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TWO DEFINITE CASES OF SUDDEN UNEXPECTED DEATH IN EPILEPSY IN A FAMILY WITH A *DEPDC5* MUTATION

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The *DEPDC5* gene (OMIM #614191), mapped to 22q12.2-q12.3, encodes the DEP domain-containing protein 5. *DEPDC5* has been associated with a variety of familial epilepsies, including familial focal epilepsy with variable foci, autosomal dominant nocturnal frontal lobe epilepsy, familial temporal lobe epilepsy, epileptic spasms, and cortical dysplasia.[1–4] Notably, *DEPDC5* has never been linked to increased risk of sudden unexpected death in epilepsy (SUDEP). We report a family with epilepsy due to *DEPDC5* mutation and 2 definite cases of SUDEP within this family.

Case report. We studied a 4-generation nonconsanguineous French-Canadian family with 9 affected individuals. Of note, all but one are male. The index case (III.3, figure) is a 39-year-old man who started having seizures at the age of 13 years. His seizures were characterized by a "dream-like" aura followed by loss of consciousness and tonic–clonic movements. Initially, seizures were mainly diurnal; in his mid-20s, they became exclusively nocturnal. He currently experiences 2–5 seizures a year on dual therapy with carbamazepine and clobazam. EEGs showed interictal epileptiform discharges over the right anterior temporal region. Brain MRI was normal.

Individuals II.4 and II.6 had definite autopsy-confirmed SUDEP at the ages of 58 and 50 years, respectively. Patient II.4 presented with nocturnal generalized tonic–clonic (GTC) seizures at the age of 9 years; he was initially treated with phenytoin, but his seizures persisted throughout life with an average of one seizure per month. A few months before his sudden death, he was switched to lacosamide because of phenytoin side effects. He was never compliant with his treatment in adulthood. Patient II.6 had GTC seizures since 2 years of age, with poor compliance to antiepileptic therapy during his entire life. Postmortem examination revealed hemorrhagic pulmonary congestion and bitten tongue.

Seizure history in this family is summarized in table e-1 at Neurology.org/ng. All patients were cognitively intact. There was no history of any cardiac symptomatology, cardiovascular risk factors, or definite cardiac condition.

Genetic analysis of the index case revealed a pathogenic heterozygous variant in the *DEDPC5* gene (p.Gln216*, c.646C>T; ENST00000536766) resulting in a premature stop codon. The index case was also tested for genes associated with SUDEP, none of which showed mutations (table e-2).

All living affected relatives (except for individual IV.1) and 4 healthy family members were clinically evaluated and had *DEPDC5* Sanger sequenced. All affected patients and individual III.1 were found to carry the same *DEPDC5* pathogenic variant as the index case (figure).

Discussion. SUDEP represents a rare but important cause of mortality in patients with epilepsy. In a Finnish long-term follow-up study of community-based pediatric epilepsy that included 220 patients, there were only 3 cases of SUDEP[5] (compared with 2 SUDEP cases in this family with 9 affected individuals; $\chi^2 = 8.46$, $p = 0.003$). While the exact pathophysiology underlying SUDEP remains poorly understood, there are consistently associated risk factors: GTC seizures, polytherapy, early onset of epilepsy, duration of seizure disorder, nocturnal seizures, and full-scale IQ less than 70.[6,7] It is worth mentioning that SUDEP does occur in patients who do not present with risk factors; indeed, the 2 individuals with SUDEP reported here were cognitively intact and not on polytherapy.

Several genes have been associated with SUDEP in human and/or animal studies (table e-2). These genes are associated with cardiac arrhythmias and/or severe epilepsies (usually in the setting of epileptic encephalopathies), neither of which apply to this family's phenotype. Based on the clinical histories of both SUDEP cases, it is unlikely that these patients carried mutations in genes previously associated with SUDEP.

An alternative hypothesis would be that patients II.4 and II.6 actually had sudden cardiac deaths instead of SUDEP. This is also highly unlikely because they had never presented any cardiac symptomatology or cardiovascular risk factors such as obesity, cigarette smoking, dyslipidemia, hypertension, or excessive alcohol intake.

This study has limitations. First, the deceased patients were not tested for SUDEP susceptibility genes; thus, we could not rule out the possibility of a second genetic variant segregating in this family. Second, a potential adverse reaction of lacosamide, a drug known

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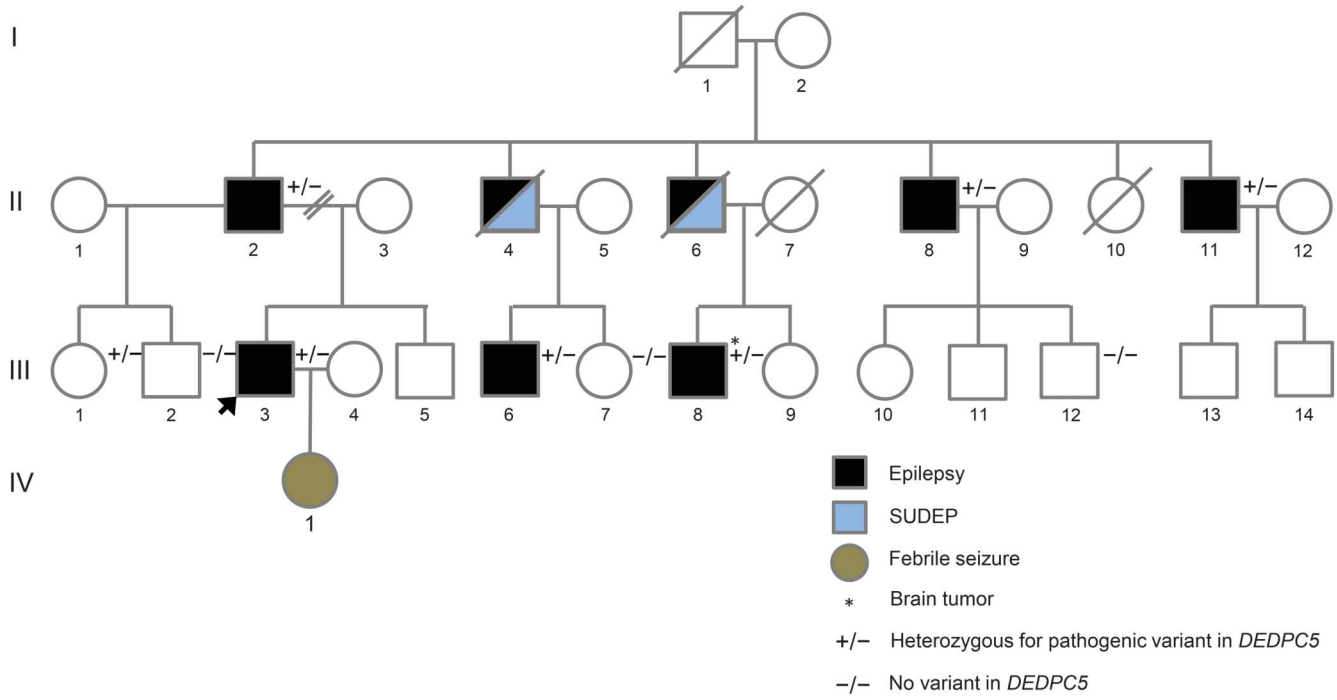
Figure Pedigree of the reported family



SUDEP = sudden unexpected death in epilepsy.

to be associated with PR interval prolongation and occasionally death,[8] cannot be completely ruled out—even in the poor medication compliance scenario related by patient II.4's family.

The findings in this family suggest that *DEPDC5* mutations may be a risk factor for SUDEP, but future studies are necessary to elucidate this association. Our report should serve as an initial cautionary note, and this particular genetic diagnosis might be highly consequential. Elucidation of the basic mechanisms connecting defective *DEPDC5* to its clinical outcomes will be of major importance.

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