

## REVIEW ARTICLE

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# Spotlight on mechanism of sudden unexpected death in epilepsy in Dravet syndrome

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Dravet syndrome (DS) is a severe and catastrophic epilepsy with childhood onset. The incidence and prevalence of sudden unexpected death in epilepsy (SUDEP) are significantly higher in DS patients than in general epileptic populations. Although extensive research conducted, the underlying mechanisms of SUDEP occurring in DS patients remain unclear. This review focuses on the link between DS and SUDEP and analyzes the potential pathogenesis. We summarize the genetic basis of DS and SUDEP and elucidate the pathophysiological mechanisms of SUDEP in DS. Furthermore, given the drug-resistant nature of this disorder, the pharmacological approach has limited efficacy and often causes side effects, therefore, the non-pharmacological approaches and precise treatment can reduce the risk of SUDEP in this condition, open a new window to cure this disease, and provide a widened landscape of treatment options for patients.

## HIGHLIGHTS

- DS is a severe, refractory childhood-onset epilepsy with extremely high premature mortality, with SUDEP being the leading cause of death.
- Inherent genetic traits could be a nexus between DS and SUDEP, and DS patients exposed to various pathogenic genes or genetic modifiers may have different susceptibilities to SUDEP.
- A confluence of different pathophysiological mechanisms synergistically triggers SUDEP in DS patients, with seizures-induced cardiopulmonary dysfunction representing a critical contributing factor.
- Combined pharmacotherapy and non-pharmacologic interventions can improve therapeutic efficacy, while gene therapy has ushered in a new era with great potential.

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## INTRODUCTION

Dravet syndrome (DS), also known as severe myoclonic epilepsy of infancy (SMEI), is a rare, severe and disastrous children-onset epilepsy [1, 2]. The estimated incidence ranges from 1 in 15,700 to 1 in 40,900 [3, 4]. In 70–80% of cases, DS is primarily attributed to de novo heterozygous loss-of-function mutations in the SCN1A gene that encodes the  $\alpha$ -subunit of the voltage-gated sodium channel Nav1.1, leading to haploinsufficiency of the channel [5–8]. Missense and truncation (e.g., nonsense, frameshift) mutations are the most common types and significantly influence the severity of epilepsy phenotypes [9, 10]. Dysfunction of Nav1.1 decreases sodium currents in different types of GABAergic interneurons, especially the parvalbumin (PV)-positive interneurons where Nav1.1 is predominantly expressed [11, 12]. The reduced sodium currents lead to an imbalance between excitation and inhibition, which may contribute to hyperexcitability and disruptions in neural network function [13], potentially increasing the risk of

epilepsy-related mortality. While multiple factors contribute to mortality, sudden unexpected death in epilepsy (SUDEP) is considered one of the primary causes.

SUDEP is defined as sudden, unexpected, witnessed or unwitnessed death in epilepsy patients without warning or other clear causes of death [14]. The public health burden of SUDEP ranks second only to stroke in terms of years of potential life lost, compared to other common neurological disorders. The incidence rate of SUDEP varies across different study cohorts, with the highest frequency observed in refractory and drug-resistant epilepsy [15]. The mechanism of SUDEP remains elusive, primarily due to its complex and multifactorial pathology, as well as the difficulty of obtaining real-time monitoring data in epileptic patients.

DS, characterized by high epilepsy-related premature mortality, is devastating and life-threatening. Death can occur at any age, but is more common during childhood. Compared to the general

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epileptic demographic, individuals with DS have an elevated risk of SUDEP. Several studies have shown that nearly half of all deaths in DS are attributed to SUDEP, which has now surpassed status epilepticus (SE) as the foremost cause of mortality [16, 17]. Despite some advancements in characterizing DS, the mechanisms underlying how DS leads to SUDEP remain unclear. Our group has long been dedicated to studying the pathogenesis of SUDEP. Since DS can cause detrimental comorbidities and is strongly associated with SUDEP, we believe a thorough exploration of the relationship between DS and SUDEP is imperative.

In this review, we integrate data from clinical and animal studies to evaluate the connection between DS and SUDEP and analyze the possible mechanisms. In addition, we discuss promising therapeutic approaches that could offer new insights for developing effective strategies to manage DS and reduce the incidence of SUDEP in DS patients.

### CLINICAL MANIFESTATIONS OF DS

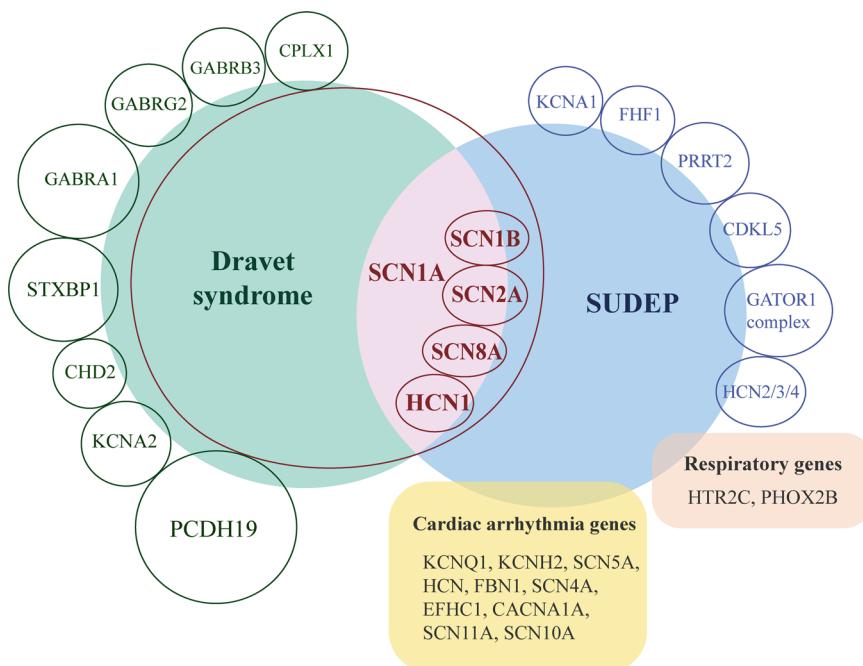
The clinical manifestations of DS are primarily divided into two categories: epilepsy-related symptoms (e.g., seizures, epilepsy-induced death) and long-term comorbidities. DS is mainly characterized by hyperthermia sensitivity and typically manifests within the first year of life in an otherwise normal infant, usually between 4 and 8 months of age [4]. The most common initial symptom is a prolonged seizure triggered by hyperthermia that can manifest as recurrent focal clonic (hemiclonic) seizures or generalized clonic seizures [18, 19]. This stage is often diagnosed as febrile convulsions. By 1.5 to 5 years of age, additional seizure types may occur (but are not always present), such as myoclonic seizures, atypical absence seizures, atonic seizures, etc [20]. Some children with DS also develop acute encephalopathy. Notably, a history of multiple seizures is a significant risk factor for SUDEP. Mortality rates in DS patients reported in different studies vary from 3.7–20.8% [2, 21, 22], which are significantly higher than those in other pediatric epilepsy cohorts. Premature death is a major problem in DS, and the main causes of death have been classified into three types: SUDEP, status epilepticus (SE), and

drowning. In a previous survey of 623 patients with DS from Japan, a total of 63 individuals died and data from 59 of these people were analyzed [23]. In this study, SUDEP was the cause of mortality in 53% of patients in this group and its incidence peaked at 1–3 and 18 years of age. In conjunction with other studies, it is evident that SUDEP most often attacks children, especially those under 10 years of age. Most dead patients were found in bed early in the morning or during sleep in the afternoon. The prevalence of SUDEP ranged from 49–61% in different studies and it is responsible for the vast majority of premature mortality in DS [16, 17].

In addition to epilepsy-related symptoms, long-term comorbidities, including developmental delay, hyperactivity, motor dysfunction, cognitive impairment, intellectual disability, and autistic-like behaviors, can also be present and become a tremendous burden [4, 24, 25]. Most living DS patients suffer from a lifelong disabling condition that limits daily activities and leads to a poor quality of life. Although less common, the incidence of SUDEP may increase with age.

### GENETIC FEATURES MAY BE A LINK BETWEEN DS AND SUDEP

While mutations in the SCN1A gene are well-known as the primary cause of DS, it is increasingly recognized that DS can also occur in individuals with non-SCN1A mutations, leading to DS-like phenotypes [26]. These cases present with clinical characteristics that closely resemble classic DS but are driven by variations in other genes. In addition, different genetic modifiers are believed to significantly influence the severity of the phenotype of SCN1A-induced DS, especially the risk of SUDEP. However, the underlying mechanisms leading to SUDEP remain unclear. Some evidence has emerged with respect to genetic susceptibility to SUDEP, suggesting that genetics is an additional important area for further understanding of SUDEP risk factors [27]. Therefore, researchers are intensifying their focus on the genetic characteristics of SUDEP. We found DS and SUDEP may have a common genetic basis, and there is an intersection of the causative genes of DS, genetic modifiers of DS, and the pathogenic gene of SUDEP



**Fig. 1 Diverse genetic features may be the linkage of DS and SUDEP.** This figure summarizes the genetic features of DS and SUDEP. The genes that appear in the pink intersection are some DS-causing genes that are the main intrinsic genetic factors in the occurrence of SUDEP in DS patients.

**Table 1.** Genes associated with DS and DS-like phenotypes.

Gene	Location	Encoded proteins	Reference
SCN1A	2q24.3	The $\alpha$ -subunit of the voltage-gated sodium channel $\text{Na}_v1.1$	[5]
SCN2A	2q24.3	The $\alpha$ -subunit of the voltage-gated sodium channel $\text{Na}_v1.2$	[32, 173]
SCN8A	12q13.13	The $\alpha$ -subunit of the voltage-gated sodium channel $\text{Na}_v1.6$	[31, 174]
SCN1B	19q13.11	The $\beta 1$ -subunit of the voltage-gated sodium channel	[33, 175]
GABRA1	5q34	The $\alpha 1$ -subunit of the GABA <sub>A</sub> receptor	[39, 40]
GABRB3	15q11.2-q12	The $\beta 3$ -subunit of the GABA <sub>A</sub> receptor	[41, 42, 176]
GABRG2	5q34	The $\gamma 2$ -subunit of the GABA <sub>A</sub> receptor	[177–179]
PCDH19	Xq22.1	Protocadherin-19(a calcium-dependent cell-adhesion molecule)	[28, 30, 31]
STXBP1	9q34.11	Syntaxin-binding protein 1	[31, 39]
CHD2	15q26	Chromodomain helicase DNA-binding protein 2	[46]
KCNA2	1p13.3	Potassium voltage-gated channel subfamily A member 2 ( $\text{K}_v1.2$ )	[36]
HCN1	5p12	Hyperpolarization-activated cyclic nucleotide-gated channel 1	[38]
CPLX1	4p16.3	Complexin 1(a presynaptic small molecule protein)	[47]

*GABA<sub>A</sub>*, gamma-aminobutyric acid type A.

(Fig. 1). The relationship between DS and SUDEP is complex, with genetic factors playing a central role in both conditions.

### Genes associated with DS

SCN1A is recognized as the most common genetic factor in DS. In addition to this, the PCDH19 gene is regarded as the secondary principal genetic cause of DS. PCDH19, expressed in the developing brains of humans, is the first member of the cadherin superfamily directly implicated in epilepsy. Depienne et al. detected that PCDH19 played an essential role in infantile epileptic encephalopathies, with a clinical spectrum overlapping that of SCN1A-DS [28]. PCDH19-related epilepsy is a special X-linked inherited disorder that mainly affects females [29]. In addition, several studies suggested that PCDH19 mutations could be found in some SCN1A-negative DS patients [30, 31].

Several genes encoding cation channels, such as SCN2A, SCN8A, SCN1B, KCNA2 and HCN1, have been proposed to be involved in DS or DS-like phenotypes. All of them control potential exchange between the extracellular and the intracellular spaces and may be tied to neuronal excitability. Mutations in these genes are linked to a spectrum of epilepsies and neurodevelopmental abnormalities. A de novo SCN2A mutation has been reported in one single case without coexisting SCN1A mutations, making it feasible to comprehend  $\text{Na}_v1.2$  dysfunction and its relationship to the etiology of DS [32]. SCN8A encodes  $\text{Na}_v1.6$ , which, unlike  $\text{Na}_v1.1$ , is primarily located in pyramidal neurons responsible for excitatory signals via glutamate release. Notably, the majority of SCN8A mutations result in the gain-of-function of  $\text{Na}_v1.6$ , causing elevated excitability and firing rates of pyramidal cells. In 2015, some patients in the reported SCN8A cohort had previously been given a preliminary diagnosis of DS. Moreover, Patino et al. presented the first case of DS attributed to a homozygous mutation in SCN1B [33], and Gong et al. also discovered two SCN1B mutations in DS patients without SCN1A mutations [34]. It should be noted that no SCN1B mutations were identified in 54 patients with DS recruited from four centers in one report [35]. These results indicate that SCN1B is an etiologic candidate underlying DS, but is not a common cause.  $\text{K}_v1.2$  encoded by KCNA2 is typically concentrated along axons and axon terminals of neurons, as well as at presynaptic sites. In a clinical study, four different de novo KCNA2 variants have been described in six patients with epileptic encephalopathy, including one with clinical features that resemble DS [36]. In an animal study, it was discovered that *Kcnna2*-null mice were more vulnerable to seizures and early death [37]. Furthermore, hyperpolarization-activated

cyclic nucleotide-gated channel 1 is a nonselective cation channel that contributes to spontaneous rhythmic activity in neurons. HCN1 encoding this channel was found in patients with DS-like phenotypes [38]. In a word, these dysfunctional channel genes make hyperexcitability of the nervous system, leading to DS.

Mutations in the GABA<sub>A</sub> receptor genes (GABRA1, GABRB3 and GABRG2) are responsible for the pathogenesis of DS as the predominantly affected inhibitory neurons are GABAergic interneurons. For instance, GABRA1 is associated with early-onset epileptic encephalopathy as well as genetic generalized epilepsy and febrile seizures. Carvill et al. sequenced the genes of SCN1A-negative DS individuals and found that four of them carried GABRA1 mutation [39]. Two patients from another study with DS-like phenotype harbored a de novo variation in GABRA1 [40]. In 2017, Le et al. performed exome sequencing in six patients with SCN1A-negative DS to identify other genes related to this disorder. In one affected individual, they detected a de novo heterozygous missense variant in GABRB3 [41], and one case report showed a girl with DS presented novel GABRB3 mutations [42], implying that GABRB3 may be a putative candidate for DS. In addition, GABRG2 mutations have been reported to be associated with early-onset epileptic encephalopathy, with some cases showing core symptoms of typical DS [43]. Different phenotypes of DS are likely due to impaired axonal transport associated with the dominant-negative effects of GABRG2 [44]. All aforementioned mutations reduce GABA signaling by disrupting structural domains important for GABA<sub>A</sub> receptor function, thereby elucidating their role in the etiology of DS.

In addition, other causative genes encoding proteins, such as STXBP1, CHD2 and CPLX1, are involved in the etiology of DS. STXBP1 is pivotal in synaptic vesicle release. After excluding abnormalities in SCN1A, STXBP1 mutations contribute significantly to DS and are associated with the motor phenotype with parkinsonian symptoms in DS patients [39, 45]. Although loss-of-function mutations in CHD2 are rare, a previous study found that individuals carrying a CHD2 mutation displayed a spectrum of fever-sensitive generalized seizures similar to DS [46]. Abnormal expression of CPLX1 can be seen in several neurodegenerative and psychiatric disorders, but is rare in malignant epilepsy. In 2017, Redler et al. first described variants in CPLX1 in two families linked to severe infantile myoclonic epilepsy, developmental delay, and intellectual disability [47]. These genes are considered as emerging genetic contributors to DS and therefore warrant further investigation to elucidate their mechanisms in this disorder.

**Table 2.** Genetic modifiers of DS.

Gene	Location	Encoded proteins	Mutations in animal studies	SUDEP risk	Reference
SCN2A	2q24.3	The $\alpha$ -subunit of the voltage-gated sodium channel Na <sub>v</sub> 1.2	Scn2a <sup>Q54</sup>	↑	[49]
KCNQ2	20q13.3	The voltage-gated potassium channel subunit Kv7.2	Kcnq2 <sup>V182M/+</sup>	↑	[49]
GABRA2	4p12	The $\alpha$ 2-subunit of the GABA <sub>A</sub> receptor	Gabra2 <sup>em1Geh</sup>	↑	[51]
HLF	17q21-22	Hepatic leukemia factor (a transcription factor)	Hlf <sup>tm1Schb</sup> (Hlf <sup>KO/+</sup> )	↑	[52]
SCN9A	2q24.3	The $\alpha$ -subunit of the voltage-gated sodium channel Nav1.7	Scn9a <sup>N641Y/N641Y</sup>	n	[53]
CACNA1A	19p13	The $\alpha$ -1A subunit of the voltage-dependent calcium channel Cav2.1 (P/Q-type)	Cacna1a <sup>M251K/M251K</sup>	n	[180]
CACNB4	2q22-23	The $\beta$ 4 subunit of the voltage-dependent calcium channel Cav2.1(P/Q-type)	n	n	[54]
POLG	15q25	Mitochondrial DNA polymerase gamma, catalytic subunit	n	n	[56]
SCN8A	12q13.13	The $\alpha$ -subunit of the voltage-gated sodium channel Nav1.6	Scn8a <sup>med-jo/+</sup> and Scn8a <sup>med/+</sup>	→	[49, 57]
CACNA1G	17q22	The $\alpha$ -1G subunit of the voltage-dependent calcium channel Cav3.1(T-type)	Cacna1g <sup>-/-</sup>	→	[58]

↑ increase; ↓ decrease; n no evidence.

In summary, all the genes mentioned can be detected in SCN1A-positive DS and SCN1A-negative DS patients (Table 1). Although the clinical characteristics caused by other genes are slightly different from classical SCN1A-DS, they represent potential inherited pathogenic factors.

### Genetic modifiers of DS

Several potential modifier genes have already been identified in human patients and Scn1a knock-out mice, including ion channel genes, GABA receptor subunit genes, and genes associated with seizures or hyperexcitability [48]. Variants in different genetic modifiers might alleviate or exacerbate clinical outcomes.

Modifiers that exacerbate the phenotype or increase DS severity include several genes. SCN2A could potentially underlie the genetic pathogenesis of DS without SCN1A mutations. Meanwhile, Scn2a mutants aggravate the phenotype and decrease the survival rate of DS mice [49]. In the same study, the combination of Scn1a and Kcnq2 mutations led to early-onset, generalized tonic-clonic seizures and juvenile lethality [49]. Similarly, variants in KCNQ2 exacerbate clinical presentation and severity in patients with DS [50]. GABRA2 is also a genetic modifier of DS. In an animal study, researchers found that a repaired Gabra2 allele increased Gabra2 expression, which dramatically lessened seizure burden and premature lethality (SUDEP-like) in the Scn1a<sup>+/-</sup> mice [51]. Furthermore, hepatic leukemia factor (Hlf) is a member of the PAR bZIP transcription factor family. Genetic deletion of Hlf increased premature mortality and exacerbated the phenotype of Scn1a<sup>+/-</sup> mice, thus also functioning as a genetic modifier of DS [52].

Similarly, SCN9A mutations have also been observed in certain patients with SCN1A mutations, correlating with a more severe phenotype [53]. In a case report, a missense mutation of CACNB4 (R468Q) was detected in one of 38 SCN1A mutation-positive DS patients, which causes greater Cav2.1 currents, thereby increasing the neurotransmitter release in excitatory neurons and enhancing seizure susceptibility [54]. Another human study has proposed that subjects with combinations of CACNA1A variants and SCN1A mutations showed a higher incidence of earlier onset, as well as longer and more severe seizures, compared to subjects with only SCN1A mutations [55]. Both CACNB4 and CACNA1A variants that alter Cav2.1 function worsen the epileptic phenotype of DS. Additionally, the rare heterozygous POLG variant impairs cortical metabolism during the high energy demands associated with status epilepticus, thereby increasing susceptibility to acute encephalopathy [56]. Although there is currently no clear evidence indicating that these genes increase the risk of SUDEP in DS patients, the more severe epilepsy phenotypes and complications they cause indirectly suggest that these genes may be associated with an increased risk of SUDEP.

Conversely, several genetic modifiers have been identified as ameliorating factors, reducing DS severity or improving survival. SCN8A mutants with reduced SCN8A expression exhibit increased resistance to induced seizures, improve survival and prolong the lifespan of DS mice [57]. In addition, CACNA1G was also recently nominated as a genetic modifier of survival in a mouse model of DS [58]. Scn1a<sup>+/-</sup> mice with decreased CACNA1G expression showed partial amelioration of the disease with improved survival and reduced spontaneous seizure frequency.

All genes can be demonstrated to be present in humans. They have been proposed as genetic modifiers leading to the variable expressivity of DS, which could provide a more accurate assessment of disease severity and alter the premature lethality of DS (Table 2). Thus, genetic modifiers may be novel risk genes associated with seizures and SUDEP, enhance our comprehension of the etiology of SUDEP in DS patients and emerge as potential targets for therapeutic intervention in patients.

## Genetic basis of SUDEP

Several pathogenic modifications in various genes have been identified as factors that increase SUDEP risk through different pathophysiologic mechanisms, which has prompted a growing number of researchers to focus on studying the genetic underpinnings of SUDEP [59]. The genes associated with SUDEP can be broadly categorized into three major groups: cardiac arrhythmia genes, respiratory genes and genes associated with genetic epilepsies.

**Genes associated with genetic epilepsies.** Pathogenic variations associated with several genetic epilepsies that carry a high risk of SUDEP may serve as useful biomarkers. SCN1A-induced DS patients face a significantly higher risk of SUDEP, while SCN1B loss-of-function mutations also contribute to an increased risk of SUDEP [60]. Previous work suggested that Scn1b deletion can increase tetrodotoxin-sensitive sodium currents, alter intracellular calcium homeostasis, and induce arrhythmias in murine hearts. These factors underlie epileptogenesis and SUDEP [61]. In addition, SCN2A and SCN8A, primarily involved in developmental and epileptic encephalopathies, are also deleterious factors contributing to SUDEP [62]. Several studies have identified DEP domain containing 5 (DEPDC5) as a pathogenic gene for SUDEP [63, 64]. Mutations in DEPDC5 are increasingly recognized as a common cause of familial focal epilepsy with variable foci [65]. NPRL2 and NPRL3, together with DEPDC5, form the GATOR1 complex, a repressor of the mechanistic target of rapamycin complex 1 (mTORC1) pathway [66]. GATOR1 complex gene mutations that lead to mTORC1 pathway upregulation are a primary cause of SUDEP [67]. KCNA1, which encodes the voltage-gated potassium channel Kv1.1 α-subunit, is linked to episodic ataxia and myokymia syndrome [68]. In animal studies, Kcna1 gene deletion mice, frequently utilized in SUDEP research, displayed malignant interictal cardiac abnormalities, including a fivefold increase in atrioventricular conduction blocks, bradycardia, and premature ventricular contractions [69]. These mice exhibited an increased susceptibility to respiratory failure during severe seizures, potentially leading to sudden death [70]. Although direct links between KCNA1 gene variants and SUDEP in humans have yet to be established, these findings suggest that this gene could be a potential risk factor. Fibroblast growth factor homologous factors (FHF) are brain and cardiac sodium channel binding proteins that modulate channel density and inactivation gating. According to a recent study, a de novo gain-of-function missense mutation in the FHF1 gene is associated with early infantile epileptic encephalopathy. This mutation enhances sodium channel Nav1.6 currents and induces SUDEP with bradycardia in mice [71]. Furthermore, variants in the PRRT2 gene, which encodes proline-rich transmembrane protein 2, are emerging as potential biomarkers for SUDEP. These variants are associated with benign familial infantile seizures. A previous case report has shown that a boy with a PRRT2 variant who had afebrile focal seizures was found dead in a supine position after having fallen asleep at the age of 14 due to probable SUDEP [72]. The potential link between mutations in the PRRT2 gene and susceptibility to SUDEP requires further investigation. In 2017, Coll et al. identified four missense variants in epilepsy-related genes—CDKL5 (associated with X-linked infantile spasm syndrome), CNTNAP2 (associated with cortical dysplasia focal epilepsy syndrome), GRIN2A (associated with focal epilepsies) and ADGRV1 (associated with recurrent febrile seizures and afebrile seizures). These variants may contribute to SUDEP and were proposed as novel candidate [73].

**Cardiac arrhythmia genes.** Cardiac arrhythmias are widely recognized as a potential pathogenic mechanism in SUDEP. Genetic variants associated with arrhythmias are found in up to 15% of SUDEP cases, most of which involve ion channel genes that disrupt normal cardiac function and may increase the risk of SUDEP.

Long QT syndrome (LQTS) is an inherited cardiac channelopathy characterized by prolonged ventricular repolarization (prolonged QT interval) and a predisposition to torsade de pointes, ventricular fibrillation, and sudden cardiac death. Most congenital LQTS cases result from mutations in KCNQ1, KCNH2, and SCN5A [74]. Notably, SCN5A variants can also cause Brugada syndrome, a fatal cardiac disease [75]. Variants in all three genes have been identified in SUDEP cases, suggesting their potential role in the genetic basis of SUDEP [76, 77]. HCN channels are involved in generating spontaneous rhythmic activity in both cardiac pacemakers and neuronal cells, which can regulate neuronal excitability. Dysfunction in these channels may result in epileptogenesis. In 2011, Tu et al. analyzed the genes in 48 SUDEP cases and identified three non-synonymous variants in HCN2 and HCN4 [78]. A systematic review also identified all four HCN genes (HCN1–4) in some SUDEP cases [79]. Hence, HCN channels are strong candidates for genetic screening in SUDEP because of their association with human diseases. Other genetic variants associated with epilepsy and encoding cardiac ion channels could explain the SUDEP phenotype. One study identified additional potential candidate genes for SUDEP, including FBN1, SCN4A, EFHC1, CACNA1A, SCN11A, and SCN10A [80]. In conclusion, these findings support the hypothesis that genetic risk factors predisposing to cardiac arrhythmia may contribute to the risk of SUDEP in certain epilepsy patients.

**Respiratory genes.** Evidence for the connection between SUDEP and genes related to neuronal regulation of respiratory function is mainly from animal studies. DBA (DBA/1 and DBA/2) mice are useful animal models to study SUDEP because they exhibit generalized tonic-clonic seizures followed by seizure-induced respiratory arrest (S-IRA) and SUDEP. DBA mice exhibit impaired expression of serotonin(5-HT) receptors in the brainstem, and TPH2, the rate-limiting enzyme for 5-HT synthesis in the CNS, is also reduced [81]. Our previous studies revealed that 5-hydroxytryptophan, the precursor for 5-HT synthesis, can reduce the incidence of S-IRA and SUDEP in DBA/1. Additionally, enhancing 5-HT function in DBA/1 mice can reduce S-IRA and improve survival, indicating that the 5-HT system plays a key role in S-IRA and SUDEP [82, 83]. An animal study found that a mouse model with 5-HT<sub>2C</sub> receptor gene(htr2c) mutants is extremely susceptible to seizures, S-IRA and SUDEP [84]. Meanwhile, a recent study also reported the first analysis of HTR2C variants found in human SUDEP [85].

Congenital central hypoventilation syndrome (CCHS) is a potentially fatal autonomic nervous system disorder characterized by hypoventilation and impaired ventilatory response to hypercapnia and hypoxemia during sleep, which is primarily caused by expansion of the alanine repeat in the homeobox gene PHOX2B. Although one human study has shown that PHOX2B mutations are not a common risk factor for SUDEP, this gene may still be a potential target for SUDEP [86]. Furthermore, in another study, no variants were identified in five genes with plausible roles in the central control of ventilation (ASCL1, BDNF, EDN3, GDNF, and RET) among our 61 SUDEP cases [59].

Emerging evidence suggests that the genetic landscape of DS and SUDEP may overlap. The identification of common genetic pathways between DS and SUDEP highlights the importance of further genetic studies of them.

Bioinformatics studies play a crucial role in understanding the complex interaction between DS and SUDEP, particularly in uncovering the genetic features underlying these conditions. Bioinformatics tools, such as genome-wide association studies (GWAS), next-generation sequencing (NGS), and RNA sequencing, enable researchers to analyze large-scale genomic data and identify novel genetic variants that may contribute to the increased risk of SUDEP in DS patients. Furthermore, bioinformatics approaches allow for the integration of genetic data with clinical and phenotypic information, providing deeper insights into how specific genetic variations interact with environmental factors.

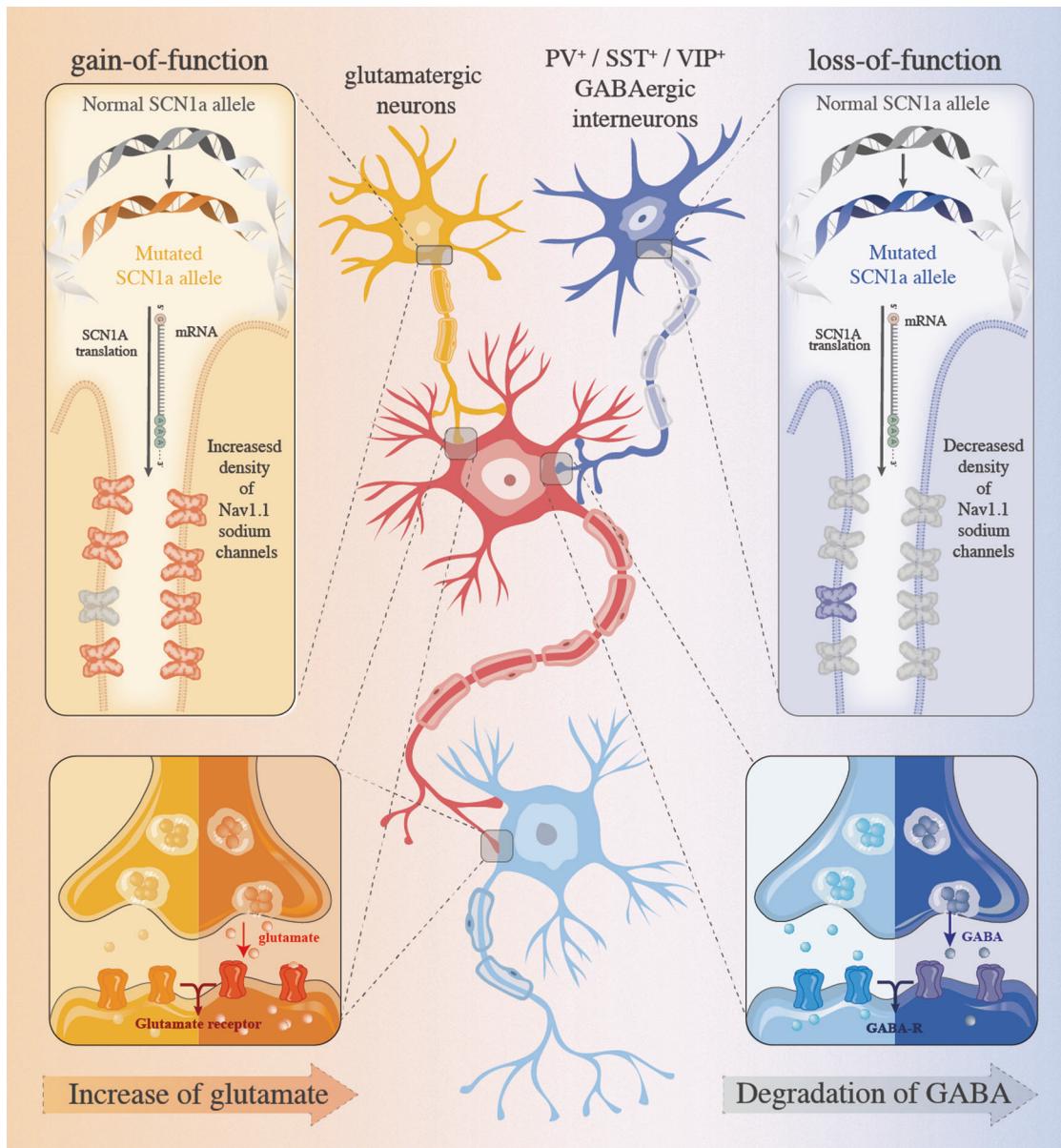
In the future, bioinformatics will help to elucidate the genetic basis of DS and SUDEP, paving the way for personalized treatment strategies, and will be instrumental in understanding the mechanisms underlying the risk of SUDEP in DS patients, leading to more effective interventions and risk assessments for patients.

## PATOPHYSIOLOGICAL MECHANISMS UNDERLYING THE OCCURRENCE OF SUDEP IN DS

### Central neuronal alteration

The “interneuron hypothesis” is the currently most well-recognized pathophysiological mechanism of DS [12]. Mutations in the main causative gene SCN1A, lead to the loss of Nav1.1 channels. In the brain, Nav1.1 is predominantly expressed in

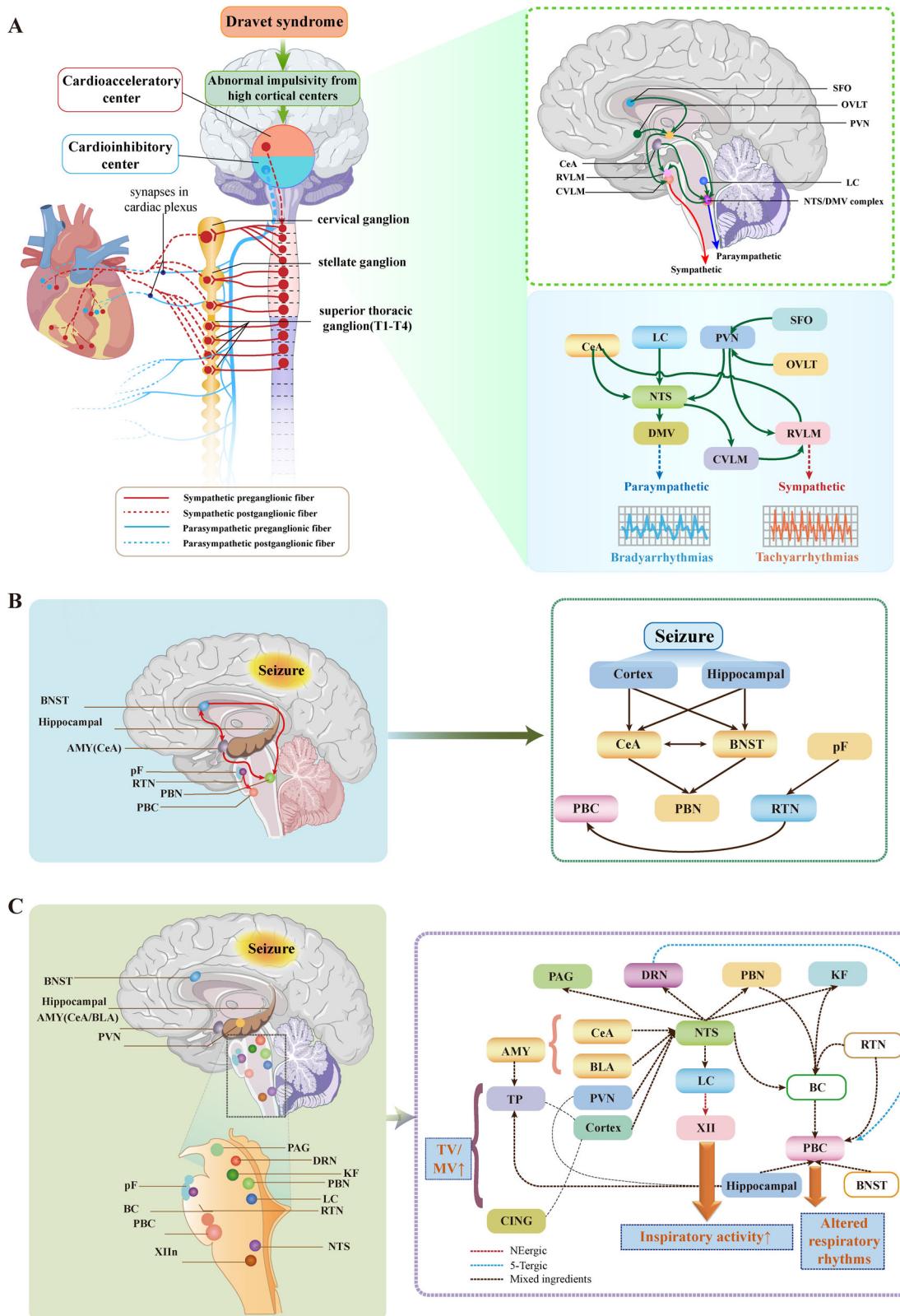
forebrain GABAergic neurons, especially in the axon initial segment and somata of PV-positive interneurons, whereas Nav1.1 is slightly expressed in excitatory pyramidal neurons [11, 12]. The mutant SCN1A results in severely impaired sodium current and action potential firing in forebrain GABAergic inhibitory interneurons without detectable changes in excitatory pyramidal neurons, leading to hypofunction of inhibitory circuits [12, 87, 88]. This leads to hyperexcitability in the neuronal network and seizures. Interneurons in the cortex and hippocampus are likely to be most affected. In contrast, Nav1.1 haploinsufficiency in excitatory neurons can ameliorate seizure-associated sudden death in a mouse model of DS [89]. Furthermore, both somatostatin-positive (SST+) and vasoactive intestinal peptide-positive (VIP+) interneurons contribute to the pathogenesis of



**Fig. 2 Alterations in central neurons causing hyperexcitability in the neuronal network are a possible mechanism leading to SUDEP in DS patients.** DS is caused by the deletion of Nav1.1 channels in GABAergic inhibitory interneurons (primarily PV+, and a few SST+ and VIP+ interneurons) due to a loss-of-function effect of SCN1A mutations, or by the excessive sodium channel activity in glutamate neurons due to a gain-of-function effect of few SCN1A mutations, both of which lead to excitation of downstream neural pathways as well as hyperactivity of neural network. Among them, the “inhibitory interneuron hypothesis” caused by GABAergic interneurons draws more popularity. Abbreviations: PV+: parvalbumin-positive; SST+: somatostatin-positive; VIP+: vasoactive intestinal peptide-positive; GABA, gamma-aminobutyric acid.

DS. The excitability of SST+ and VIP+ interneurons is impaired in DS mice, leading to disrupted synaptic transmission [90]. The three major subtypes of GABAergic inhibitory interneurons (PV+, SST+, and VIP+ interneurons) synergistically affect the excitability of neural networks in the brain. It's worth noting that Mistry et al. showed that elevated sodium current density in excitatory

pyramidal neurons correlates with lethality in DS mice [91]. In addition, an animal study highlighted a novel perspective that the decline in acetylcholine and the excitability of pyramidal cells, along with inhibitory interneurons, are responsible for network hyperexcitability [92]. Decreased acetylcholine can lead to hippocampal excitation, as this neurotransmitter typically interacts



**Fig. 3 Cardiac autonomic imbalance and respiratory dysfunction are possible causes of SUDEP in DS patients.** **A** DS patients, during seizures, produce abnormal impulsivity from cortical regions, which alters the direct input of DMV and RVLM from the upstream nuclei and results in sympathetic or parasympathetic hyperexcitability. Among them, bradycardia due to parasympathetic dominance accounts for the vast majority of DS patients. **B** Respiratory circuits and neural nuclei previously validated in DS studies cause respiratory dysfunction, and abnormalities in these circuits and neural nuclei lead to SUDEP. **C** We outline conceivable respiratory pathways that may lead to respiratory dysfunction during DS followed by SUDEP. There may be a circuit among these that explains the mechanism of breathing disorders in DS and SUDEP. Abbreviations: CeA: central amygdala; CVLM: caudal ventrolateral medulla; DMV: dorsal motor nucleus of the vagus; LC: locus coeruleus; NTS: nucleus tractus solitarius; OVL: organum vasculosum of the lamina terminalis; PVN: paraventricular nucleus; RVLM: rostral ventrolateral medulla; SFO: subfornical organ; AMY: amygdala; BC: Bötzinger complex; BLA: basolateral amygdala; BNST: bed nucleus of the stria terminalis; CING: cingulate gyrus; DRN: dorsal raphe nucleus; KF: Kölliker-Fuse; MV: minute ventilation; PAG: periaqueductal gray; PBC: preBötzinger complex; PBN: parabrachial nucleus; pF: parafacial nucleus; PVN: paraventricular nucleus of the hypothalamus; RTN: retrotrapezoid nucleus; TP: temporal pole; TV: tidal volume; XII: hypoglossal nucleus.

with muscarinic receptors on GABAergic interneurons. This aligns with previous findings showing the protective effect of acetylcholine esterase inhibitors on triggered seizures in DS mice [93, 94]. Another group of GABAergic neurons expressing SCN1A is located in the nucleus reticularis thalami (nRT), which is thought to regulate information transmission between the thalamus and cortex. Alterations in the function of the corticothalamic circuit may underlie the mechanism of DS [95].

The origin of DS could also be explained by another mechanism. Different variants can alter the structure of the SCN1A-encoded protein in different ways, resulting in diverse functional outcomes [96]. Some SCN1A mutations have a gain-of-function effect and lead to overactivation of glutamatergic neurons. For example, electrophysiological analysis of iPSC-derived glutamatergic neurons from patients revealed a hyperexcitable state of enlarged and persistent sodium channel activation as well as typical epileptic spontaneous action potentials. This study suggested that at least a proportion of DS patients exhibit excessive activation of excitatory neurons [96]. Additionally, one study reported that enhanced NMDA receptor-mediated glutamatergic transmission facilitates abnormal neuronal excitability [97].

The neural network becomes overactive due to the hyperexcitability of glutamatergic neurons and/or the hypoexcitability of GABAergic neurons. This imbalance between excitation and inhibition is thought to be the primary cause of seizures [98]. SUDEP is closely associated with seizures. The most important risk factor for SUDEP is frequent generalized tonic-clonic seizures (GTCS) [99, 100], and SUDEP is more prevalent in patients with GTCS. Both poor management of GTCS and long-term GTCS duration are strongly linked to SUDEP. Similarly, focal seizures also can increase the incidence of SUDEP. Therefore, alterations in the neuronal network involved in epileptic seizures could be a potential etiology of SUDEP in DS patients (Fig. 2).

### Cardiac dysfunctions

Cardiac arrhythmias are considered common causes of sudden death and potential risks for SUDEP. These arrhythmias are diverse and can occur during different types of seizures. Patients with DS often exhibit an imbalance in cardiac autonomic function, which may increase their risk of cardiac arrhythmias. A previous study suggested that parasympathetic nervous system hyperactivity, which disrupts cardiac regulation, can lead to severe bradycardia and electrical dysfunction of the ventricle [101]. This suggests that bradycardias pose a serious threat of death and may lead to cardiac arrests. Several case-control studies have investigated the alteration of heart-rate variability (HRV) in DS patients, consistently showing reduced HRV [102–104]. HRV is used to measure the balance between the sympathetic and parasympathetic systems, with decreased HRV values indicating increased adrenergic tone or sympathetic upregulation [105, 106]. In addition to HRV, increased QT interval and P wave dispersion can occur due to excessive sympathetic activity [105]. These are important indicators of cardiac autonomic dysfunction and may serve as potential

biomarkers for SUDEP in DS. When the sympathetic system is overactivated and dominant, tachyarrhythmias occur, increasing the risk of life-threatening ventricular arrhythmias. Thus, patients have different types of arrhythmias due to parasympathetic or sympathetic dominance, which can progress to ventricular fibrillation, asystole, and death (Fig. 3A). However, bradycardias account for the vast majority of DS patients, distinguishing them from arrhythmias observed in other epilepsy disorders.

The pathogenic SCN1A gene is expressed in both the heart and brain. As a neuronal gene, it can cause a CNS phenotype. Its product, Nav1.1, is also present and functionally important in the cardiomyocytes and the sinoatrial node [8]. Therefore, maintaining normal cardiac rhythm is crucial. SCN1A gene mutation leads to altered sodium current and is responsible for cardiac channelopathies. Some studies revealed DS mice and iPSC-derived cardiac myocytes exhibit increased sodium current, which contradicts the loss of Nav1.1 channels [107, 108]. This may be due to alterations in the expression of other ion channels, such as Nav1.5.

Overall, the cardiac autonomic imbalance and altered cardiac electrophysiology in DS patients are associated with an increased incidence of SUDEP, suggesting that cardiac dysfunctions may be a potential cause of death in a portion of DS patients.

### Respiratory dysfunction

Respiratory dysfunction during seizures is considered the primary mechanism of SUDEP [109]. Some clinical case reports suggested that DS patients exhibited altered respiratory rhythms, central and obstructive apnea, as well as respiratory failure [70, 110, 111]. Seizures can cause laryngospasm, leading to complete or partial airway occlusion [112]. These respiratory dysfunctions result in reduced oxygen saturation followed by SUDEP. Seizure-induced respiratory arrest (S-IRA) is the leading cause of different respiratory dysfunctions. Our previous studies have shown that deficits in 5-HT and norepinephrine (NE) neurotransmission play an important role in the pathogenesis of S-IRA in the DBA/1 mouse model. We found that atomoxetine-mediated reduction of S-IRA evoked by acoustic stimulation or PTZ, can be significantly reversed by prazosin, a selective NE α-1 receptor antagonist. Additionally, the incidence of S-IRA can be reduced by administering 5-hydroxytryptophan, a precursor for serotonin synthesis [82, 113]. DS mice, like DBA/1 mice, also exhibit respiratory arrest prior to SUDEP. DS mice present respiratory phenotypes, such as hypoventilation and central apnea, which rapidly cause hypoxemia within seconds [114]. Hypoxemia then directly affects the heart, leading to bradycardia following respiratory arrest. Consistent with these findings in animal models, clinical studies have shown that DS patients initially experience peri-ictal respiratory dysfunction and apnea, followed by cardiac arrest and SUDEP. It was reported a child with acute and persistent postictal hypoventilation later died of SUDEP. These results suggest that immediate and fatal respiratory arrest may be a terminal event in DS patients and could serve as a biomarker for those at high risk. Other DS mice exhibited an increased respiratory rate and rapid, shallow breathing postictally [101, 115]. This respiratory

abnormality is accompanied by tachycardia rather than the bradycardia previously mentioned.

Evidence shows that different brain regions are involved in respiratory dysfunctions in DS. In DS patients, hippocampal firing is increased, indicating hyperexcitability. Stimulation of the hippocampus induces consistent apnea via subcortical projections to brainstem respiratory centers [116]. Similarly, activation of the central amygdala (CeA) also produces fatal apnea in DS mice, possibly due to the spread of seizures to the CeA [117]. There is a bidirectional projection between the CeA and the bed nucleus of the stria terminalis (BNST), both of which project to the parabrachial nucleus (PBN). Research shows neurons projecting from the BNST to PBN are hypoexcitable in DS mice [118]. The BNST receives inputs from cortical and hippocampal regions and integrates these signals to influence downstream respiratory pathways. Further, the retrotrapezoid nucleus (RTN) is an important respiratory control center and functions as a central respiratory chemoreceptor to regulate respiratory depth and frequency. In DS mice, inactivation of inhibitory neurons in the RTN caused by loss of SCN1A function leads to enhanced sensitivity of glutamatergic chemosensitive RTN neurons [119]. In addition, SST<sup>+</sup> parafacial neurons likely contribute to RTN chemoreception and regulate respiratory activity [120]. The RTN detects signals related to carbon dioxide and/or pH and transmits them to the preBötzinger complex (PBC) and other brainstem regions. GABAergic interneurons are located in the PBC, a brainstem region essential for respiratory rhythm generation and regulation. Loss of Nav 1.1 channels in DS could impair PBC function and cause respiratory dysfunctions that may contribute to the mechanisms of SUDEP in DS [121]. These cerebral nuclei are critical components of the neural pathway responsible for respiratory dysfunction in DS, leading to SUDEP. In summary, closely monitoring fatal respiratory dysfunction in DS patients may be conducive to preventing SUDEP. In Fig. 3, we illustrate the tested and possible respiratory circuits in DS (Fig. 3B, C).

### Other possible mechanisms

The interaction between sleep and DS may have long-term effects, increasing susceptibility to SUDEP. SUDEP in DS patients typically occurs during sleep, highlighting its close relationship with sleep. DS patients frequently experience disrupted sleep due to seizures, which can, in turn, lead to more frequent and severe sleep disorders. Sleep disorders create a positive feedback loop, promoting seizures and increasing the risk of poorly controlled seizures and SUDEP [122]. Thus, sleep disturbances, including disorders of excessive somnolence and sleep-wake transition disorders, are important issues that cannot be ignored in DS [123]. The interactions between the brainstem arousal system and sleep control during seizures, as well as the circadian disruptions, significantly impact sleep disorders and SUDEP. Impaired circadian phenotype and sleep-wake regulation are present in DS patients. The SCN1A-encoded NaV1.1 channel is expressed in brain regions important for circadian rhythms and sleep-wake regulation, including the GABAergic neurons in the suprachiasmatic nucleus (SCN) of the hypothalamus, thalamic reticular nucleus (RTN), and cortex [124, 125]. The SCN contains a master circadian clock that controls circadian rhythms and regulates various circadian activities in the body. GABA, a neurotransmitter found in most SCN neurons, acts as a crucial signal to mediate the properties of the SCN neuronal network [126]. Decreased excitability of GABAergic interneurons in SCN due to dysfunctional NaV1.1 channels is a primary contributor to circadian defects, which may increase the risk of SUDEP. In addition, altered clock gene expression acts in conjunction with the impairments caused by SCN1A deficiency to result in aberrant circadian rhythmicity [126].

Tau, a microtubule-associated protein, is implicated in a number of neurodegenerative diseases, such as Alzheimer's disease [127]. Intraneuronal accumulation of abnormal tau can explain their

pathogenesis. However, no evidence shows that DS mice have microscopically visible accumulations of abnormal tau aggregates in neurons. In DS models, global genetic reduction of tau alleviates seizures and network hyperexcitability and improves survival [128]. Selective tau ablation in excitatory neurons also reduces SUDEP, epileptiform activity, and autism-like behaviors in DS mice [129]. These results suggest that nonaggregated tau has a pathogenic role in DS and may be a potential factor for SUDEP.

### THERAPEUTIC APPLICATIONS

Despite our increased knowledge of DS, the fact that DS pathogenesis remains poorly understood accounts for the limited therapeutic development of this disease to date. DS is drug-resistant and complete seizure control is generally not achievable with current therapies [130]. For the management of this disorder, the crucial aim is to significantly reduce seizure frequency and minimize the adverse effects of antiepileptic therapies [131]. In addition to seizure control, treatment must also focus on the comorbidities that afflict patients with DS, which may have an even greater negative impact on the quality of life of the patient and their families. Many treatment options are being investigated to increase the longevity of patients, including pharmacotherapy, ketogenic diet, neuromodulation therapy, and gene therapy.

### Pharmacological approach

A wide variety of antiepileptic drugs (AED) can be utilized to treat seizures in DS. Accepted first-line agents include broad-spectrum valproic acid (VPA) and clobazam (CLB). VPA, with multiple mechanisms of action, is effective for diverse types of seizures. Evidence of its efficacy in DS patients is derived from some retrospective studies, suggesting VPA is beneficial in DS [132, 133]. Like VPA, due to its good tolerability, safety profile, and broad-spectrum antiepileptic activity, CLB is commonly used to treat developmental and epileptic encephalopathy, including DS [134]. However, in most cases, seizures in DS cannot be absolutely controlled with VPA and CLB, and additional medications must be added if the seizures continue. That is why polypharmacy is common in DS. Due to the pathogenesis of most DS, it is indeed important to enhance GABA signaling, which may ameliorate seizures and comorbidities. Topiramate is regarded as a second-line drug for DS, and it is also a broad-spectrum AED, with several mechanisms of action, including enhancement of GABAergic activity [131]. Topiramate is effective and safe in both generalized and localized epilepsies in children. Several observational studies have evaluated the efficacy of topiramate in patients with DS and found that it can lead to a decrease in seizure frequency [135, 136]. Moreover, clonazepam is a positive allosteric modulator of GABA<sub>A</sub> receptors that protects against myoclonic and generalized tonic-clonic seizures. Given the synergistic GABA-enhancing effect of clonazepam and tiagabine gave increased seizure protection and decreased toxicity, the combination of these two drugs may be well tolerated and effective for controlling seizures in DS [137]. However, there are no clinical trials of clonazepam and tiagabine in DS patients. Other antiepileptic drugs, such as levetiracetam, zonisamide ethosuximide, and bromide, are later options for DS patients as a complementary therapy. Since the adverse effects of zonisamide may be related to the inhibition of carbonic anhydrase, it is best not to coadminister it with other carbonic anhydrase inhibitors (eg, topiramate). These four drugs may be capable of suppressing seizures, but their exact efficacy and safety require further evaluation [131, 138].

The results of new drugs for DS, including stiripentol and cannabidiol, are very promising. There is a consensus on the use of stiripentol as a first- or second-line treatment option. Stiripentol in combination with VPA and CLB can achieve better curative efficacy [139]. Therefore, Stiripentol is recommended as an adjuvant treatment for refractory generalized tonic-clonic seizures

**Table 3.** Various possible pharmacological agents to treat DS.

<b>Medications</b>		<b>Mechanism of action</b>	<b>Side effects</b>	<b>Reference</b>
Traditional drugs	Valproate acid	-Increasing GABA synthesis and decreasing GABA degradation -Inhibiting voltage-dependent sodium and calcium channels -Reducing glutamate synthesis	-Vomiting -Nausea -Sedation -Increased or decreased appetite -Hair loss -Pancreatitis -Hyperammonemia	[148, 181]
	Clobazam	Positive allosteric modulator of the GABA <sub>A</sub> receptor	-Dizziness -Agitation -Ataxia -Sedation -Increased salivation -Behavioral disinhibition	[131, 148]
	Topiramate	-Enhanced GABA transmission via GABA <sub>A</sub> receptors -Inhibiting kainite and AMPA glutamate receptors -Blockage of voltage-dependent sodium and calcium channels -Inhibiting carbonic anhydrase	-Weight loss -Ataxia -Paresthesias -Behavioral changes -Hypohidrosis	[136]
	Levetiracetam	-Binding to SV2A and reducing the rate of vesicle release -Blockage of voltage-dependent calcium channels	-Somnolence -Dizziness -Irritability -Moodiness -Fatigue	[182]
	Zonisamide	Blocking the repetitive firing of voltage-dependent sodium channels and reducing T-type calcium currents	-Weight loss -Mood changes -Memory problems -Decreased appetite	[131, 183]
	Ethosuximide	-Reducing the threshold of the calcium current in the thalamus -Inhibiting the sodium-potassium ATPase system	-Drowsiness -Headache -Nausea -Vomiting	[131, 158]
	Bromide	Causing hyperpolarization of postsynaptic membranes	-Accumulation poisoning -Hypotonia -Fatigue -Ataxia and tremor -Rash	[184]
	Clonazepam	Positive allosteric modulator of GABA <sub>A</sub> receptors	-Motor and cognitive impairment -Anxiety disorders -Myasthenia	[137]
Emerging drugs	Tiagabine	GABA reuptake inhibitor	-Dizziness -Tremor -Drowsiness -Nausea	[137]
	Stiripentol	- Enhanced GABA transmission via GABA <sub>A</sub> receptors - Non-competitive inhibition of LDH	-Decreased appetite -Weight loss -Sedation -Ataxia -Tremor	[185]
	Cannabidiol	-Inhibiting GPR55 and TRPV1 receptors -Modulating adenosine signaling	-Decreased appetite -Diarrhea -Fatigue -Somnolence -Vomiting -Pyrexia -Elevated transaminases	[140, 142, 186]
	Fenfluramine	-5-HT <sub>1D</sub> , 5-HT <sub>2A</sub> and 5-HT <sub>2C</sub> receptors agonist -Modulator of sigma-1 receptors	-Decreased appetite -Diarrhea -Fatigue -Somnolence -Increased risk of cardiac valvulopathy	[187–189]

**Table 3.** continued

Medications	Mechanism of action	Side effects	Reference
Clemizole	5-HT <sub>2A</sub> receptor agonist	-Fatigue -Drowsiness -Gastrointestinal disorders	[145]
Lorcasirin	5-HT <sub>2C</sub> receptor agonist	-Headache -Nausea -Dizziness -Weight loss	[145, 190]
Trazodone	-5-HT reuptake inhibitor -5-HT <sub>2A</sub> and 5-HT <sub>2C</sub> receptors inverse antagonist	-Drowsiness -Fatigue -Dizziness	[145]
Soticlestat	Cholesterol 24-hydroxylase inhibitor	-Fatigue -Drowsiness -Astriction	[146, 191]
Verapamil	-Voltage-dependent calcium channel blocker - Inhibition of the P-glycoprotein	-Elevated transaminases -Cardiac toxicity -Dizziness	[147]

SUDEP sudden unexpected death in epilepsy; GABA gamma-aminobutyric acid; SV2A synaptic vesicle protein 2A; LDH, lactate dehydrogenase; GPR55, the orphan G protein-coupled receptor-55; TRPV1, transient receptor potential vanilloid-1.

in DS patients together with VPA and CLB. However, stiripentol, when used with VPA and CLB, increases somnolence and gastrointestinal adverse events. Additionally, in animal studies, it is shown that cannabidiol was beneficial in seizures and behavioral comorbidities, as well as survival [140, 141]. In line with these observations in animal models, a randomized controlled trial reported that cannabidiol significantly reduced convulsive-seizure frequency and thus was effective in treating DS patients [142]. However, it should be noted that cannabidiol is associated with higher rates of adverse events, such as pyrexia and elevated transaminases. Thus, when treating patients with cannabidiol, it is important to provide patients with medical guidelines that describe crucial details about the usage and risks of this drug. Cannabidiol has a bidirectional interaction with clobazam potentially leading to increased somnolence and sedation, thus requiring dose reduction [134]. Some medications that modulate 5-HT signaling pathways, including fenfluramine, clemizole, lorcasirin, and trazodone, have recently emerged as potential treatments for DS. Previous studies have shown that 5-HT is significantly reduced in the head of DS zebrafish and 5-HT receptor subtypes can be targeted to trigger the antiseizure effects in DS, especially 5-HT<sub>1D</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> receptors [143, 144]. For example, fenfluramine, which was recently approved to suppress seizures, is considered a second-line drug for DS and acts as an agonist of these three receptor subtypes. Clemizole, a recognized antihistamine, is an H1-receptor antagonist. However, the antiepileptic effect of clemizole is based on its affinity for the 5-HT<sub>2A</sub> receptor, and clemizole is under development as a therapeutic agent for DS [145]. Soticlestat, a novel cholesterol 24-hydroxylase inhibitor, reduces seizures and premature death in DS mice and is currently under clinical investigation for the treatment of DS [146]. The long-term efficacy and safety of soticlestat are being assessed and it is found that the adverse events of soticlestat are noticeably less severe. In addition, its unique mechanism of action increases the possibility of combining it with other drugs. Another possible pharmacological agent is the modulator of calcium channels, and the administration of verapamil influences epileptic activity [147]. Add-on treatment with verapamil appears to have an effect on controlling seizures in DS patients, but further studies are needed to confirm its function. Importantly, one point to note is the influence of contraindicated medications. Seizures are typically worsened with sodium-channel agents, including lamotrigine, carbamazepine, oxcarbazepine and phenytoin [148]. Hence, these drugs must be

avoided. Overall, although pharmacotherapy is the most important treatment, its efficacy is inadequate and even causes some side effects, necessitating non-pharmacological intervention.

In Table 3, we summarize the multiple drugs that may be effective against DS (Table 3).

### Non-pharmacological approach

The common non-pharmacological approaches include ketogenic diet (KD) and neuromodulation techniques. KD is a high-fat, adequate-protein, and low-carbohydrate diet that uses fat as a replaceable fuel for glucose to alter energy metabolism [149]. The combination of high-fat intake and lowering glucose levels is thought to be the key to the effectiveness of this diet. Current studies have shown that KD can be used to rescue many different conditions, including obesity [150], type 2 diabetes [151], neurodegenerative disorders(e.g., Alzheimer's disease, Parkinson's disease) [152], and autism spectrum disorders [153]. Furthermore, the antiepileptic effects of KD have long been known, and it is a recognized, effective nonpharmacologic management option for refractory epilepsy in children, such as DS patients [154]. The production of ketones, which provides a more efficient source of energy than glucose for brain cells and leads to beneficial downstream metabolic changes, such as increasing adenosine levels, which may have an impact on seizure control, is considered to be the fundamental mechanism of this treatment. Evidence suggests that the gut microbiota can regulate brain GABA levels, alter inflammatory signaling and mediate the anti-seizure effect of the KD. KD-induced microbial changes correlated with a lower seizure density in Dravet mice and microbiota-gut-brain axis may be a novel potential target of KD for epilepsy patients [155, 156]. In addition to seizure control, KD treatment could improve survival rates and decrease behavior disturbances. KD can reduce premature mortality by reducing the incidence of S-IRA, a major cause of SUDEP [157]. Prior consensus papers from North America consider KD a second-line treatment for DS [158]. Complete seizure control is typically not achieved with pharmacotherapy alone in DS patients. The KD has fewer neurotoxic side effects than drug treatments, making it a relatively safe and effective therapeutic strategy.

While KD benefits seizure control, its metabolic shifts may negatively impact cardiac health.  $\beta$ -hydroxybutyric acid produced by KD may impair mitochondrial biogenesis, depleting energy in cardiomyocytes and triggering apoptosis and cardiac fibrosis [159]. KD can lead to electrolyte imbalances and sodium channel

alterations, increasing depolarization and cardiac excitability [160], thereby exacerbating arrhythmia risks and compromising cardiac function, which is closely tied to cardiac events and SUDEP in DS patients. SCN1A mutations may further influence susceptibility to cardiac effects, underscoring the need for monitoring cardiac health in DS patients undergoing KD therapy, particularly in those at risk [161]. KD remains a powerful therapeutic option for seizure control, but its cardiac risks and side effects require careful assessment to ensure patient safety and optimize therapeutic benefits.

Another nonpharmacological approach is neuromodulation techniques, mainly including vagus nerve stimulation (VNS) and deep brain stimulation (DBS). In some DS patients, reduced seizure frequency and shorter recovery time could be observed after the application of VNS, suggesting VNS may be beneficial in the treatment of DS [162]. However, it does not guarantee improvement of the disease and carries the risk of infection and subsequent device failure [163]. With regard to DBS, there is no strong evidence for its curative effect on DS, and the role of DBS in DS needs further study [164]. Nevertheless, neuromodulation therapy is an emerging addition to the DS treatment landscape with significant unexplored potential for further optimization.

### Novel genetic therapy

In the last few years, there have been significant advances in the field of gene therapy, which has expanded the potential treatment options for DS. Currently, the dominant gene therapies are antisense oligonucleotides (ASOs), viral vectors-mediated gene modulation, and gene editing strategies, and some of these are in transition to clinical trials [165, 166]. Since DS is mainly caused by mutations in one of the copies of the SCN1A gene, gene therapies aim to reduce seizures and severe comorbidities by utilizing the non-mutant copy of the SCN1A gene to upregulate Na<sub>v</sub>1.1 protein and restore normal Na<sub>v</sub>1.1 levels. STK-001, developed by Targeted Augmentation of Nuclear Gene Output (TANGO) technology, is an investigational new medicine for DS and is currently being evaluated in ongoing clinical trials [167]. STK-001 is an ASO designed to bind to pre-mRNA to enhance the level of productive SCN1A mRNA and then improve the production of the Na<sub>v</sub>1.1 protein. Preclinical studies suggested a positive impact of Scn1a-ASO on seizures and the incidence of SUDEP in DS mice [168]. Similarly, data from clinical trials indicated that STK-001 was well tolerated, with 70.6% of individuals treated with it experiencing a decrease in seizure frequency. Thus, this medicine could represent a major advance in gene therapy for DS patients. In addition, several different types of viral vectors have recently come up as emerging avenues for gene therapy carrying the potential to treat DS, yet adeno-associated virus (AAV) is by far the most widely used one. Transcriptional activators and CRISPR-Cas9-mediated gene editing techniques can be applied to facilitate AAV-based SCN1A gene upregulation [169]. EXT is a GABAergic interneuron selective AAV containing an engineered transcription factor for the upregulation of SCN1A expression. The efficacy of ETX101 has also been validated in preclinical studies: ETX101 administration reduced seizures and the risk of sudden death in DS mice and was well tolerated in nonhuman primates, and this medicine will probably start clinical trials soon [170]. Further, the CRISPR-Cas9 technique has shown promising results in several studies. This approach could restore inhibitory interneuron excitability and ameliorate epileptic and behavioral phenotypes in DS mice, suggesting that it may be an effective treatment for seizures and behavioral deficits [171, 172]. However, additional investigation is needed to further elucidate its role in human patients. The clinical utility of these mentioned therapies is limited to DS patients with SCN1A variants that result in Nav1.1 haploinsufficiency and therapies targeting other gene variants are supposed to emerge in the future as well. In conclusion, gene therapy, as a form of precision medicine and targeted therapeutics, holds great promise

to provide sustained seizure freedom, reduce the risk of SUDEP risk, and even completely cure devastating DS.

### CONCLUSION AND PERSPECTIVES

In this review, we focus on DS, a severe form of intractable pediatric epilepsy with a notably high incidence of SUDEP. The pathogenesis of SUDEP in DS is complex, and progress in understanding it has been hindered by the unpredictable and irreversible nature of the disease. Here, we review the currently identified pathogenesis of DS and consider the association between DS and SUDEP, proposing potential explanations for the occurrence of SUDEP in DS patients. Genetic factors may provide a link between DS and SUDEP. Different genetic mutations underlying DS may affect the susceptibility to SUDEP. Genetic modifiers may exacerbate or alleviate this risk. Additionally, pathophysiological factors are equally important. Proposed mechanisms, such as fatal arrhythmias and respiratory dysfunction, offer significant insights into the pathogenesis of SUDEP in DS patients. Moreover, the increased frequency and severity of seizures, coupled with sleep disorders, create a positive feedback loop that may ultimately lead to SUDEP.

DS remains a serious public health issue, complicated by drug resistance and a lack of effective preventive and therapeutic measures. Combining pharmacological treatments with non-pharmacologic therapies holds promise for improving therapeutic outcomes. Future therapeutic strategies are likely to focus on precision medicine. For example, recent advancements in gene therapy highlight its potential to revolutionize the treatment of epilepsy. Gene therapy may play a critical role in developing novel therapies for epilepsy, though further research is necessary to understand the interactions between gene therapy and conventional treatments, as well as their respective advantages and limitations in DS.

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## AUTHOR CONTRIBUTIONS

HHZ and WHS designed and conceptualized this review. WHS wrote the original and revised drafts, drew the figures, and reviewed and edited the original and revised manuscripts. LL and JXG drew the figures and reviewed and edited the original and revised manuscripts. YY, YXW and ZYZ reviewed and edited the original and revised manuscripts. QX, YLW, YS, LYG, and YC reviewed the manuscript and participated in the revisions. All authors contributed to the final version of the manuscript.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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