, Ph.D.

Nav1.5 α-actinin

Slide not available

James Offord, PhD

DS patient iPSC-CMs have increased beating rates

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Helen Zhang

DS iPSC CMs have increased Na^+ current density

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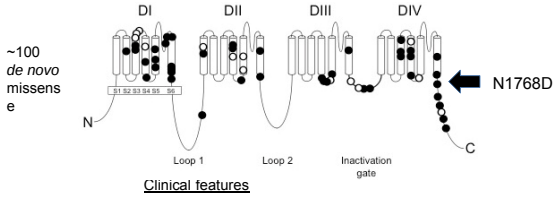
Chad Frasier

Is the iPSC model informative for other genetic epilepsies?

SCN8A mutations in early-infantile epileptic encephalopathy (EIEE13, OMIM #614558)



Clinical features

- Seizure onset 0-18 months
- Refractory to treatment
- Developmental delay and/or regression
- Intellectual disability
- Movement disorders
- Risk of SUDEP

Acutely isolated neurons from *SCN8A*-EIEE13 mice have increased persistent Na^+ current

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SCN8A-EIEE13 patient iPSC neurons have increased persistent Na^+ current

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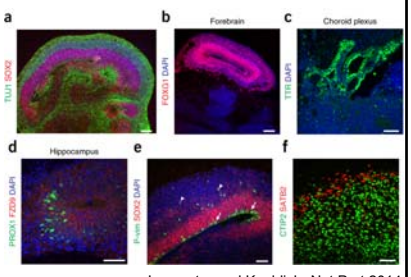
Luis Lopez-Santiago, PhD and Andrew Tidball, PhD

What is the next step for iPSCs?

Cerebral Organoid Cultures from Human iPSCs

- Human iPSCs can generate 3D organoid cultures
- Yield VZ, SVZ and cortical layers
- Show radial migration of excitatory and tangential migration of inhibitory neurons



Lancaster and Knoblich, Nat Prot 2014

hiPSC-derived cerebral organoid – 1 month

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Xi Du

At 1 month, organoids form a pseudostratified ventricular zone that expresses Sox2 and Pax 6 around a ventricular-like lumen.

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Xi Du

CSR THE CENTER FOR SUDEP RESEARCH

DRAVET SYNDROME

EPILEPSY FOUNDATION

CURE EPILEPSY

AMERICAN EPILEPSY SOCIETY

National Institute of Neurological Disorders and Stroke

UNIVERSITY OF MICHIGAN Rare Disease Initiative

Center for Organogenesis

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#AESmtg15

AMERICAN EPILEPSY SOCIETY

69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Application of Precision Medicine in Patients with *KCNT1* Mutation

Ethan M. Goldberg, MD, PhD
Division of Neurology
The Children's Hospital of Philadelphia

December 8, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

Commercial Interests: none.

The speaker will be discussing the off-label use of quinidine for the treatment of epilepsy.

Learning Objectives

- Recognize genetic causes of epilepsy that may be amenable to a precision medicine approach
- Provide an update on emerging findings in precision medicine in the epilepsies
- Counsel patients and families regarding opportunities for and limitations of a precision medicine approach to treatment of the epilepsies

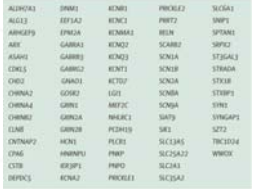
Personalized/Precision Medicine: What is it?

- To allow clinicians to accurately predict the most efficacious treatment (*typically a drug*) and/or avoid potential complications of treatment, using patient-specific (*often genetic*) data
- Hypothesis: Use of a marker to match treatment to mechanism of disease will provide clinical benefit

Personalized/Precision Medicine: what is it?

- The practice of medicine – including the care of patients with epilepsy – is *im*precise.
  - physiology/pathophysiology is complicated
  - in many cases, the cause of epilepsy is not known
- Genetics is a potential source of increased precision.
  - Genetics contributes to the complexity of physiology
  - provides a potential mechanism for disease. Without a mechanism, it can be difficult or impossible to determine the optimal treatment for a given disease

Genetics is an important cause of epilepsy



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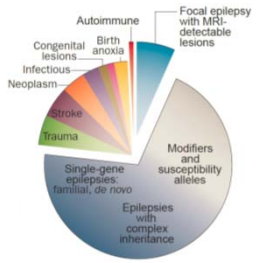

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Personalized Medicine in Epilepsy: Pharmacogenetics

Pharmacogenomics: Actionable somatic (non-tumor genetic variants and associated medications)

Genetic variation	Medications	Side effect
TPMT	Mercaptopurine, thioguanine, azathioprine	myelotoxicity
CYP2D6	Codeine, tramadol, tricyclic antidepressants	"ultrametabolism"
CYP2C19	Tricyclic antidepressants, clopidogrel, voriconazole	"poor metabolizers"
CYP2C9	Warfarin, **phenytoin**	reduced drug clearance
VKORC1	Warfarin	increased sensitivity
HLA-B	Allopurinol, abacavir, **carbamazepine** (HLA-B*15:02), **phenytoin**	SCAR; SJS
CFTR	Ivacaftor	CFTR potentiator
DPYD	Fluorouracil, capecitabine, tegafur	toxicity (mucositis, etc)
G6PD	Rasburicase	hemolysis
UGT1A1	Irinotecan, atazanavir	toxicity (neutropenia, etc)
SLCO1B1	Simvastatin	myopathy
IFNL3 (IL28B)	Interferon	improved response
CYP3A5	Tacrolimus	increased clearance

3. PharmGKB. CPIC Genes/Drugs. PharmGKB https://www.pharmgkb.org/cpic/pairs (2015).

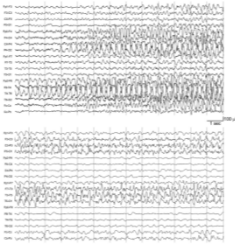
Personalized Medicine in Epilepsy: Examples of targeted/precision treatments

Precision medicine for genetic epilepsies

Epilepsy syndrome	Gene	Treatment	Mechanism of action	Effect on seizure frequency	Development/ cognition	Reference
KCNQ2 encephalopathy	*KCNQ2*	retigabine	KCNQ channel activator	--	--	Orhan et al, 2014
Epilepsy-aphasia spectrum disorders	*GRIN2A*	memantine	Multiple; low-affinity NMDA-R antagonist	Decrease from 11 to 3 seizures/week	None	Pierson et al, 2014; Yuan et al, 2014
Epilepsy of Infancy w/ Migrating Focal Seizures (EIMFS)	***KCNT1***	**quinidine**	KCNT1 antagonist; multiple targets	Seizure-free; previously 5-20 seizures per day	improved alertness, language, motor function	**Bearden et al, 2014**
PMSE ("Pretzel syndrome")	*STRADA*	rapamycin	mTOR inhibitor	4/5 patients seizure-free		Parker et al, 2013
Tuberous sclerosis	TSC1 & 2	everolimus	mTOR inhibitor	≥50% reduction in 12 of 20 patients	improved behavior	Krueger et al, 2013
pyridoxine-dependent epilepsy	*ALDH7A1*	vitamin B6	replacement			Mills et al, 2006
GLUT1 deficiency syndrome	*SLC2A1*	Ketogenic diet	alternative energy source			Klepper et al, 2005

Targeted treatment of Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) due to *KCNT1* mutation with quinidine

- seizure onset at 10 weeks
- focal EEG discharges "migrate" between left/right hemispheres
- arrest of psychomotor development
- Pharmacoresistance
- normal MRI of the brain
- Whole exome sequencing revealed *de novo* mutation in *KCNT1* (p.Arg428Gln)



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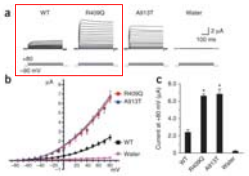
De novo activating mutation of *KCNT1* is a cause of Epilepsy of Infancy w/ Migrating Focal Seizures

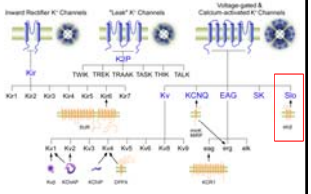
- **Genetic pleiotropy** of *KCNT1*: mutations in *KCNT1* are associated with a range of epilepsy phenotypes (EIMFS, ADNFLE, Ohtahara syndrome; Møller et al, 2015)
- **Genetic heterogeneity** of EIMFS: EIMFS is associated with mutation in multiple genes (*KCNT1, PLC-β1, SLC25A22, SCN1A, SCN2A, SCN8A, TBC1D24*)



4. Barcia, G., Fleming, M.R., Deliniere, A., *et al*. 2012. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nat Genet; 44(11):1255-9.

De novo activating mutation of *KCNT1* is a cause of Epilepsy of Infancy w/ Migrating Focal Seizures

- *KCNT1* encodes the pore-forming subunit of the sodium-activated potassium channel Slo2.2 (Slack)
- Voltage- and sodium-dependent
- Highly expressed in brain
- Regulate neuronal excitability
- Directly interacts with FMRP (Brown *et al*, 2010; Zhang *et al*, 2012)



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6. Brown, M.R., Kronengold, J., Gazula, V.R., *et al* (2010). Fragile X mental retardation protein controls gating of the sodium-activated potassium channel Slack. Nat Neurosci; 13: 819–821.
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Multiple mechanisms of epilepsy-associated ion channel/transmitter receptor gene mutation

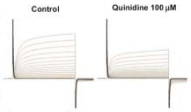
- Promoter mutations leading to reduced transcription
- Early exon nonsense mutations leading to impaired translation of truncated subunits (via NMD)
- Nonsense mutations with ER retention of truncated subunits
- Missense mutations leading to misfolding and degradation of subunits (via ERAD)
- **Impaired receptor function** (hypo- or **hyperfunction**)

8. Slide provided by Robert L. Macdonald, M.D., Ph.D., Department of Neurology, Vanderbilt University.

Targeted treatment of EIMFS due to *KCNT1* mutation with quinidine

Pharmacologic inhibitors of *KCNT1* activity

Category	Agent	IC_{50} (mM)	References
Peptide toxins			
	charybdotoxin		
	iberiotoxin		
Gating inhibitors			
	Ca	6.5	Paulais et al, 2006.
	bepridil	5.0 - 6.0	Anderson et al, 2006; Bhattacharjee et al, 2003; Yang et al, 2006.
Channel blocking antagonists			
	quinidine	1.7 - 2.0	Bhattacharjee et al, 2005.
	TEA	4.0	Yang et al, 2006.

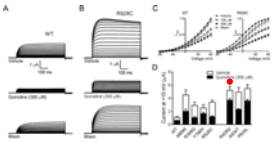


- **From 5-20 seizures per day to seizure-free**
- Sustained seizure freedom for > 1 year on quinidine at 45 mg/kg/day
- Serum quinidine levels monitored and remained 2-5 µg/mL
- Frequent EKG to monitor for LQT
- no change in levels of other anti-seizure medications

9. Yang, B., Gribkoff, V.K, Pan, J., *et al*. (2006). Pharmacological activation and inhibition of Slack (Slo2.2) channels. Neuropharmacology; 51(4):896-906.

Quinidine normalizes currents due to pathological *KCNT1* mutations *in vitro*

- Quinidine inhibits *KCNT1* mutant currents
- R428Q mutation exhibits very large current and inhibition by quinidine
- mutant current magnitude not clearly related to phenotype (Kim et al, 2014)
- R398Q (Møller et al, 2015) and G288S (Kim et al, 2014) cause both phenotypes



10. Milligan, C.J., Li, M., Gazina, E.V., *et al.* (2014). *KCNT1* gain-of-function in two epilepsy phenotypes is reversed by quinidine. Ann Neurol; 75(4):581-90.
11. Mikati, M.A., Jiang, Y.-H., Carboni, M., *et al*. (2015). Quinidine in the treatment of KCNT1 positive epilepsies. *Ann Neurol*. Sep 15. doi: 10.1002/ana.24520. [Epub ahead of print].
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Targeted treatment of EIMFS due to *KCNT1* mutation with quinidine

- Cross sectional survey/case series of 10 patients with EIMFS and *de* novo *KCNT1* mutation
- Two patients seizure-free
- Three additional patients with EIMFS without *KCNT1* mutation had no response to quinidine
- Mikati *et al* (2015) report a case of EIMFS due to *KCNT1* mutation with 80% seizure reduction with quinidine; a patient with ADNFLE due to *KCNT1* mutation did not respond to quinidine.

Quinidine for EIMFS due to *KCNT1* mutation

Patient	Age at initiation (months)	Dose (mg/kg/d)	Serum levels (µg/mL)	Mutation	Side effects	Response
1	25	45	1.5 - 2.1	p.R428Q	None	**Seizure-free**; Improved cognition
2	9	120	1.1 - 4.1	p.R961S	LQT	**Seizure-free**; Improved cognition
3	15	60	1.2	p.M267T	None	~50% reduction in seizures
4	20	107	2.1	p.G288S	Irritable	~50% reduction in seizures
5	9	60	2.0 - 5.5	p.D413N	None	~50% reduction in seizures
6	31	200	3.0 - 6.9	p.R398Q	Reflux	Slight reduction in seizures
7	33	58	--	p.R474C	LQT	Slight reduction in seizures
8	15	60	--	p.M354R	LQT	None
9	4	60	--	p.R474H	None	None
10	36	60	--	p.M889I	None	None

13. Bearden, D., Strong, A., Ehnot, J., *et al*. (2015). Targeted treatment of migrating partial seizures of infancy with quinidine. Neurology vol. 84 no. 14 Supplement I6-2B.
14. Mikati, M.A., Jiang, Y.-H., Carboni, M., *et al*. (2015). Quinidine in the treatment of KCNT1 positive epilepsies. *Ann Neurol*. Sep 15. doi: 10.1002/ana.24520. [Epub ahead of print].

Is quinidine an anti-seizure medication?

- Crystalline alkaloid; stereoisomer of quinine
- Class 1a antiarrhythmic via use dependent block of sodium current; also blocks multiple potassium channels.
- Blocks connexin 36 channel gap junctions (Srinivas et al, 2001)
- Combined with dextromethorphan for treatment of pseudobulbar affect in patients with MS and ALS
- Indicated (not first-line) treatment of *P. falciparum* malaria

Block of sodium (Na) channels by quinidine

Channel/ Subunit	Gene symbol	Inhibited (Y/N)	Action	IC_{50} (mM)	Associated disease
Nav1.1	*SCN1A*	N			DS spectrum; GEFS+; other EE; FHM3
Nav1.2	*SCN2A*	N			BFIS; EIEE11
Nav1.3	*SCN3A*	N			
Nav1.4	*SCN4A*	N			Congenital myasthenic syndrome; NPP
Nav1.5	*SCN5A*	Y	Pore block	4.4-5.0	Brugada syndrome 1; LQT3
Nav1.6	*SCN8A*	N			EIEE13; cognitive impairment w/ ataxia
Nav1.7	*SCN9A*	N			Erythermalgia; modifier of DS?
Nav1.8	*SCN10A*	N			Pain syndromes[2]
Nav1.9	*SCN11A*	N			Pain syndromes[3]

Is quinidine an anti-seizure medication?

- Long been known to have anticonvulsant properties (Steriade and Stoica, 1960a; 1960b; 1961) in experimental animals
- Overdose can cause seizures in humans (Kerr et al, 1971)
- Ineffective in 3 cases of non-*KCNT1* EIMFS (Bearden et al, 2015)
- Ineffective in the treatment of ADNFLE due to *KCNT1* mutation (*n* = 1; Mikati et al, 2015)

Inhibition of Potassium (K) channels by quinidine

Subfamily	Channel/ Subunit	Gene symbol	Other names	Affinity IC_{50} (mM)	Affinity pK	Affinity Conc (mM)	References	Other channel blockers/inhibitors	Associated disease
Ca2+-activated (3/8)									
	KNa1.1	*KCNT1*	Slo2.2; Slack	4.0			Yang et al, 2006.	ChbTx; IbTx; TEA; bepridil	EIMFS; ADNFLE; etc
	KNa1.2	*KCNT2*	Slo2.1; Slick	--		1.0	Bhattacharjee et al, 2003.	ChbTx; IbTx; TEA; Ba^{2+}	
	KCa5.1	*KCNU1*	Slo3	--		--	Tang et al, 2010.	ChbTx; IbTx; TEA	
Inwardly rectifying (0/15)									
Voltage gated (5/40)									
	Kv1.4	*KNCA4*		3.7			Yamagishi et al, 1995.		Epilepsy Kv1.4$^{-/-}$ mice
	Kv1.5	*KCNA5*			5.2		Snyders et al, 1992.		
	Kv1.7	*KCNA7*			4.8		Bardien-Kruger et al, 2002.		
	Kv10.1	*KCNH1*	EAG1	5.8			Schönnher et al, 2002.		
	Kv10.2	*KCNH5*	EAG2	3.8			Gessner et al, 2004.		Epileptic encephalopathy
Two-pore (0/15)									

Targeted treatment of Epilepsy of Infancy with Migrating Focal Seizures due to *KCNT1* mutation with quinidine: *Summary*

- Quinidine may be an effective treatment for seizures in a subset of patients with EIMFS due to *KCNT1* mutation, perhaps in patients with mutations that produce markedly increased currents that are effectively inhibited by quinidine
- The mechanism of this effect is unknown, but is presumed to be due to normalization of *KCNT1* mutant current
- Only mild effects on development/cognition

Targeted treatment of Epilepsy of Infancy with Migrating Focal Seizures due to *KCNT1* mutation with quinidine: *Future Directions*

- Dose-finding study; Multicenter RCT
- What is the mechanism by which quinidine reduces seizure frequency in patients with EIMFS due to *KCNT1* mutation?
- What is the basis of the genetic pleiotropy seen in the *KCNT1* epilepsy spectrum?
- Can a more specific agent yield better results, such as greater improvement in development/cognition?

Targeted treatment of Epilepsy of Infancy with Migrating Focal Seizures due to *KCNT1* mutation with quinidine: *The case report approach*

- Disadvantages
  - Heavily subject to bias
  - Failures unlikely to be reported
- Advantages
  - Inexpensive
  - Easily replicable
  - Can provide a novel insight into treatment of disease
  - Can fill a gap in knowledge when larger series do not exist

Personalized/Precision Medicine: *Limitations*

- Results of early-stage testing in the cancer field correlates poorly with performance of drugs in later, larger-scale trials.
- Successes may be syndrome-, gene-, mutation-, or even patient-specific
- the development of novel compounds may be required, that are subunit- or even mutation-specific
- Moves us away from “one treatment to cure all epilepsy”
- What about effects on epilepsy-associated comorbidities?

Personalized/Precision Medicine: *The Future*

- To provide a greater mechanistic insight into rare causes of epilepsy, which in turn might yield general principles that apply to all epilepsy
- Involvement of partners in the pharmaceutical industry
- Parent groups: offers unique opportunity for high participation rates in trials
- Look for “super responders” (as in immunotherapy for cancer)
- Develop time- and cost-efficient ways to test for and implement precision medicine therapies

Impact on Clinical Care and Practice

- **Clinical utility**: whether the use of a test leads to improved clinical outcome for patients while avoiding adverse effects attributable to the test
- **Forward-and-backward translation** between clinicians and researchers
- **Multi-center clinical trials**

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National Institute of Neurological Disorders and Stroke

Clayton's Hope Organization

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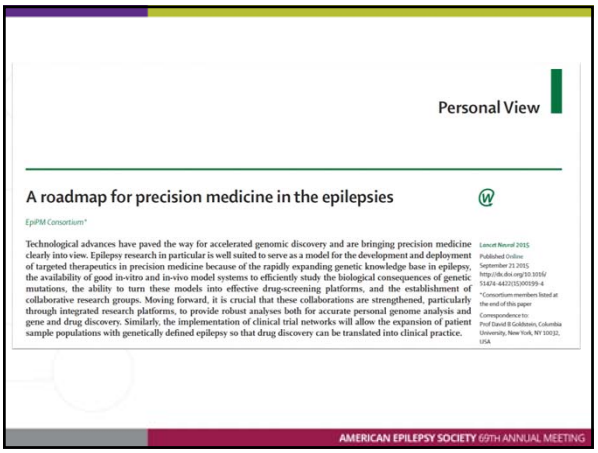
Jude Rouslin - *Grey Abstract*


Personal View
A roadmap for precision medicine in the epilepsies
EpiPM Consortium*
Technological advances have paved the way for accelerated genomic discovery and are bringing precision medicine clearly into view. Epilepsy research in particular is well suited to serve as a model for the development and deployment of targeted therapeutics in precision medicine because of the rapidly expanding genetic knowledge base in epilepsy, the availability of good in-vitro and in-vivo model systems to efficiently study the biological consequences of genetic mutations, the ability to turn these models into effective drug-screening platforms, and the establishment of collaborative research groups. Moving forward, it is crucial that these collaborations are strengthened, particularly through integrated research platforms, to provide robust analyses both for accurate personal genome analysis and gene and drug discovery. Similarly, the implementation of clinical trial networks will allow the expansion of patient sample populations with genetically defined epilepsy so that drug discovery can be translated into clinical practice.
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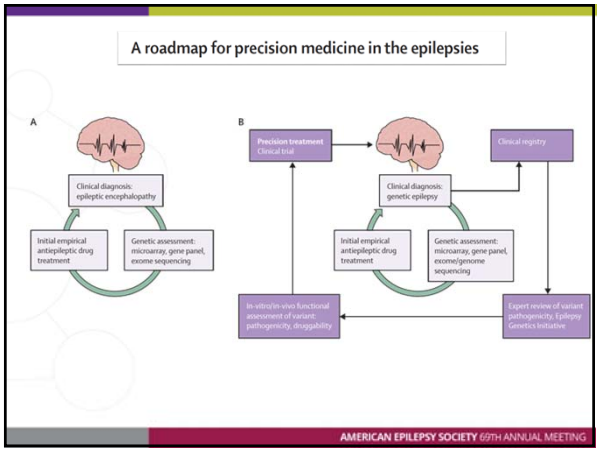
AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING


A roadmap for precision medicine in the epilepsies
A
Clinical diagnosis: epileptic encephalopathy
Initial empirical antiepileptic drug treatment
Genetic assessment: microarray, gene panel, exome sequencing
B
Precision treatment Clinical trial
Clinical registry
Clinical diagnosis: genetic epilepsy
Initial empirical antiepileptic drug treatment
Genetic assessment: microarray, gene panel, exome/genome sequencing
In-vitro/in-vivo functional assessment of variant: pathogenicity, druggability
Expert review of variant pathogenicity, Epilepsy Genetics Initiative
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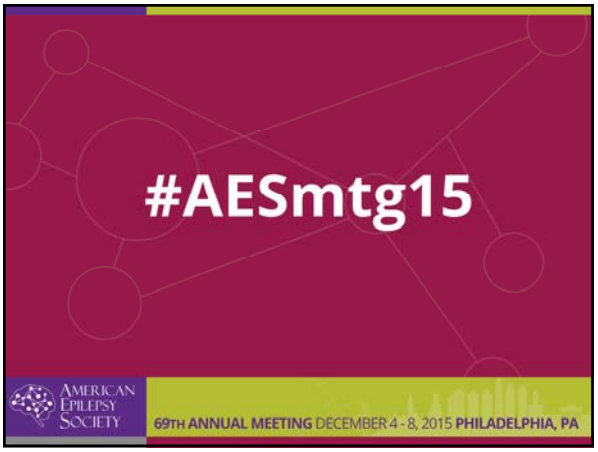
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