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INVITED REVIEW

Sudden unexpected death in epilepsy: A subject that spans from neurology to forensic sciences and genetics

Sude Danışman[1], Caner Beşkoç[2], Emrah Yücesan[1], Nihan Hande Akçakaya[2]

[1]Department of Neurogenetics, İstanbul University - Cerrahpaşa, Institute of Neurological Sciences, İstanbul, Türkiye
[2]Ministry of Justice, Council of Forensic Medicine, İstanbul, Türkiye

ABSTRACT

Sudden unexpected death in epilepsy (SUDEP) is one of the most devastating complications of epilepsy, posing a significant challenge for clinicians, geneticists, and forensic specialists. It is defined as a sudden, unexpected, nontraumatic, and nondrowning death in individuals with epilepsy, with no identifiable toxicological or anatomical cause found during postmortem examination. It accounts for a significant portion of epilepsy-related mortality. The heterogeneous nature of SUDEP complicates accurate diagnosis, classification, and epidemiological assessment, particularly in cases lacking comprehensive death scene investigation or autopsy. Emerging evidence suggests that SUDEP is a multifactorial phenomenon involving complex interactions between seizure-induced respiratory dysfunction, autonomic instability, and cardiac arrhythmogenesis. Findings from monitored cases indicate that terminal apnea often precedes cardiac arrest, underscoring the central role of postictal respiratory failure. However, conventional autopsy often fails to reveal specific structural abnormalities, making SUDEP a diagnosis of exclusion in forensic practice. The integration of molecular autopsy has significantly advanced the understanding of SUDEP by identifying pathogenic variants in genes associated with cardiac channelopathies and epilepsy syndromes. Next-generation sequencing technologies have enabled comprehensive genetic screening in autopsy-negative cases, linking neuronal excitability and cardiac electrophysiology. These findings highlight the shared molecular mechanisms underlying epilepsy and sudden cardiac death and offer opportunities for family-based risk assessment and preventive interventions. A multidisciplinary approach that combines clinical evaluation, standardized forensic investigation, and genomic analysis is essential to improve diagnostic accuracy and risk stratification. Continued research integrating genetic, physiological, and epidemiological data is crucial to advancing precision medicine strategies and reducing the global burden of SUDEP.

Keywords: Epilepsy, molecular autopsy, sudden death, SUDEP.

DEFINITION AND EPIDEMIOLOGY OF SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)

Sudden unexpected death in epilepsy is defined as the sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death of individuals with epilepsy, with or without evidence of a seizure, excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomical cause of death, as originally described by Nashef[1] in 1997.

In forensic medicine, sudden death is defined as a fatality arising from natural causes occurring within 24 h of the onset of terminal symptoms or signs.[2] In addition to SUDEP, which falls fundamentally within this definition, other neurology-related definitions categorized by age group are presented in the Table 1.

The incidence of SUDEP ranges from 0.09 to 2.4 per 1000 person-years. This variability is thought to be related to differences in age distribution, epilepsy type, and disease severity among the study populations.[3] Accurate identification of SUDEP cases is essential for determining the incidence rates and advancing research; however, the heterogeneous nature of SUDEP poses significant diagnostic challenges.

Correspondence: Nihan Hande Akçakaya, PhD. Adalet Bakanlığı, Adli Tıp Kurumu, 34196 Bahçelievler, İstanbul, Türkiye.
E-mail: nhakcakaya@gmail.com
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TABLE 1
Classification of sudden unexpected deaths

Sudden Cardiac Death (SCD)
• Sudden unexplained death in young people related to exercise
• Sudden arrhythmic death syndrome
• Sudden unexpected death in epilepsy (SUDEP)
• Sudden unexpected death in pediatrics (SUDP)
• Sudden infant death syndrome (SIDS)

Sudden deaths are etiologically categorized as either cardiac-related or epilepsy-related. However, when examining age-specific classifications, there is an absence of a distinct etiological definition for the pediatric population.

CLASSIFICATION OF SUDEP AND DIAGNOSTIC CHALLENGES

To address diagnostic uncertainty, a classification system consisting of six categories was proposed:[4] definite SUDEP, probable SUDEP/probable SUDEP plus, possible SUDEP, near-SUDEP/near-SUDEP plus, not SUDEP, and unclassified (Box 1). From a forensic perspective, accurate classification of SUDEP depends not only on the availability of autopsy but also on the completeness of the death scene investigation, medical history review, and standardized documentation of epilepsy-related circumstances, including recent seizure activity, medication adherence, body position at discovery, and resuscitation attempts. Incomplete scene information and limited access to clinical data remain major contributors to SUDEP misclassification and underreporting.[4,5]

The primary distinction between definite and probable SUDEP lies in the availability of an autopsy. In definite SUDEP, death remains unexplained despite a complete postmortem examination. However, in approximately 5% of cases, the cause of death cannot be determined even after comprehensive toxicological, microbiological, histological, or biochemical analyses, resulting in a negative autopsy.[6]

In 2021, Fialho et al.[7] suggested that molecular autopsy be used together with the classification proposed by Nashef et al.[4] to improve the SUDEP classification (Figure 1). After cases are classified according to Nashef et al.'s[4] SUDEP classification, if a molecular autopsy has been performed, it is recommended that they be classified as "molecular autopsy positive" or "molecular autopsy negative" based on the results. If a molecular autopsy was not performed, it should be indicated as "no molecular autopsy". However, the question of which genes should be investigated in molecular autopsy, which is emphasized by researchers, highlights the fact that the genetic basis of SUDEP needs to be elucidated.

Box 1. Definitions of SUDEP categorization

Definite SUDEP: Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration ≥ 30 min or seizures without recovery in between), in which postmortem examination does not reveal a cause of death.

Definite SUDEP Plus: Satisfying the definition of definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of terminal event did not prove the concomitant condition to be the cause of death.

Probable SUDEP/Probable SUDEP Plus: Same as definite SUDEP but without autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death.

Possible SUDEP: A competing cause of death is present.

Near-SUDEP/Near-SUDEP Plus: A patient with epilepsy survives resuscitation for more than 1 h after a cardiorespiratory arrest that has no structural cause identified after investigation.

Not SUDEP: A clear cause of death is known.

Unclassified: Incomplete information available; not possible to classify.

MOLECULAR AUTOPSY AND GENETIC FINDINGS

Postmortem genetic analyses performed in cases classified as negative autopsy are referred to as molecular autopsy.[8] Molecular autopsy is defined as the investigation of potential underlying genetic diseases in individuals whose cause of death remains undetermined following a conventional autopsy and subsequent toxicological, microbiological, or histopathological examinations. However, other supplementary tests are also categorized under this heading in the literature. For instance, across all age groups,

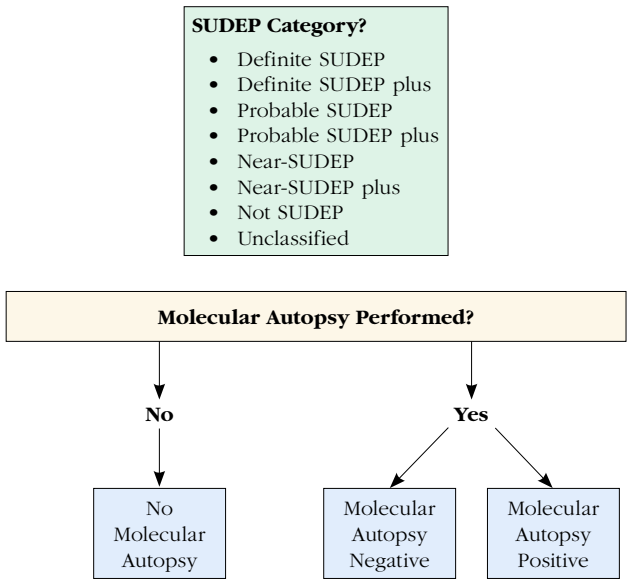

Figure 1. Classification of SUDEP.
SUDEP: Sudden unexpected death in epilepsy.

neurodegenerative diseases involve functional loss due to atrophic involvement of the brain; however, the neurological condition itself is often not the immediate cause of death. Typically, a secondary infection superimposed on the neurological clinical picture results in death. Nevertheless, neurodegenerative findings identified during autopsy, combined with the patient's medical history, can indicate an underlying neurological disorder. Similarly, in cases classified as sudden cardiac death (SCD), where cardiomyopathy is detected during autopsy, the identification of potentially pathogenic variants in cardiomyopathy-related genes also falls under this scope. The terms "postmortem genetic testing" or "molecular autopsy" represent the etiological understanding of rare diseases with similar pathophysiological outcomes, such as epilepsy or cardiomyopathy, that cannot be fully differentiated clinically, facilitated primarily by advancements in genetics.[9]

In forensic practice, the diagnostic yield of molecular autopsy is highly dependent on appropriate postmortem sample collection and storage. The lack of standardized protocols for DNA preservation, delayed sampling, and the use of suboptimal tissue sources frequently limit the interpretability of genetic findings in SUDEP investigations.[10,11]

This diagnostic gap has led to the emergence of molecular autopsy. Molecular autopsy can identify genetic changes that may explain the cause of death and facilitate the identification of variant carriers within the family, enabling early diagnosis and preventive measures.[8] In recent years, molecular autopsy has emerged as a powerful tool in cases of negative autopsy, enabling the identification of pathogenic or likely pathogenic variants associated with cardiac arrhythmias, epilepsy, or both conditions.

Indeed, studies have shown that pathogenic variants in genes associated with cardiac arrhythmias may be detected in cases of SUDEP.[12] Therefore, evaluating genetic variants identified through molecular autopsy in family members, regardless of whether they have epilepsy, is crucial for implementing preventive strategies against sudden unexpected deaths.

DEVELOPMENT OF SUDEP THROUGH GENETICS

First examples of postmortem genetic testing:

The first case was reported in 1999 in the USA and involved a 19-year-old female patient. The patient had enrolled in a weight loss program and was discovered in a swimming pool while exercising. Following prolonged resuscitation, the patient was monitored in the intensive care unit for 12 days with a low Glasgow Coma Scale score, during which an elongated QT interval was detected on electrocardiogram. At that time, four cardiac-related genes under investigation were analyzed using Sanger sequencing. Although the results did not fully elucidate the definitive cause of death, the detection of a six-base deletion in the *KCNQ1* gene marked the beginning of genetic studies on sudden deaths at a young age.[13]

Subsequently, in 2001, the same research group reported a second case involving a 17-year-old found dead in his sleep with a negative autopsy; a five-base deletion in the same gene was identified, which notably did not segregate within the family.[14] Consequently, mutation screening of selected cardiac genes provided the first genetic data capable of explaining the cause of death, leading to the sequential publication of case series in the literature. These early reports also represent the first shift in the role of forensic autopsy from a purely morphological investigation to a multidisciplinary diagnostic model in which postmortem genetics became an integral component of death certification and family risk assessment.[11,15,16]

Case series prior to the advent of next-generation sequencing:

Among 270 sudden death cases aged 13 to 30 years reported over a 13-year period in the USA, known mutations were detected in two out of 12 negative autopsy cases evaluated as probable SCD.[17] One year after this study, a new series was published in Italy. From a cohort of 1,023 cases, 10 individuals under the age of 30 with negative autopsies, considered probable cardiac deaths, were selected. Similarly, two out of these 10 cases were identified as positive for mutation.[18] Screening for SCD continued in this manner over the years; when examining studies cumulatively through 2009, approximately 35% of cases tested positive for mutations in the four screened genes, representing a notably high diagnostic yield.[19]

Emergence of epilepsy in the diagnostic landscape of negative autopsies via next-generation sequencing:

Next-generation sequencing (NGS) technologies have enabled the rapid and simultaneous analysis of vast numbers of genes. Despite its diagnostic advantages, studies in this field remain limited due to high initial costs. In the first such study conducted in France in 2015, a genetic pathology was identified in 50% of cases with cardiac pathologies across 23 selected genes.[20] In another study published the following year, 148 of 348 negative autopsy cases under the age of 50 were classified as having SCD. Following the autopsy, nine cases were excluded as they were under the age of one. Furthermore, 20 patients exhibiting signs of cardiomyopathy or ventricular hypertrophy were excluded. Additionally, 52 cases with nondiagnostic findings were removed from the cohort. Consequently, a mutation-positive rate of 34% was established across 100 screened genes in 61 strictly autopsy-negative cases.[21] This meticulous study demonstrated that even with a comprehensive cardiac gene panel and a well-selected case series, the diagnostic yield did not differ significantly from that of a decade prior. At this juncture, neurological diseases entered the debate, leading to the hypothesis that higher diagnostic rates could be achieved by incorporating neurological screening.

The first molecular autopsy series utilizing whole exome sequencing (WES) was conducted in 2016 and 2022.[22,23] In the first series, a molecular diagnostic rate of 41% was achieved among 25 patients under the age of 45 selected from probable SCD patients. This initial WES series marked the first time that neurological genes were identified in this context.[22] In the second series, pediatric cases, including infants, were screened, and the molecular diagnostic rate was approximately 11%. Although the diagnostic yield in pediatric cases was lower, the prevalence of potentially pathogenic variants in neurological genes was significantly higher among undiagnosed patients.[23] This situation highlights a gap in genetic knowledge regarding neurological diseases. Due to this knowledge gap, the National Association of Medical Examiners recommends the mandatory preservation of DNA in all cases of sudden unexpected death in individuals under the age of 40. It is well known that biobanking is utilized in various fields, with international stakeholders contributing to banking services and engaging in collaborations. Adopting similar approaches within Forensic Sciences is undoubtedly essential.[24]

GENETIC SYNDROMES ASSOCIATED WITH SUDEP

Several genetic syndromes and channelopathies have been implicated in the increased risk of SUDEP.[25] Dravet syndrome, one of these genetic syndromes described as severe myoclonic epilepsy in infancy, is a rare and severe childhood-onset epilepsy characterized by treatment-resistant seizures. Approximately 70 to 80% of Dravet syndrome cases are caused by de novo heterozygous loss-of-function variants in the *SCN1A* gene.[26]

The *SCN1A* gene encodes the alpha subunit of the voltage-gated sodium channel Nav1.1. Pathogenic variants in this gene lead to Nav1.1 dysfunction and a reduced sodium current in GABAergic interneurons, resulting in neuronal hyperexcitability and epileptogenesis.[27] This pathophysiological mechanism is believed to substantially contribute to the elevated SUDEP risk observed in Dravet syndrome and is considered one of the leading causes of mortality in these patients.[28] Additionally, loss-of-function variants in *SCN1B* may increase the risk of SUDEP in patients with Dravet syndrome.[29]

Long QT syndrome, a channelopathy that can occur in some cases of SCD, has been associated with SUDEP.[30] Approximately 90% of long QT syndrome cases are caused by pathogenic variants in *KCNQ1, KCNH2*, and *SCN5A*.[31] The *KCNH2* and *SCN5A* genes, which encode potassium and sodium channels, respectively, have also been associated with SUDEP.[32,33]

Another syndrome that increases the risk of SUDEP by causing severe and antiepileptic drug-resistant seizures is caused by the duplication of the 15q11.2q13 region.[34] Epileptic seizures in isodicentric chromosome 15 syndrome typically begin at an early age and are associated with infantile spasms.[35]

NEXT-GENERATION SEQUENCING AND MOLECULAR AUTOPSY IN SUDEP

Next-generation sequencing is a technology that enables the sequencing of DNA and RNA to investigate diseases and biological processes. Sequencing technologies, which have been developed over time (Box 2), are now used in many different fields. This progress has made it possible to clarify the cause of death and determine the genetic causes, particularly in cases such as SUDEP, which may result in negative autopsy findings. From a medicolegal standpoint, the interpretation of variants of uncertain significance represents a major challenge. In SUDEP investigations, such variants cannot be used to establish a definitive cause of death and should be reported cautiously, with a clear distinction between research findings and certifiable causes of death.[10,22]

Box 2. Brief History of NGS

During the development of DNA and RNA sequencing, the first nucleic acid sequencing was achieved in 1965. Holley et al.[36] sequenced the alanine transfer RNA of *Saccharomyces cerevisiae*. In 1977, Maxam and Gilbert[37] developed a technique for sequencing DNA by breaking it down through a chemical process. In the same year, Sanger et al.[38] introduced a chain termination-based sequencing technique using dideoxynucleotides. Then, in 1987, the Applied Biosystems ABI 370 device was introduced to automate the Sanger sequencing technique, using fluorescently labeled probes and capillary electrophoresis. These studies, which laid the foundations for NGS, are considered first-generation sequencing.[39] Second-generation sequencing technologies enable the simultaneous sequencing of millions of DNA molecules through the use of a massive parallel sequencing method.[40] Although different techniques such as pyrosequencing and Ion Torrent sequencing have been developed, Illumina platforms are widely used.[41] Third-generation sequencing consists of Oxford Nanopore and PacBio technologies, which use long reads, unlike Illumina platforms that perform sequencing using short reads.[42]

DNA molecules can be analyzed using whole genome sequencing (WGS) or targeted sequencing strategies, such as WES and panel sequencing. Whole genome sequencing provides sequencing of an organism's entire genome, while WES allows for the sequencing of exons, which constitute approximately 1.5–2% of the genome. Panel sequencing enables the sequencing of specific genes or specific regions of genes.[39] The ability of WGS to detect variants in noncoding regions is a significant advantage over the other two methods.[43] Ribonucleic acid sequencing, which enables the sequencing of RNA molecules, allows for the analysis of gene expression as well as the examination of messenger RNA splicing and non-coding RNA molecules.[44]

In a study examining 39 cases of SUDEP, a total of 133 genes associated with epilepsy and arrhythmia were analyzed using panel sequencing. At least one variant associated with epilepsy or arrhythmia was identified in 72% of the SUDEP cases.[45] In another study, NGS was performed on nine SUDEP cases using a panel of 73 genes associated with cardiac disorders. Previously reported variants were identified in five of the cases.[46] In another study, WES was performed on 61 SUDEP cases. Variants that could explain the condition were identified in 46% of cases. Furthermore, variants associated with long QT syndrome were identified in 7% of cases.[12]

RISK FACTORS AND SUDEP PREDICTION MODELS

The risk of sudden unexpected death is approximately 20-fold higher in individuals with epilepsy than in the general population.[47] Among the various risk factors identified, the presence and frequency of generalized tonic-clonic seizures (GTCS) are the most consistent and robust predictors of SUDEP.[48,49]

Nocturnal seizures have also been shown to significantly increase the risk of SUDEP, with studies indicating a two-fold higher risk in patients experiencing nocturnal seizures than in those with exclusively diurnal seizures.[50,51]

Several scoring systems have been developed to estimate the risk of SUDEP. The SUDEP-7 Inventory, proposed by DeGiorgio et al.[52] in 2010, was based on the findings reported by Walczak et al.[53] in 2001 and later revised in 2015.[54] Recently, the SUDEP-3 Inventory was introduced by Tarighati Rasekhi et al.[55] in 2021 as a simplified

alternative. Although these scoring systems have shown promise in certain studies, they remain controversial, and no consensus has yet been reached regarding their clinical applicability.[56-59] Therefore, further refinement and validation of risk prediction tools are required.

PATHOPHYSIOLOGICAL MECHANISMS OF SUDEP

In adults, SUDEP is most commonly attributed to cardiorespiratory dysfunction occurring during or after GTCS, which represents the most significant risk factor. The MORTEMUS (Incidence and Mechanisms of Cardiorespiratory Arrests in Epilepsy Monitoring Units) study, published in 2013, provided critical insights into the physiological events surrounding SUDEP by analyzing video electroencephalography and electrocardiography data recorded during fatal events.[5]

The study demonstrated that following GTCS, the respiratory rate initially increased (18 to 50 breaths per minute), followed by postictal generalized electroencephalography suppression (PGES). Subsequently, transient or terminal cardiorespiratory dysfunction developed within approximately 3 min. In cases where the dysfunction was transient, it recurred with terminal apnea approximately 11 min after seizure termination, followed by sudden cardiac arrest. Notably, terminal apnea consistently precedes terminal asystole,[5] suggesting that respiratory dysfunction may be the primary initiating mechanism in SUDEP. The forensic interpretation of these mechanisms is complicated by the fact that postmortem examinations rarely demonstrate the specific anatomical correlates of terminal respiratory or autonomic failure. Therefore, SUDEP frequently remains a diagnosis of exclusion, even when robust physiological mechanisms have been demonstrated in monitored clinical settings.[5,60]

RESPIRATORY DYSFUNCTION AND PGES

Several hypotheses have been proposed to explain seizure-induced fatal respiratory arrest, largely based on animal models and observations from patients who survived nonfatal respiratory compromise.[60] In mutant mouse models, apnea began prior to terminal asystole, consistent with the MORTEMUS study findings.

Importantly, the observation that animals either fully recovered or died following tonic-phase apnea suggests that apnea alone is insufficient to cause SUDEP and that additional mechanisms, such as impaired brainstem-mediated respiratory recovery, are likely involved.[60,61]

Postictal generalized electroencephalography suppression is characterized by decreased brain activity and flattening of electroencephalography recordings after a seizure and is associated with brainstem dysfunction. In a study examining 10 cases of SUDEP, it was shown that each 1-sec increase in PGES duration increased the risk of SUDEP by 1.7%.[62] However, another study examining 19 cases of SUDEP found no correlation between PGES and SUDEP, but rather a significant association with GTCS.[63] Therefore, although PGES is frequently observed in patients with GTCS, its relationship with SUDEP is not definitive.

CARDIAC ABNORMALITIES AND SCD

Seizures may induce various cardiac abnormalities, including ictal tachycardia and bradycardia.[64] Although SCD is defined differently from SUDEP, it shares many pathophysiological features.[25] Cardiovascular comorbidities are common in patients with chronic epilepsy.[65] Simultaneously, the risk of sudden cardiac arrest is higher than that in the general population.[66] Unlike SUDEP, SCD in patients with epilepsy typically occurs during daily activities rather than in close temporal association with seizures, and approximately 65% of these deaths are not seizure-related.[65]

Sudden unexpected death in epilepsy remains one of the most devastating and least understood complications of epilepsy, representing a complex interplay between seizure-related physiological disturbances, underlying genetic susceptibility, and environmental or clinical modifiers. Despite advances in epilepsy management, SUDEP continues to pose significant diagnostic and preventive challenges, largely due to its heterogeneous presentation, frequent occurrence in unwitnessed settings, and absence of definitive findings on conventional postmortem examination. Current evidence supports a multifactorial pathophysiological framework in which generalized tonic-clonic seizures act as a central trigger, initiating a cascade of respiratory, autonomic, and cardiac dysfunction, with impaired postictal recovery emerging as a critical determinant of fatal outcomes.

The increasing recognition of the genetic contributions to SUDEP has substantially reshaped our understanding of its underlying mechanisms. Channelopathies and epilepsy-associated genetic syndromes highlight the shared molecular pathways linking neuronal excitability and cardiac electrophysiology, emphasizing that SUDEP cannot be viewed solely as a neurological phenomenon. In this context, molecular autopsy has become an indispensable tool for uncovering pathogenic or likely pathogenic variants in cases with negative autopsy findings, offering not only mechanistic insights but also tangible opportunities for family-based risk assessment, early diagnosis, and targeted preventive strategies.

Advances in NGS technologies have further expanded the scope of postmortem and clinical investigations, enabling comprehensive interrogation of epilepsy- and arrhythmia-related genes and, increasingly, noncoding and regulatory regions of the genome. The integration of genomic data with detailed clinical, electrophysiological, and neuropathological information holds promise for refining SUDEP risk stratification and moving toward more individualized preventive approaches. Nevertheless, important challenges remain, including the interpretation of variants of uncertain significance, the need for standardized molecular autopsy protocols, and ethical considerations surrounding postmortem genetic testing and familial disclosure.

In conclusion, reducing the burden of SUDEP will require a multidisciplinary approach that bridges clinical epileptology, genetics, cardiology, and forensic medicine. From a forensic medicine perspective, SUDEP represents one of the most challenging categories of sudden death, requiring systematic death scene investigation, standardized postmortem protocols, and structured collaboration between forensic pathologists, neurologists, and geneticists. The integration of molecular autopsy into routine forensic workflows is essential not only for etiological clarification but also for public health surveillance and family counseling.[5,11,67] Continued efforts to integrate molecular autopsy findings with clinical risk models and to translate genomic discoveries into practical preventive strategies are essential. Such an approach not only advances scientific understanding of SUDEP but also has profound implications for patient safety, family counseling, and the broader goal of precision medicine in epilepsy care.

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Author Contributions: S.D.: Literature review, writing the article; C.B.: Control and critical review; E.Y.: Concept, supervision, writing the article, critical review; N.H.A.: Idea, design, critical review.

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