

NINDS Center for SUDEP Research (CSR)

Who? When? Why? How can we intervene?

GOAL: Clinical biomarkers, predictive genes, and basic mechanisms of SUDEP

Baylor College Medicine ([Goldman, Noebels](#))

Case

Columbia

Harvard ([Anderson](#))

Jefferson

NYU

UCSF ([Mueller](#))

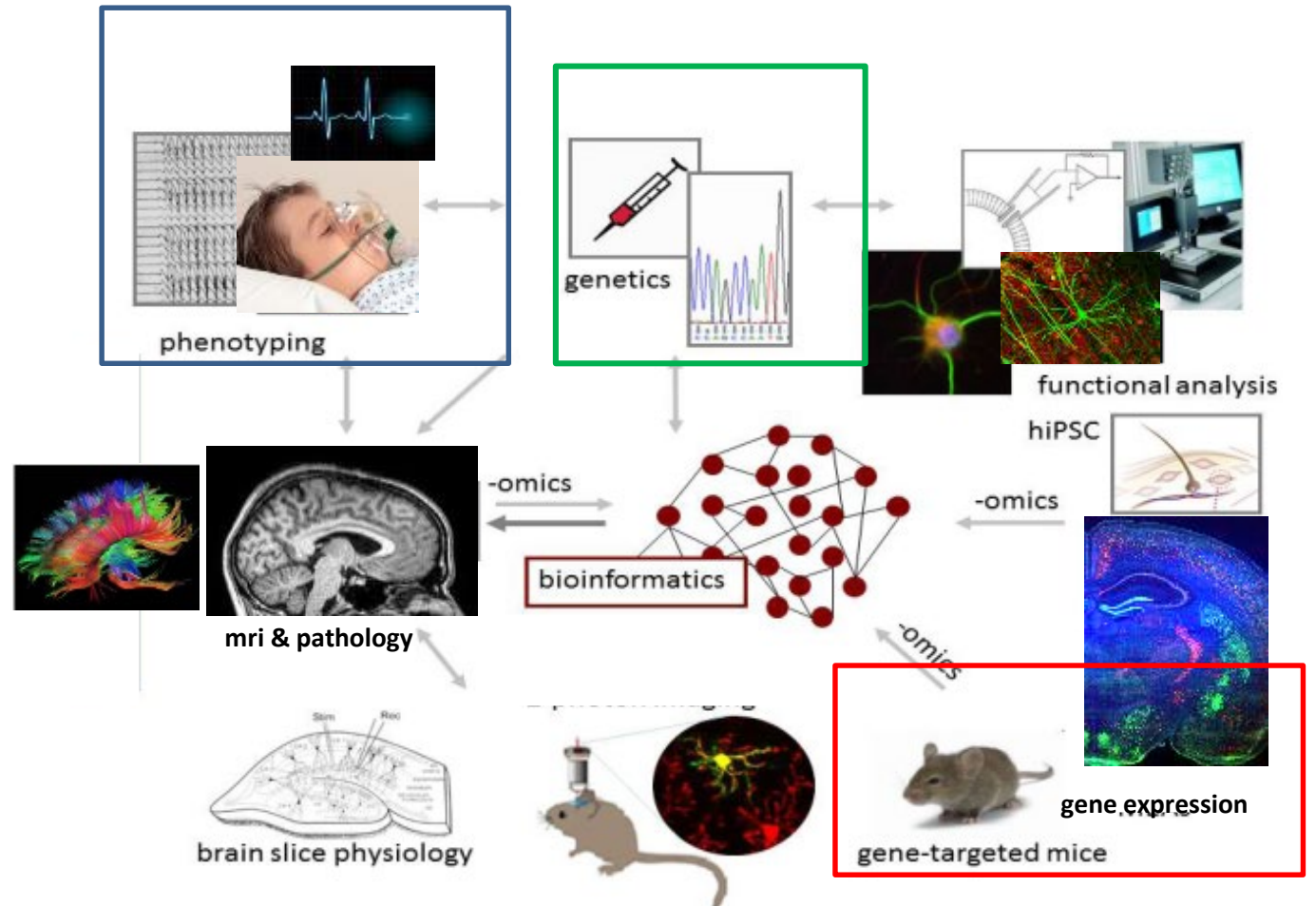
UCLA

UC London

U. Chicago Lurie

U. Michigan ([Isom, Parent](#))

U. Iowa ([Richerson](#))



Pathogenic Mechanisms of SUDEP

10 years ago:

- SUDEP risk was based upon **population risk**:
age, severe seizure history, pharmacoresistance
- **No validated biomarkers for specific individual risk.**
- **No recognized brain or cardiac lesions** (by definition)
even baseline EKGs not routine, brainstem MRI not scrutinized
- Since SUDEP population mortality 1:1000
 - *little reason to warn*
 - *little to check (just AED levels)*
 - *little evidence for new targets or pathways for intervention*

} *No Longer true!*

Major Conceptual Advances 2011-2021 driven by CSR labs

*Exomes, Imaging, Models, and Stem Cells: **new research biomarkers** with implications for families*

No mechanism

Only population-based risk factors

Pillow suffocation a leading hypothesis

Cardiac contribution unclear

Unclear which seizure will be the last

“SUDEP” (one mechanism)

Solid Mechanistic Evidence

25 **single genes** conferring >> population risk

Post-ictal *central apnea* (**monitoring, hypercapnia test**)
SUDEP pathway *amygdala* → *brainstem* (**MRI**)
Postictal *respiratory depression* (**genes**)

Monogenic LQT arrhythmias signal risk
patient-based functional variant assays (IPSCs)

Brainstem spreading depolarization threshold
2nd hit for lethal seizure; awaits human confirmation
but 5 human SUDEP genes lower this threshold in mice

“SUDEPS” (many)

1st Gene for SUDEP, KVLQT1: most common human gene for 'cardiac' SUD



RESEARCH ARTICLE

October 14, 2009

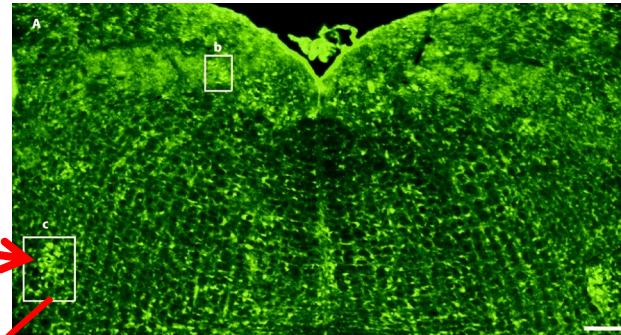
NEUROLOGY

Arrhythmia in Heart and Brain: KCNQ1 Mutations Link Epilepsy and Sudden Unexplained Death

A. M. Goldman, E. Glasscock, J. Yoo, T. T. Chen, T. L. Klassen, J. L. Noebels*

↑ Parasympathetic Mechanism

Brainstem Kcnq1 expression



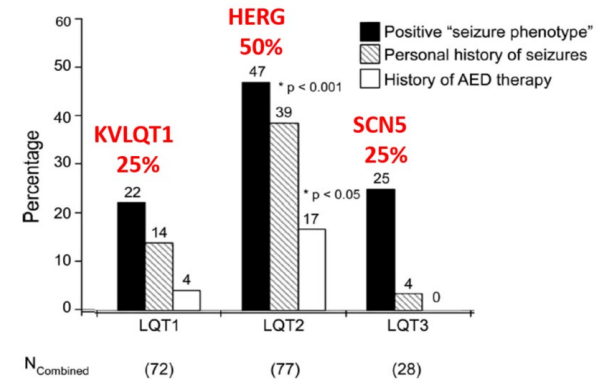
n.XI

Vagus



Ackerman group, Mayo Clinic

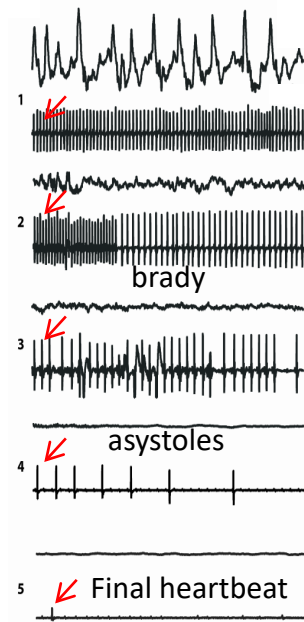
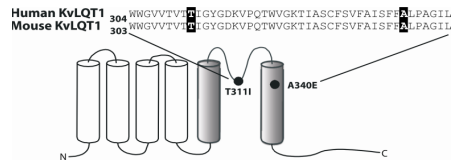
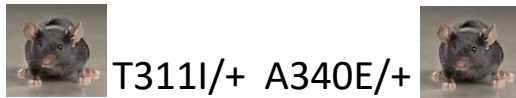
25-50% of cardiac syncope patients with LQT mutations had epilepsy



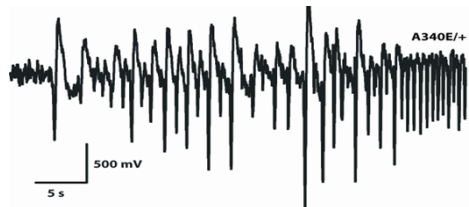
Johnson et al, Neurology 2009

Two patient mutations

SUDEP pattern



SEIZURES



Hyperexcitability in vagal axons causes excess release of Ach onto SA node → sinus bradycardia, asystoles

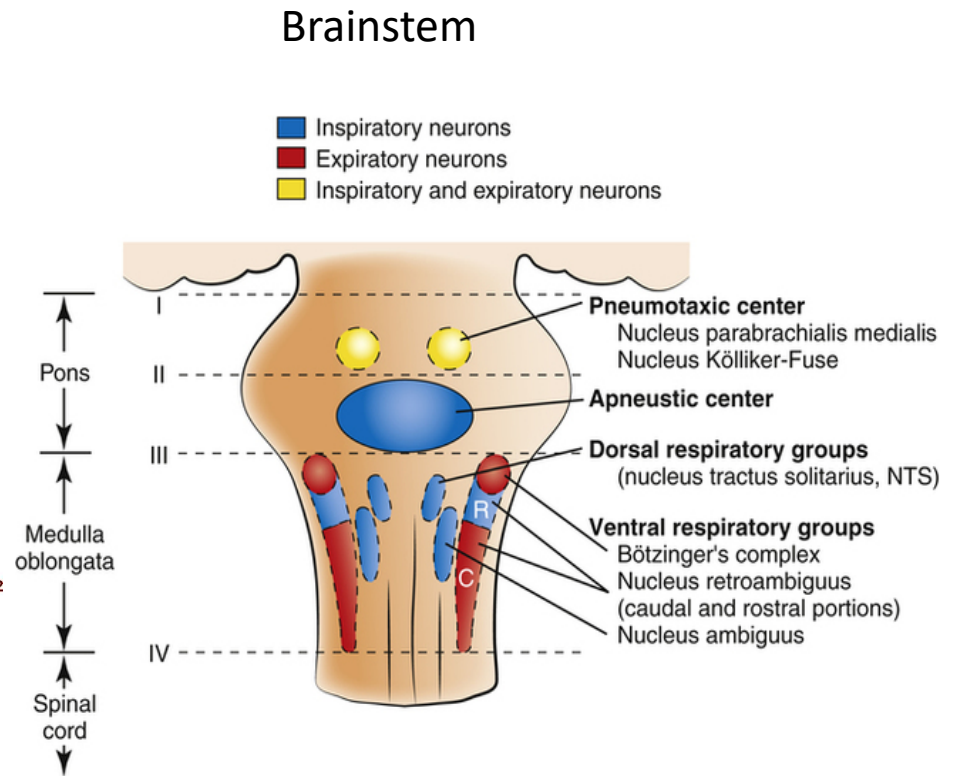
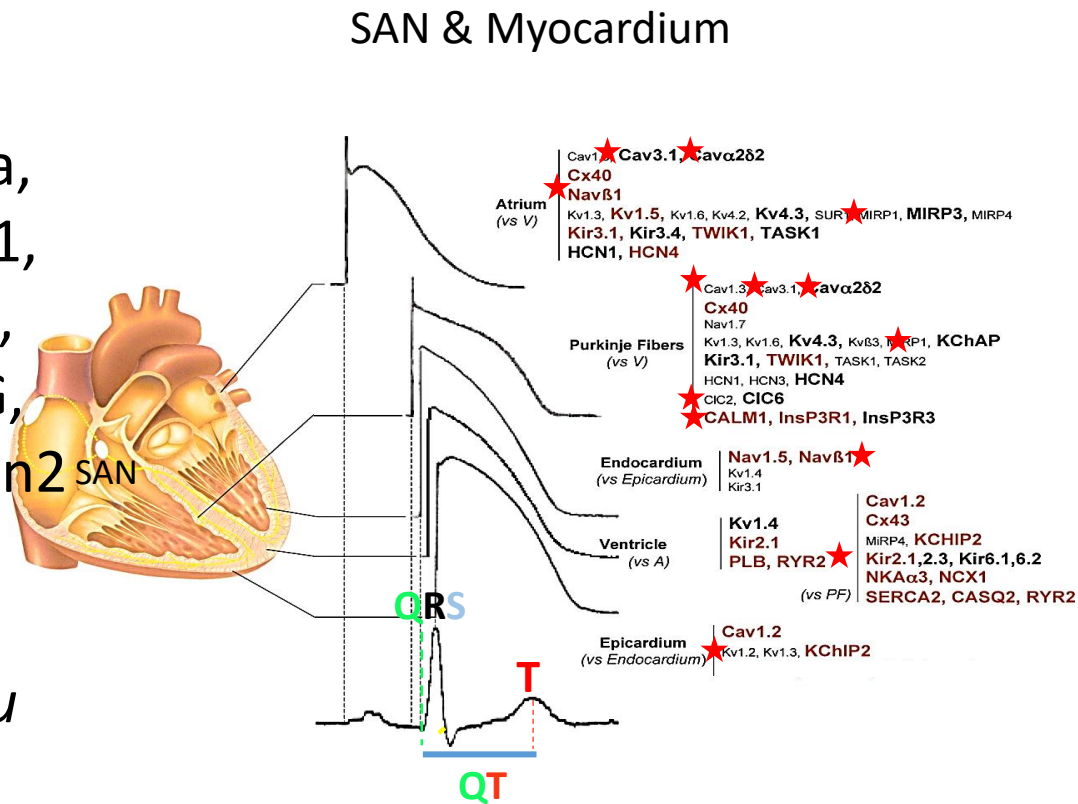
Central Hypothesis: single genes are linked to SUDEP risk

certain brain ion channels and other genes for epilepsy that are also expressed in heart and central cardiorespiratory pathways are candidate risk genes for seizures, postictal apnea, lethal cardiac arrhythmia

> 20 genes

Kcna1, Scn1a, Scnb1, Kcnq1, Kcnq2, RYR2, Senp2, AnkG, Sptan1, Sptan2

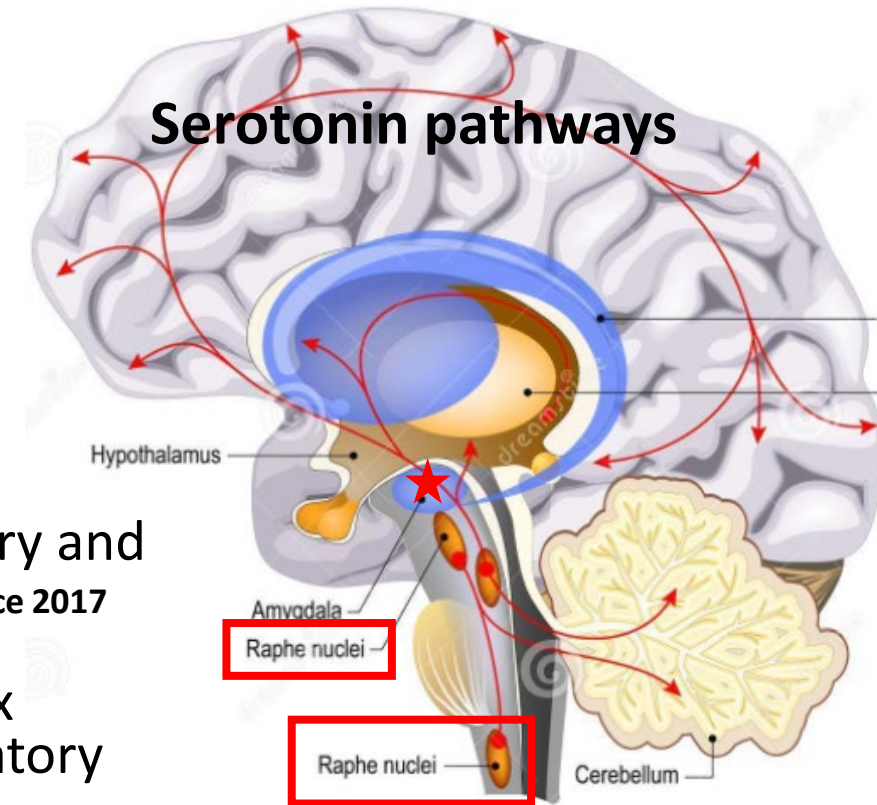
Protective:
Cacna1a, tau



How and where do seizures depress respiration?

George Richerson Lab: > 25 reports on roles of amygdala, genes, serotonin, CO2 reflex

- Seizures in human amygdala ★ inhibit brainstem respiratory circuitry. Dlouhý, *J Neurosci* 2015, Marinovich, *Epi Behav.* 2019
- SCN1A/SCN8A (mouse and human): dying begins with primary postictal respiratory arrest, followed by cardiac arrest. Patients have impaired response to CO2 (Kim, *JCI*, 2018)
- Loss of serotonin neurons in raphe depresses respiratory recovery and CO2 induced arousal. Buchanan, *J Physiol* 2014, Brust *Cell Rep* 2014, Cerpa, *Neuroscience* 2017
- Subset of pts in EMU have blunted interictal bedside HCVR reflex response to CO2 that correlates with prolonged postictal respiratory depression. Sainju, *Epilepsia* 2019.



When combined with other risk factors, apnea risk can help stratify individual risk.

CSR Morphometrics Core (Alica Goldman, Suzanne Mueller)

High resolution volumetric mapping of MRI's in 75 SUDEP cases

* Dorsal medulla atrophy in 2 patients who died of sudep. Mueller *Neuroimage Clin*, 2014

- *Brainstem network disruption: A pathway to sudden unexplained death in epilepsy?* Mueller SG, ... Goldman AM. *Human Brain Mapping* 2018

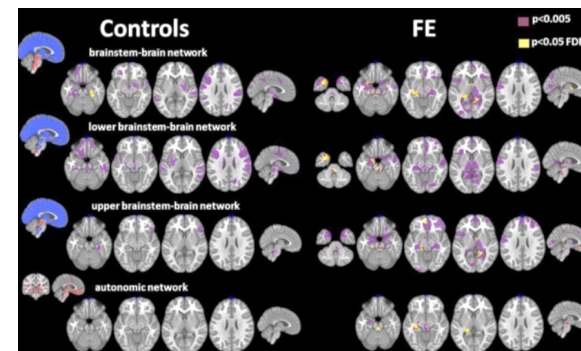
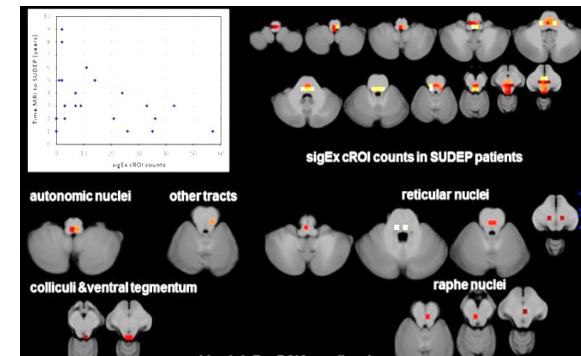
26 cases with 1 or more MRIs before SUDEP. Focal brainstem defects in raphe and medulla that mediate abnormal HRV reflexes

Two major findings:

1. Focal epilepsy can lead to progressive brain stem damage.
2. More widespread forebrain-brainstem pathway atrophy is associated with central autonomic reflexes.

- *Brainstem atrophy in focal epilepsy destabilizes brainstem-brain interactions.* Mueller, Bateman, ...Goldman, Laxer. *Neuroimage Clin*. 2019

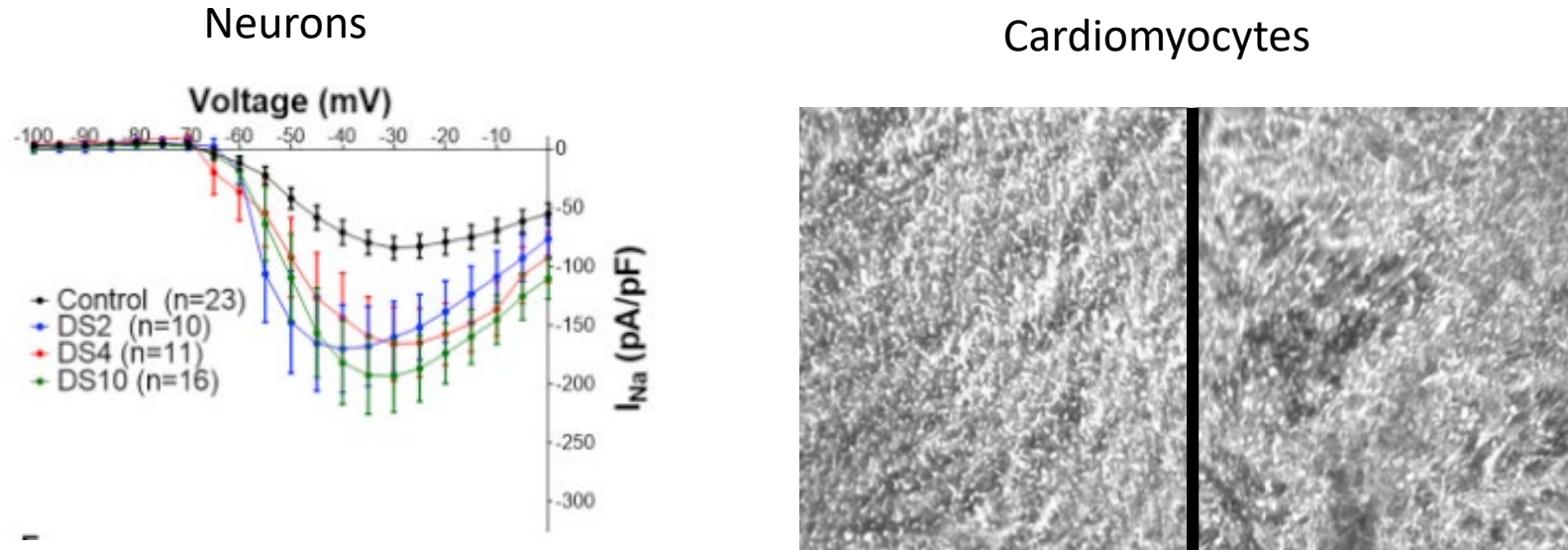
Extended findings to connectivity defects between brainstem and forebrain seizure areas.



Jack Parent and Lori Isom

Engineer and analyze new models of SUDEP in heart and brain of mice, rabbit

Human IPSCs: era of “personalized” functional assays for SUDEP variant risk



- Hyperexcitability and cardiac bradyarrhythmia in cardiomyocytes in a mouse model of Scn8a. **PNAS, 2016**
- Elevated persistent sodium current in GoF SCN8a mutant model, **PNAS, 2017**
- Rapid generation of “virtual patient” IPSC SUDEP models of SCN1B, SCN8a, CHD2, PCDH1 **Stem Cell Reports, 2017**
- Dravet Syndrome Patient-derived myocytes show arrhythmia biomarker in vitro **Stem Cell Reports, 2018**
- Patient variants of SCn8a demonstrate specific defects to screen for precision therapies. **Brain, 2020**

Genetic Complexity of SUDEP Risk

High-resolution molecular genomic autopsy reveals complex sudden unexpected death in epilepsy risk profile.
 Klassen, ...J Noebels, A Goldman **Epilepsia**, 2013

- SUDEP in 3-year-old proband with severe myoclonic epilepsy of infancy (SMEI) revealed complex combinations of single nucleotide and copy number variants in genes expressed in both neurocardiac SCN1A, KCNA1, RYR3, and **respiratory control HTR2C** pathways.

Cases from CSR StopSUDEP Registry

Table 1 Summary of SUDEP and SIDS cases with *HTR2C* variation

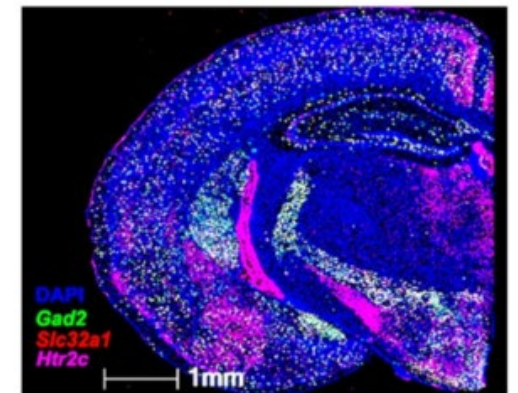
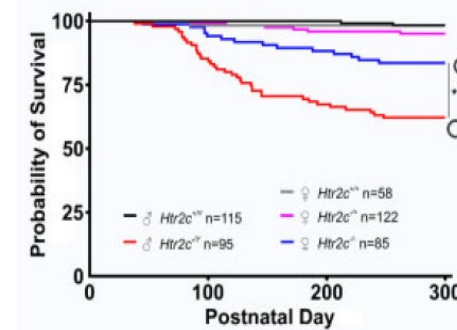
Case	Pheno	Sex	AAD	Chr: Position ClinVar	Variant†	AA change	Type
2273	SUDEP	M	26 Y	X: 114082728	c.512C>T	p.Ala171Val	Ns
2353	SUDEP	F	32 Y	X: 113965907	c.240G>A	p.Met80Ile	Ns
2347	SUDEP	F	33 Y	X: 113965926	c.259G>A	p.Ala87Thr	Ns
2354	SUDEP	F	31 Y	X: 114141802	c.1201G>A	p.Val401Ile	Ns
2232	SUDEP	M	12 Y	X: 114141856	c.1255A>G	p.Thr419Ala	Ns
2475	SIDS	M	3.5 Mo	X: 113965847	c.181_196delGTCATCATAATAATCA	p.Val61Ter	Fs
2099	SIDS	M	3 Mo	X: 114141797	c.1196C>T	p.Pro399Leu	Ns
2086	SIDS	M	5 Mo	X: 114141535	c.934G>A	p.Val312Ile	ns
2478	SIDS	F	4 Mo	X: 114141468	c.874_876delAAG	p.Lys292del (in frame)	del
2474	SIDS	M	2 Mo	X: 113965886	c.220delG	p.Val74Ter	fs

Time to start genotyping in the adult epilepsy clinic?



X-linked serotonin 2C receptor is associated with a non-canonical pathway for sudden unexpected death in epilepsy

Cory A. Massey,¹ Samantha J. Thompson,¹ Ryan W. Ostrom,¹ Janice Drabek,¹ Olafur A. Sveinsson,^{2,3} Torbjörn Tomson,³ Elisabeth A. Haas,⁴ Othon J. Mena,⁵ Alica M. Goldman¹ and Jeffrey L. Noebels^{1,6,7}



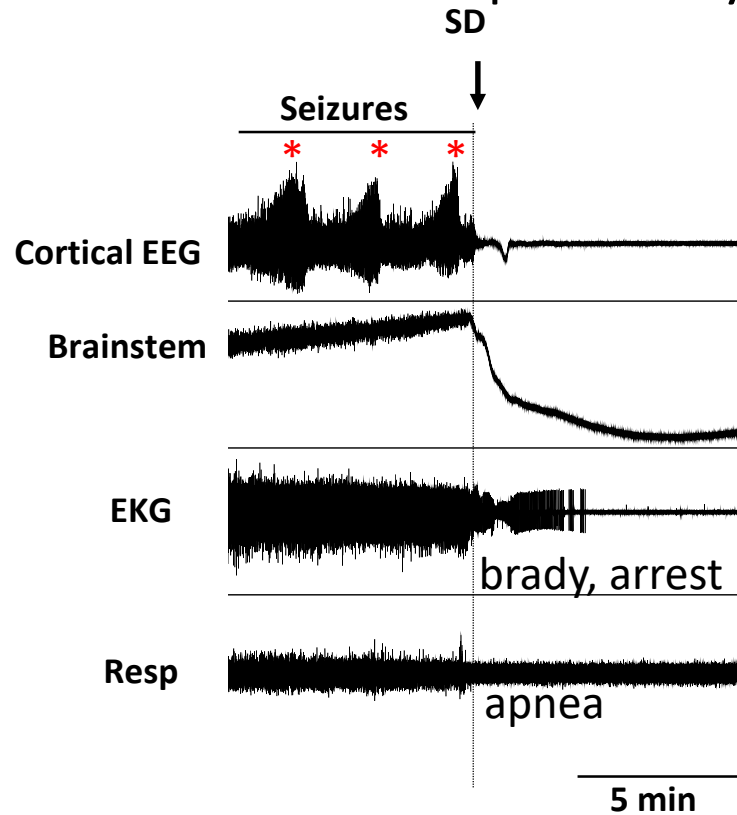
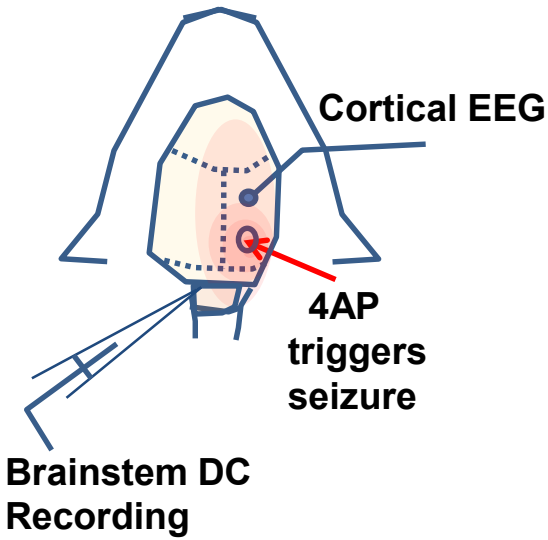
1. Male > females
2. Late onset GTCS
3. New gene for “respiratory SUDEP”



Aiba & Noebels, 2015

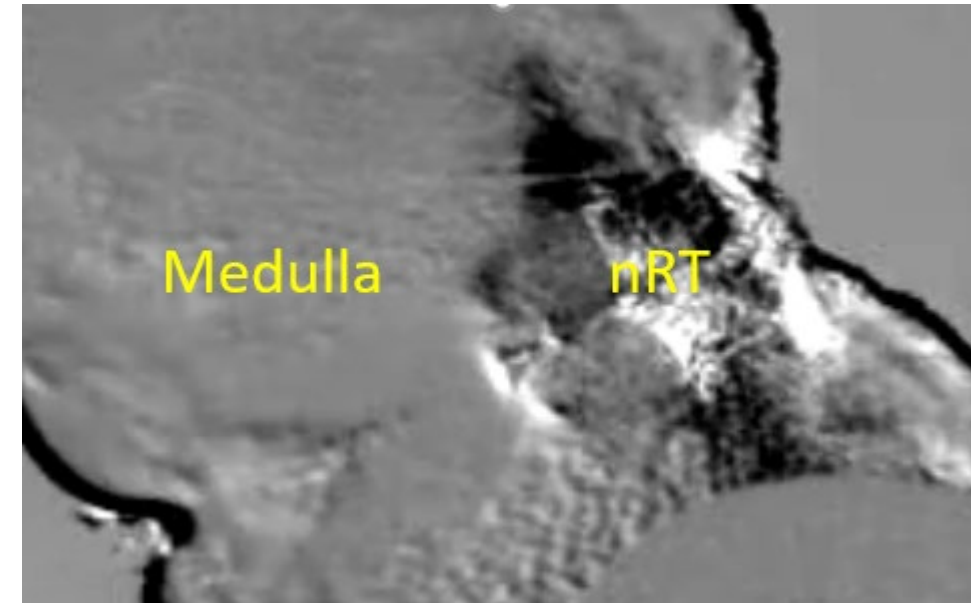
The last seizure: a two hit mechanism?

Wave of spreading depolarization in the brainstem silences cardiorespiratory region in mouse SUDEP model



+/+ = 0 SD, 0 died
 Kv1.1 = 11 SD, 11 died

Hypoxia triggers SD wave in brainstem



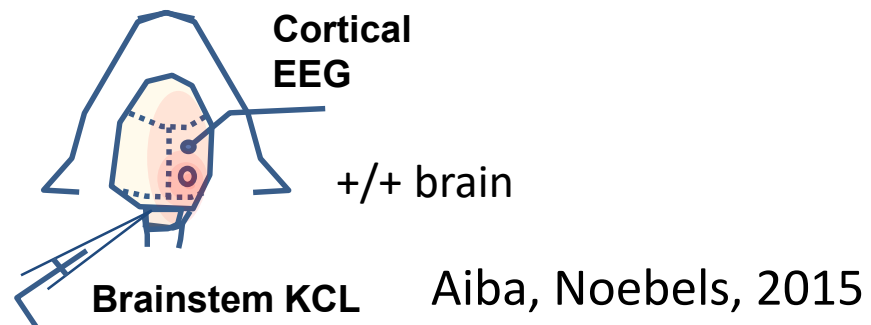
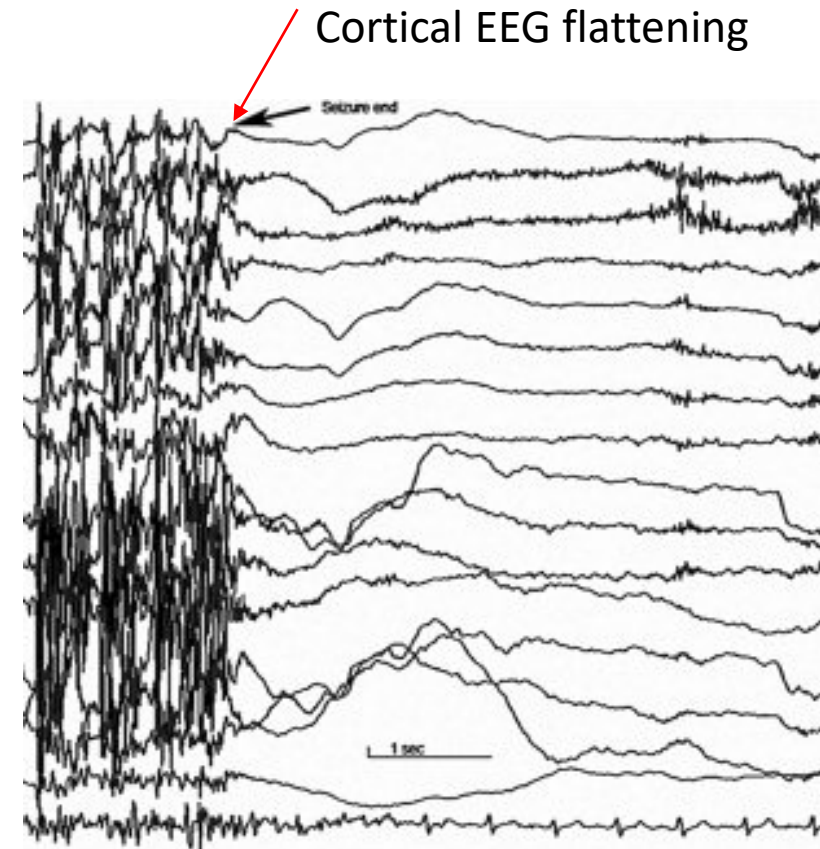
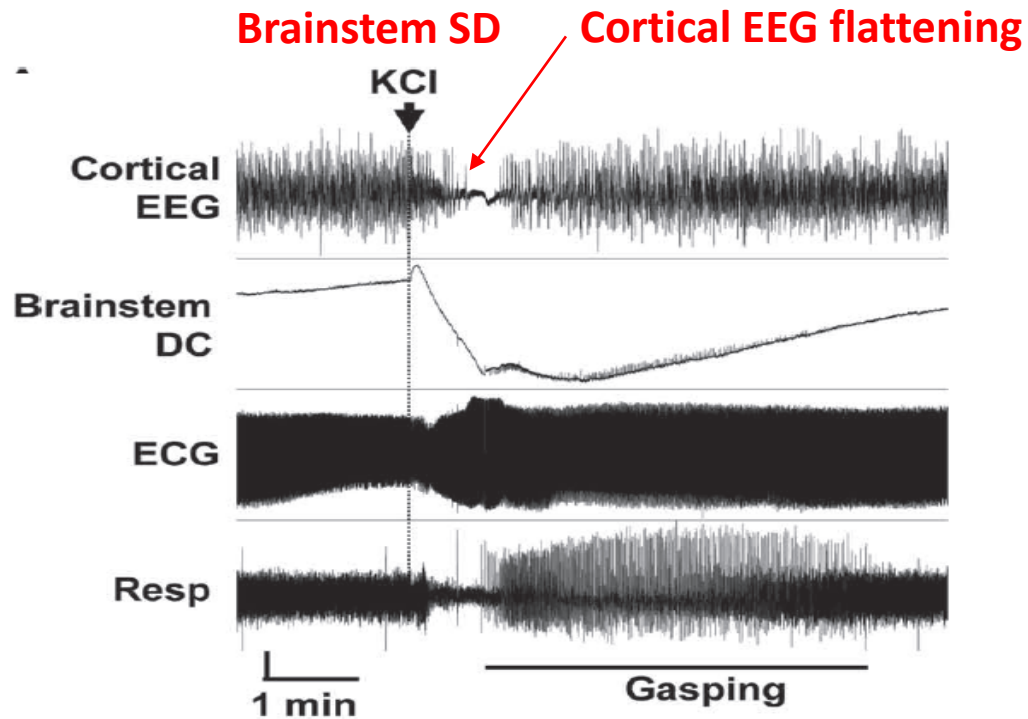
Nucleus of tractus solitarius: "mission control"

Input: from lungs/heart/throat

Output: cardiorespiratory nuclei, amygdala

+ reticular neurons that 'activate' cortex

Brainstem depolarization: one possible origin of PGES?



PGES seen in 15/30 cases who later died of SUDEP

* Lhatoo, Ann Neurol, 2010