

# Cardiac Role in Sudden Unexplained Death in Idiopathic Epilepsy is Observed in Animal Models

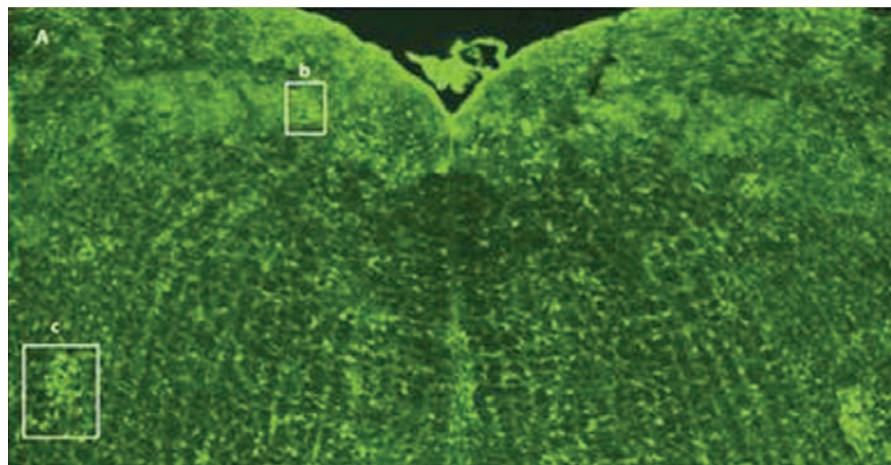
BY ROBERTA FRIEDMAN, PHD

## ARTICLE IN BRIEF

**A mutation in a potassium ion channel expresses itself in both brain and heart tissue and can produce both epileptic activity and abnormal cardiac rhythms when engineered into mice, strengthening a link between cardiac problems and sudden unexplained death in epilepsy.**

**M**ice that express a mutated human gene for an ion channel show EKG abnormalities and epileptic brain activity, according to an Oct. 14 report published online ahead of the print edition of *Science Translational Medicine*. The mutated gene produces Long QT syndrome (LQTS) in people, so the mouse findings strengthen a link already suspected between LQTS and sudden, unexplained death in idiopathic epilepsy (SUDEP), a catastrophe that causes 18 percent of the mortality in that disorder.

In epileptics, disrupted heart rhythm has been ascribed to an effect of the epileptic brain activity; in LQTS, vice versa: low blood perfusion could produce seizures in the brain. The new mouse experiments show that at least one mutant potassium channel responsible for LQTS



**DISTRIBUTION of KvLQT1 immunoreactivity in brainstem regions in the adult mouse brain. (A) Coronal sections of the medulla oblongata. KvLQT1 immunofluorescence was strong in somata of cardiac-related nuclei, including the dorsal motor nucleus of the vagus and the nucleus ambiguus, which are boxed and shown at higher magnification in (B) and (C), respectively. (B) High-magnification view of KvLQT1 somatic staining in the dorsal motor nucleus of the vagus. (C) High-magnification view of KvLQT1 somatic staining in the nucleus ambiguus.**

is expressed in both the heart and brain, and can produce abnormal activity in both organs that can be fatal.

Lead investigator Alicia M. Goldman, MD, PhD, assistant professor of neurology at Baylor College of Medicine in Houston, TX, told *Neurology Today* that several case series, including a 2008 report in *Neurology* have documented the

coexistence of cardiac arrhythmias and epileptic seizure. “Up to now we were for the most part spectators witnessing our patients experiencing asystolic episodes or seizures coupled with arrhythmias,” Dr. Goldman said in an e-mail message. “The beauty of our mouse model is that it brought us closer to understanding one of the possi-

ble mechanisms behind this dual phenotype. We are actively trying to better understand the relationship between cardiac arrhythmias and epileptic seizures.”

The Baylor researchers studied mice expressing a human gene for channel KvLQT1, mutated at a place in the gene that is changed in half of the LQTS cases genotyped. The altered channel is produced in heart and hair cells, making the mice and people deaf.

**‘We as neurologists need to be more vigilant about assessing our patients for potential cardiac dysrhythmias.’**

Prior studies failed to find the messenger RNA from this gene in the mouse brain. The Baylor scientists found it in the cortex, hippocampus, and notably, in the dorsal motor nucleus of the vagus and the

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## Pilocytic Astrocytomas

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growth of tumors.

In the current study, which was published online on Sept. 30 ahead of the Nov. 10 print edition of *Neurology*, Dr. Gutmann and colleagues reported that two-thirds (42 of 70) of the children with sporadic pilocytic astrocytoma had alterations in the *BRAF* gene, but none of the children with neurofibromatosis 1 had these mutations. After further exploration, they showed that the active end on the back end of the *BRAF* molecule — the one with enzymatic activity — gets fused to another gene in the region and the result is overactive *BRAF* protein function

*BRAF* normally regulates cell growth. In cells with overactive *BRAF* signaling, there is increased growth, culminating in astrocytoma development.

“Now that we understand the signa-

ture mutation in these common pediatric tumors, we can now think about designing treatments that alter this pathway,” said Dr. Gutmann. “Knowing that *BRAF* is involved allows us to find clever ways to treat pilocytic astrocytoma.”

Currently, besides standard chemotherapy, no treatments specifically target the molecular alterations seen in pilocytic astrocytoma. While surgery is often curative, these tumors frequently arise in regions of the brain that are not surgically accessible, including the optic nerve and brainstem. Moreover, radiation of these intrinsic tumors can lead to long-term cognitive deficits.

## IMPLICATIONS OF THE STUDY

The Washington University study is the largest and most comprehensive study to date, said Scott Pomeroy, MD, PhD, chief of neurology at Children’s Hospital in Boston, who was not involved with the

study. That *BRAF* alterations did not pop up in the patients with neurofibromatosis type 1 provides even more support that *BRAF* is the driving force behind these tumors in patients without the condition.

The Washington University scientists are now working on a mouse model using *BRAF* alterations to see whether the animals develop these benign tumors. They want to understand exactly how *BRAF* is involved in cell growth. Previously, Dr. Gutmann’s group developed a mouse model of neurofibromatosis type 1 associated optic glioma — the most common location for pilocytic astrocytoma in children with the disorder.

“Low-grade pilocytic astrocytomas are very slow growing, insidious and most often can be difficult to reach (surgically),” said Dr. Pomeroy. “For a long time we didn’t have a good feel about the molecular problems. Now, we have a good target for possible new treatments.”

The recent findings from Dr. Gut-

mann and others all point to the same molecular pathway. Once this pathway is over-active, it can drive cells to become tumors. Thus, finding ways to shut down this over-active pathway may inhibit further tumor growth. With such a targeted treatment “we can be much more specific than we can with radiation or chemotherapy,” said Dr. Pomeroy.

He added that that the findings should generate clinical trials for young patients with these tumors in the coming months. “Everyone agrees that these pathways are critical to tumor growth,” said Dr. Pomeroy. •

## REFERENCE:

- Yu J, Deshmukh H, R. Gutmann DH, et al. Alterations of *BRAF* and *HIPK2* loci predominate in sporadic pilocytic astrocytoma. *Neurology* 2009; E-pub 2009 Sept 30.

## SUDEP, Cardiac Role

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nucleus ambiguus, brain stem centers that send signals to control the heart.

“We showed that, more often than by chance, a discharge in the brain could apparently trigger a cardiac asystole,” said the senior study author Jeffrey L. Noebels, MD, PhD, professor of neurology, neuroscience, and molecular and human genetics at Baylor College of Medicine.

“One mechanism for this may be the presence of the mutant channel in the vagus nerve, which may potentiate parasympathetic signaling to the heart,” he said. “However, the two tissues are only loosely coupled, and many abnormal events seem to occur independently. This likely allows for long asymptomatic periods, and potentially an entire lifetime, in individuals with these mutations.”

The mice all showed epileptic EEG signals and also EKG arrhythmias as well as frank epilepsy. Awake mice had various heart beat alterations including atrial-ventricle conduction block. Simultaneous EEG and EKG recording showed prolonged RR intervals and asystoles correlating to discharges in the brain cortex.

Dr. Noebels noted that that other mutations might also lead to epilepsy and cardiac disturbance. “Although two independent ‘loss of function’ mutations in this (potassium channel) gene caused the same clinical disturbance,” he said, “more research will be required to determine whether any mutation in this gene, or other ‘LQT syndrome’ genes, presents an equal risk.”

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### EXPERTS COMMENT

The findings “raise the question: Could we be missing cardiac disease in our epilepsy patients?” said Maromi Nei, MD, associate professor of neurology and associate director of the Clinical Neurophysiology Fellowship Program at the Jefferson Comprehensive Epilepsy Center at Thomas Jefferson University in Philadelphia.

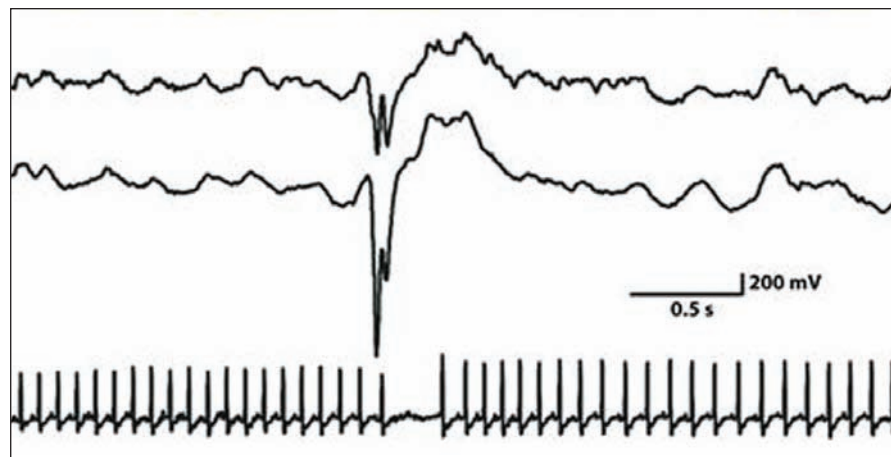
Dr. Nei, who was not involved with the study, cited case studies published earlier this year in *Neurology* and *Epilepsia* where problems in both organs could have been

at work, and noted that Mayo Clinic researchers reported the same situation in some of their Long QT patients, “but they did not have EEG confirmation” of epilepsy, she noted. More investigation is needed to confirm this in people, she added.

Dr. Nei said that perhaps the same mutation can produce different pheno-



**DR. ALICIA M. GOLDMAN:**  
“Up to now we were for the most part spectators witnessing our patients experiencing asystolic episodes or seizures coupled with arrhythmias. The beauty of our mouse model is that it brought us closer to understanding one of the possible mechanisms behind this dual phenotype. We are actively trying to better understand the relationship between cardiac arrhythmias and epileptic seizures.”



**ABERRANT BRAIN-HEART** events in *Kcnq1* mutant mice during interictal discharges and cortical seizures. (A) EEG recordings show frequent bilateral interictal discharges over temporal cortical regions of A340I homozygote with concomitant AV conduction block after P wave in ECG tracing. (B) Representative example of the intermittent nature of cortical-cardiac cycle events in *KvLQT1* mutant mice. Cortical EEG discharges sometimes, but not always, coincided with cardiac events (Table 1). ECG events occur concurrently with the two initial EEG ictal spikes but not with the third. The scale bar is the same in both (A) and (B).

types — in some people, epilepsy, in others, cardiac abnormalities, or, she said, one problem could predispose to the other. “We should be asking more questions about a history of cardiac disease or sudden death,” Dr. Nei said, “just a family history can be helpful.” She added that Long QT is difficult to diagnose and may not appear in a single EKG recording.

Michael Ackerman, MD, PhD, professor of medicine in the departments of cardiovascular diseases and pediatrics and director of the Long QT Syndrome Clinic at the Mayo Clinic in Rochester, MN, said: “At least in the mouse, they have knocked it out of the park in a very elegant way. They recorded truly a neurological origin of electrical misbehavior.”

But finding the mutation expressed in the brainstem means the chicken and egg question of a heart or brain origin of the disrupted cardiac function is still unanswered, Dr. Ackerman added. “The cardio-neuronal road travels in both directions.” He noted that the hearts of the mice having seizures were not showing long QT problems but instead, bradycardia, vagal tone, and in general the way the heart reacts during epilepsy.

“Perhaps we should be doing screening EEGs to find any epileptiform activity, and we have not been doing that,” he said, adding that most of the time the patients can be medically managed with beta blockers.

“We as neurologists need to be more vigilant about assessing our patients for potential cardiac dysrhythmias,” said Dr. Goldman.

Added Dr. Noebels: “Patients with new onset idiopathic epilepsy should have complete cardiology assessments including EKG evaluation of cardiac



**DR. JEFFREY L. NOBELS:**  
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rhythm disturbances, just as they currently do for syncope. Logistically this could be performed at the same time as the EEG. Our finding highlights a critical opportunity to save lives among persons with epilepsy. We should start now.” •

### REFERENCES:

- Goldman AM, Glasscock E, Noebels JL, et al. Arrhythmia in heart and brain: *KCNQ1* mutations link epilepsy and sudden unexplained death. *Sci Transl Med* 2009. E-pub 2009 Oct. 14.
- Ackerman J, Johnson J, Hofman N, et al. Identification of a possible pathogenic link between congenital long QT syndrome and epilepsy. *Neurology* 2009; 72:224-231.
- Rubboli G, Bisulli F, Michelucci R, et al. Sudden falls due to seizure-induced cardiac asystole in drug-resistant focal epilepsy. *Neurology* 2008;70:1933-1935.
- Espinosa PS, Lee JW, Dworetzky BA, et al. Sudden unexpected near death in epilepsy (SUDEP): Malignant ventricular arrhythmia from a partial seizure. *Neurology* 2009;72:1702-1703.
- Omichi C, Momose Y, Kitahara S. Congenital long QT syndrome presenting with a history of epilepsy: Misdiagnosis or relationship between channelopathies of the heart and brain? *Epilepsia* 2009; E-pub 2009 Aug. 19.