

Unraveling the genetic basis of sudden unexpected death in epilepsy

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Generalized 3 Hz spike and wave discharges in a child with childhood absence epilepsy. Credit: Wikipedia.

The leading cause of epilepsy-related death is a poorly understood phenomenon known as sudden unexpected death in epilepsy (SUDEP). The risk factors and causes of SUDEP remain unclear but researchers have proposed explanations ranging from irregular heart rhythm to genetic predisposition to accidental suffocation during sleep. Three studies to be presented at the American Epilepsy Society's (AES) 69th Annual Meeting parse the contributions of genetics to SUDEP in hopes of uncovering new strategies for prevention.

Researchers from the Universities of Melbourne and Sydney report (abstract 3.339|C.01) that genetic variants associated with cardiac sudden death may be to blame for SUDEP. The authors examined DNA samples from 62 people who died from SUDEP, searching for [mutations](#) in genes known to contribute to [cardiac arrhythmia](#), respiratory function and epilepsy.

Their results reveal that nearly a quarter of people who experienced SUDEP carried mutations linked to cardiac sudden death, suggesting that irregular [heart rhythms](#) may underlie a significant number of deaths in epilepsy. Furthermore, one-quarter of the cases had genetic mutations associated with epilepsy.

"These findings raise the possibility that SUDEP might be prevented in some cases by avoiding the use of anti-epileptic drugs known to alter the heart's electrical activity" says Douglas Crompton, M.D., Ph.D., a neurologist at the University of Melbourne. "In some cases, it may be advisable to recommend beta blockers, pacemakers or implantable defibrillators."

In a second study, (abstract 2.348) researchers from New York University's Langone Medical Center find that genetic mutations altering the transmission of electrical impulses in the heart and brain may raise the risk of SUDEP in people.

The authors searched for genetic mutations that might explain the disproportionately high risk of SUDEP in people with poorly controlled focal epilepsy, which, by definition stems from a specific area of the brain. To identify genetic [risk factors](#) for SUDEP, the authors analyzed brain tissue that had been removed during epilepsy surgery from 8 people who later experienced SUDEP and from seven living people with similar histories.

The study found mutations in 607 genes in brain tissue from patients who died from SUDEP that were not seen in the tissue from the living people. Analysis of affected genes revealed possible functional effects from 532 of the mutations. Three of people who experienced SUDEP had mutations in six genes linked to cardiac arrhythmia. The other five people who died from SUDEP had mutations in seven genes involved in GABA/Glutamate pathways.

"Genetic testing for these mutations could potentially allow for the early identification of people with epilepsy who are at high risk of sudden death," notes author Daniel Friedman, M.D., an assistant professor of neurology at NYU.

A third study (abstract 2.0521A.08) pinpoints a specific genetic mutation that may raise the risk of SUDEP in patients with early-infantile epileptic encephalopathy - a severe, drug-resistant disorder that manifests in the first 3 months of life. Researchers from the University of Michigan set out to explore whether [genetic mutations](#) in voltage-gated Na⁺ channels (VGSCs), which promote the transmission of [electrical impulses](#) in the heart and brain, increase the risk of SUDEP in patients with early-infantile epileptic encephalopathy.

The authors reproduced this disorder in mice to explore whether mutations in a particular VGSC, encoded by the SCN8A gene, increase the risk of cardiac arrhythmia, which might, in turn, influence

susceptibility to SUDEP. Animal experiments revealed that mice carrying a mutated SCN8A gene had reduced heart rate compared with their healthy littermates, and that administration of caffeine produced an abnormal heart rhythm known as accelerated idioventricular rhythm. Examination of cardiac cells revealed a number of molecular changes that further altered the heart rhythm.

"Taken together, our results suggest that SCN8A mutations in [people](#) with early-infantile epileptic encephalopathy may increase the risk of SUDEP by creating an environment in which the heart has a higher susceptibility to arrhythmias," explains author Chad Frasier, Ph.D., a postdoctoral researcher at the University of Michigan.

Provided by American Epilepsy Society

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