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Review

Short QT Syndrome and Drug Treatment: A systematic Literature Review and PRISMA Analysis

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Abstract: Short QT Syndrome (SQTS) is a rare inherited myocardial ion channel disease characterized by abbreviated cardiac repolarization and shortened QT interval in ECGs, resulting to a high incidence of sudden death and malignant arrhythmias. While various gene mutations that encode subunits of K^+, Ca^{2+}, and Na^+ channels, as well as the SLC4A3 gene mutation associated with plasma membrane anion exchange, have been implicated, targeted gene screening remains relatively low. In this review, we searched multiple databases, such as PubMed, ScienceDirect, Embase, Web of Science, and Medline, and followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to conduct a systematic review of literatures in SQTS. We first used VOSviewer to analyze the co-authorship, co-occurrence of countries, organizations, authors, and keywords in the published literatures of SQTs, and then surveyed evidences regarding the impact of single or polygenic gene mutations identified is SQT patients on the electrophysiological properties of IKr, IKs, IK1, ICa-L, INa, and the anion exchanger AE3. Additionally, this review also surveyed current progress in the understandings of potential mechanisms underlying arrhythmogenesis of the SQT gene mutations, and possible drug therapy, unraveled by both experimental and simulation studies.

Keywords: short QT syndrome; sudden death; malignant arrhythmia; computational model; gene mutation

1. Introduction

Short QT Syndrome (SQTS) is described as an expedited ventricular myocardium repolarization that is manifested by a shortened QT interval in electrocardiograms (ECGs). SQTS are associated with high incidence of syncope and sudden cardiac death (SCD) [1]. Since the first report of the diagnosis of SQTS in their published article called “Idiopathic Short QT Interval: A New Clinical Syndrome?” by Gussak et al. in 2000 [2], a number of genetic variants have been confirmed in eight genes, which account for approximately 20–30% of the SQTS family. These variants include gain-of-function mutations in K^+ channel genes (SQT1-3), loss-of-function mutations in L-type Ca^{2+} channel subunit genes (SQT4-6), Na^+ channel gene (SQT7), and anion exchanger gene (SQT8). It has been observed that SQTS can cause fatal incidents in any age, including young individuals and particularly in infants [3]. The likelihood of experiencing cardiac arrest exceeds 40% by the age of 41, with 4% occurring under 1 year old, and then 1.3% occurring between the ages of 20 and 40 [3]. Owing to the high incidence of malignant arrhythmias and SCD in SQTS, it has been included in the guidelines for the prevention and treatment of SCD issued by the American Heart Association (AHA) [4].

SQTS is a family genetic disease, but the genetic pathogenesis has not been fully clarified [5]. In basic studies, the pathogenesis of SQTS can only be studied at the microscopic level of genes, cells, proteins, and molecules by cardiac physiopathologists. This approach allows for the examination of the specific effects of gene mutations on the characteristics of their coded ion channels. In clinical studies, the manifestations of SQTS can only be examined at the macroscopic level based on the analysis of surface ECGs. In supplement to the microscopic molecular and macroscopic clinical approaches, the use of multi-scale virtual heart models establishes a platform for underpinning potential functional and causative links between microscopic molecular defects to the macroscopic dysfunctions of the heart. So far, combined approaches of molecular, clinical and computational modellings have been implemented to investigate possible mechanisms underlying the pro-arrhythmic effects of SQT gene mutations. Now it is necessary to conduct a systematic literature review of these studies to provide a comprehensive knowledge of current progress in the understandings of SQTS.

In this review, we retrieved multiple databases and then followed the guidelines of the PRISMA analysis to obtain eligible articles, encompassing both experimental and simulation studies. All the selected articles were obtained following the initial screening. In the results, we systematically examine the single or polygenic basis of SQTS resulting from gene mutations in cardiac ion channels. Meanwhile, we also systematically reviewed possible mechanisms of arrhythmogenesis and the therapeutic drug research in SQTS.

2. Review Method

2.1. Search Strategy

In this study, a search of scientific papers and statements known to the authors was conducted on PubMed, Sience Direct, Embase, Web of Science and Medline with the keywords listed in Table 1: which include “short qt syndrome” “Sudden death”, and “gene mutation”. These key words were used to serach for pulications in collrelating QT shortening to clinical risks of sudden death. The MeSH keyword generated was ((“Short Qt Syndrome” [Supplementary Concept]) AND (“Arrhythmias, Cardiac/chemically induced” [Mesh] OR “Arrhythmias, Cardiac/classification” [Mesh] OR “Arrhythmias, Cardiac/congenital” [Mesh] OR “Arrhythmias, Cardiac/diagnosis” [Mesh] OR “Arrhythmias, Cardiac/diagnostic imaging” [Mesh] OR “Arrhythmias, Cardiac/drug therapy” [Mesh] OR “Arrhythmias, Cardiac/epidemiology” [Mesh] OR “Arrhythmias, Cardiac/genetics” [Mesh] OR “Arrhythmias, Cardiac/immunology” [Mesh] OR “Arrhythmias, Cardiac/mortality” [Mesh] OR “Arrhythmias, Cardiac/pathology” [Mesh] OR “Arrhythmias, Cardiac/physiopathology” [Mesh] OR “Arrhythmias, Cardiac/prevention and control” [Mesh] OR “Arrhythmias, Cardiac/therapy”[Mesh])).

Table 1. Literature retrieve keywords for five main databases.

Database	Keywords	Filter Criteria	Search Result (Number of Publications)
PubMed	short qt syndrome	All results	517
Science Direct	Title, abstract, keywords: short qt syndrome	Languages: English	382
Embase	Title, abstract, keywords: short qt syndrome	Diseases: Short qt syndrome	582
Web of Science	Topic: short qt syndrome	Languages: English	1879
Medline	Title, abstract, MeSH headings and qualifiers: short qt syndrome	Languages: English	1100

2.2. Inclusion Criteria

Articles were eligible for inclusion when reported in human patients, either congenital, drug-induced, or a combination of both.

2.3. Exclusion Criteria

Exclusion criteria included studies that do not meet the inclusion criteria or are published in non-English languages.

2.4. Selection of Studies

In our systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1). The search and article selection was mainly conducted by two authors. The studies that fit the inclusion criteria underwent a second round of screening after a full-text review and quality assessment.

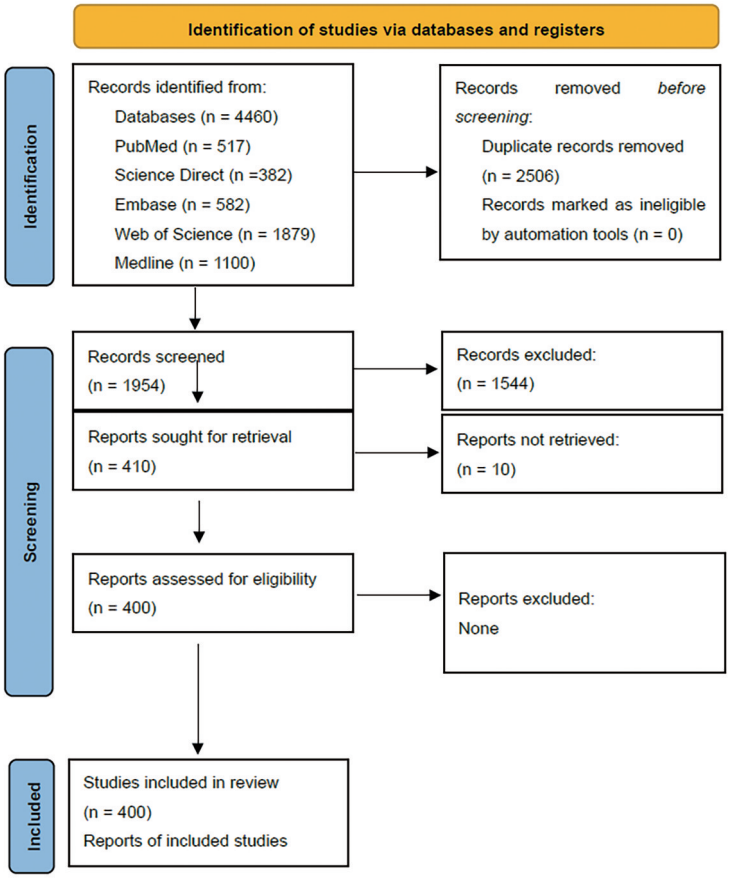

Figure 1. Chart flow for identification of studies via databases and registers following the guidelines of the PRISMA analysis.

3. Results

3.1. Visualization of Analysis

3.1.1. Keywords Co-Occurrence Analysis

Using the bibliometric software of VOSviewer (version 1.6.20), visualization of analysis of the co-occurrence of keywords, co-authorship of countries, organizations, and authors were obtained. The co-occurrence of keywords was adopted to identify its research frontiers over time period of 1999–2024. A total of 414 keywords plus were included, of which 53 keywords with a frequency of more than 3 occurrences. The top 3 keywords was "short qt syndrome" with 85 occurrences (O) and 209 total link strength (TLS), followed by "sudden cardiac death" (45 O, 124TLS) and "long qt syndrome" (29O, 92 TLS). Figure 2 presents a overlay visualization network obtained by analysing the knowledge domain map of keywords co-occurrence cluster using VOSviewer, which was coloured coded for the times period of 1999–

2024. The size of the nodes showed the averaged times of keywords occurrence, where the red nodes indicated the latest research hotspot keywords. Obviously, "SLC4A3", "human-induced pluripotent stem cell-derived cardiomyocytes", "implantable cardioverter defibrillator", "electrocardogram", "ion channel", "antiarrhythmic drugs" and so on were keywords that frequently appearing in recent years, indicating that they may be hotspots for future research.

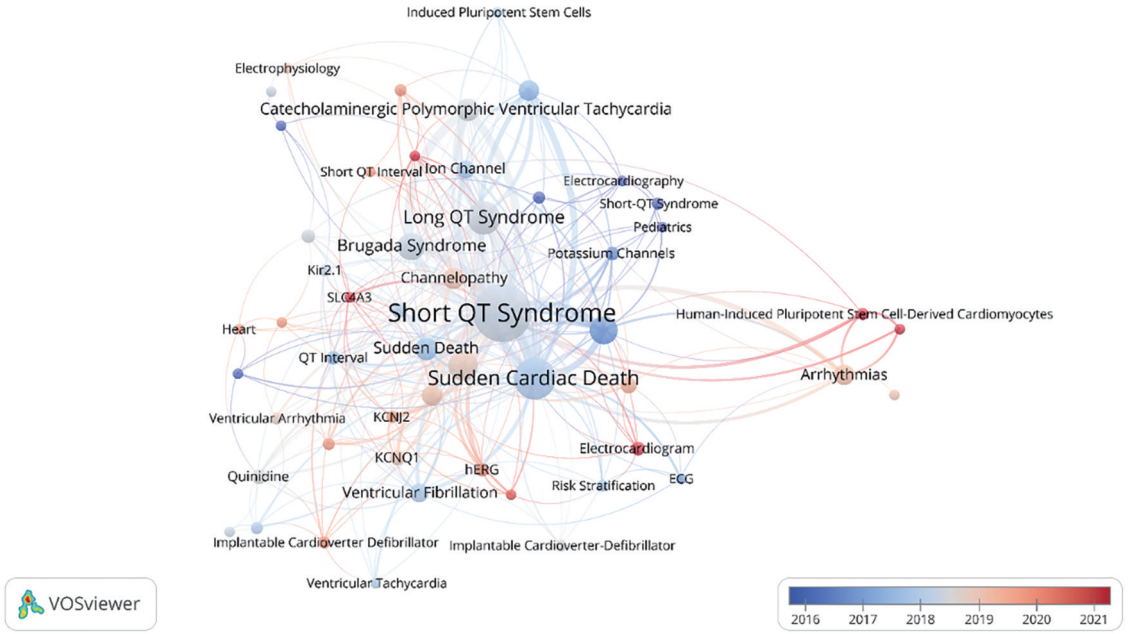

Figure 2. Visualization map of co-occurrence keywords network obtained using VOSviewer. The size of the nodes denotes the averaged times of keywords occurrence, and their colors represent for the average published year in which keywords appear.

3.1.2. Top Productive Countries/Authors

To discover the co-authorship between countries/organizations/authors, we plotted the visualization map of the co-authorship network using VOSviewer. Results are shown in Figure 3. Figure 3A illustrated international cooperations among countries over time, with 54 countries meeting the threshold of a minimum 2 documents produced by each of them. However, some of the 25 items are not connected to each other. Each node represents a different country, the size showing the number of their publications, and the line between nodes indicating collaboration between countries (the thickness of the line indicates the closeness of collaborations). It can be seen that China and England collaborated most frequent recently. In terms of the number of documents produced over the period, the United States ranked first (75), followed by Germany (43), China (30), Italy (27). Figure 3B shows the network visualization map of 126 authors' collaboration with a minimum of 3 documents produced by an author. For the documents published by all 121 authors, Martin Borggrefe from the University of Heidelberg ranked first productive authors with 37 articles. Henggui Zhang from the University of Manchester, Rainer Schimpf and Christian Wolpert from the University Hospital Mannheim have 28 articles to jointly ranked second. Carla Giustetto from the University of Torino and Jules C Hancox from the University of Walk both have 26 articles to jointly ranked three. As shown in the map, Martin Borggrefe, Rainer Schimpf, Christian Wolpert, Carla Giustetto and Fiorenzo Gaita had the strongest collaboration connections.

The published studies presented above have provided significant clinical findings and insightful understandings into molecular mechanisms underlying arrhythmogenesis of SQTS, which are surveyed below.

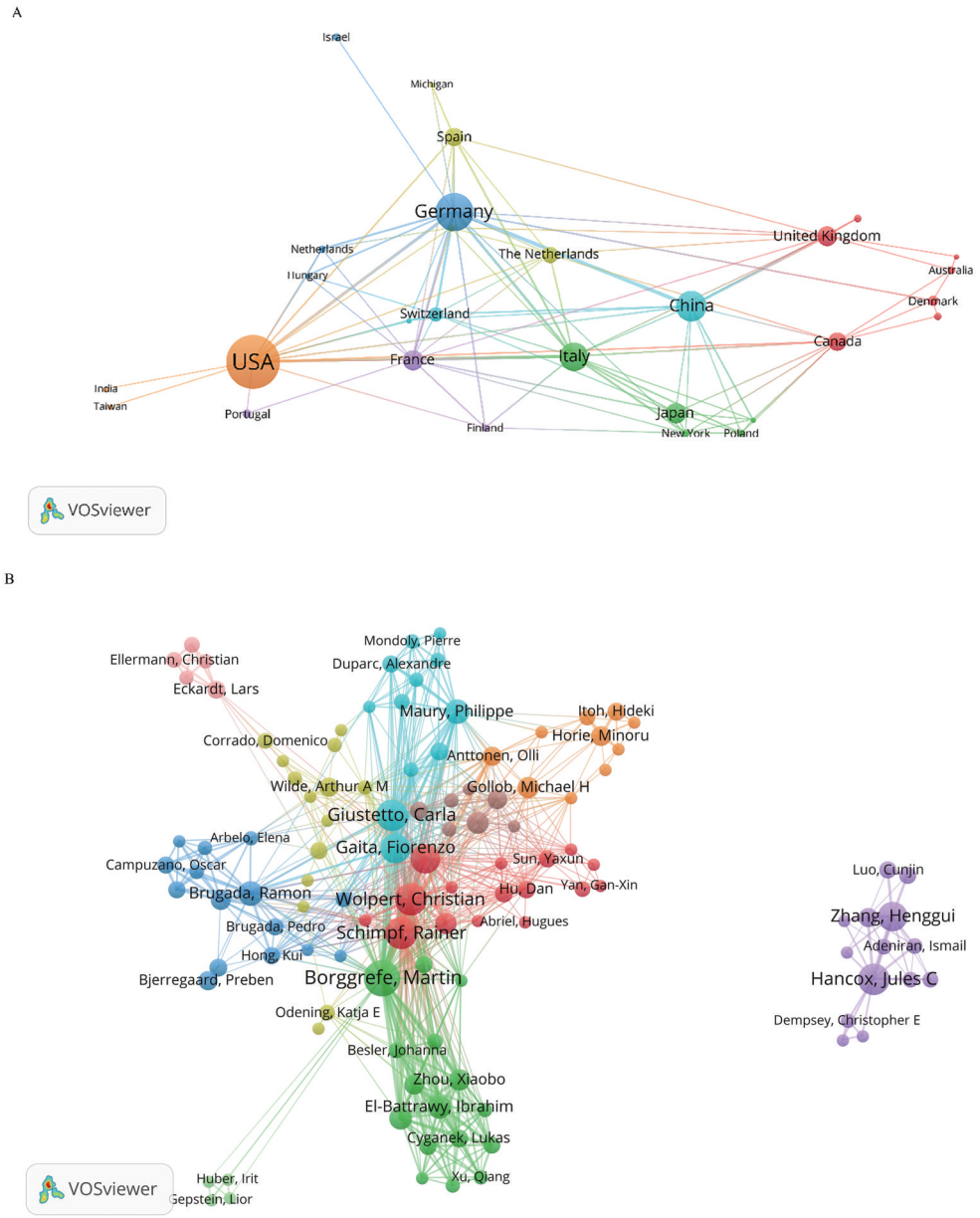

Figure 3. Visualization map of international collaborations. (**A**): co-authoring countries network. (**B**): co-authoring authors network. Results were obtained by using VOSviewer for the publication period of 1999–2024.

3.2. Clinical Findings

SQTS Diagnosis and Treatment

For the diagnosis of SQTS, it is important to be aware of the rate-dependence of the QT-interval of ECGs [6], and therefore, various diagnostic criteria have been developed. These criteria include the use of corrected QT interval (QTc) by using formulas such as those of Bazett, Hodges, Framingham, and Fridericia [7]. However, it is worth noting that the correction formulas for QTc tend to overcorrect the QT interval in individuals with short QT Syndrome (SQTS) compared to those with a normal QT interval. Despite this limitation, the use of QTc is still commonly employed in the diagnostic recommendations for SQTS. In order to avoid extreme overcorrection with this correction formula, ECG measurements should be repeated at as close to 60 beats min^{-1} as possible to alleviate such issues [7]. A significantly higher $T_{(peak\text{-}end)}$/QT ratio and PQ segment depression is observed in patients with arrhythmic risk, such as SQTS, long QT syndrome (LQTS), Brugada syndrome (BrS), atrial tachyarrhythmias [8, 9]. Currently, a novel electrocardiographic criteria of

SQTS patients in childhood and adolescence has been proposed as QTc < 316 ms, J-T_{peak} < 181 ms by using Bazett's formula [10]. The relatively low success rate in identifying the genotype in SQTS cases (approximately 1/4 of those tested) highlights the importance of accurately distinguishing between acquired and congenital SQTS. It is also crucial to recognize that patients with SQTS can present symptoms as early as the neonatal period or as late as 80 years old. Additionally, the cumulative risk of experiencing a cardiac arrest by the age of 40 is greater than 40% [3,11]. Cardiac arrest was seen as an initial presenting symptom in nearly 30% patients [11,12]. Therefore, it is important for early diagnosis and management of SQT patients.

Despite some progress in assessing the organ-level pathophysiology and genetic changes of SQTS [13], the discovering of an optimal therapy has lagged. Undoubtedly, the main treatment for SQTS patients is the use of implantable cardioverter defibrillator device (ICDs), however, effective treatments of SQTS using various drugs are needed due to risks of inappropriate shocks due to T wave oversensing by ICDs [14]. As such, the ICD device might mistakenly interpret a normal T wave as a dangerous rhythm, leading to unnecessary shocks. Furthermore, it has been observed that the incidence of inappropriate shocks in children with SQTS is higher compared to adults, suggesting that managing ICD devices in young patients can be more challenging [15]. While the insertion of an ICDs as a secondary prevention in the SQTS patient is well documented, the benefit of primary prevention is controversial and has not been demonstrated by reliable data. Therefore, it is crucial to consider the use of pharmacological methods in the management of SQTS. Research on the therapeutic effects of drug preparations can greatly contribute to our understanding of the mechanisms underlying SQTS. Currently, the single agent shown to be most effective in the treatment of SQTS is (hydro)quinidine [16], but it often has intolerable side-effects which has been removed in several countries. For a comprehensive review of the research on therapeutic drugs for SQTS, please refer to the section 3.5 "Therapeutic Drug Research" below. Further research is required to fully understand the potential benefits of pharmaceutical preparations in treating SQTS. The optimal treatment for SQTS, similar to other hereditary diseases, may involve molecular genetic methods to correct any underlying mutations. Note that the implementation of such an approach is unlikely in the near future, the most commonly drug treatments in the clinical setting warrants to be further investigated.

3.3. Genetic Basis

3.3.1. Potassium Channels

Eight gene mutations with SQTS have been reported, which are *KCNH2*, *KCNQ1*, *KCNJ2*, *CACNB2b*, *CACNA1C*, *CACNA2D1*, *SCN5A*, and *SLC4A3* (Figure 4). Comprehensive genetic analysis of all known mutants revealed that nearly 30% of the cases were diagnosed with potentially impairing mutations, and nearly 30 SQTS-related potential pathogenetic variants have been identified [17]. SQT1-SQT3 are associated with gene mutation of potassium channels, including *KCNH2*, *KCNQ1* and *KCNJ2*. SQT1 related to *KCNH2* gene mutation encoding the "hERG" (human Ether-à-go-go-Related Gene) channel [18]. It is responsible for 15% of all SQTS cases [19].

Using genetic testing, 7 mutations located in the hERG channel encoding the rapid delayed rectifier potassium channel current (I_{Kr}), were reported in variant-1 type of SQTS (SQT1), including: (1) N588K, the same amino acid change in the S5-P loop region [18]; (2) R1135H, a C-terminal *KCNH2* mutation [20]; (3) E50D, a C-terminal *KCNH2* mutation [21]; (4) T618I, the most common clinical mutation in all SQTS variants (25.9% of probands, followed by N588K, 18.5%) [22,23]; (5) L499P, the structural changes of S4 domains; (6) I560T, occurring in the transmembrane segment of the hERG channel [24]; and (7) S631A [25].

Variant-2 type of SQTS (SQT2) is related to *KCNQ1* gene mutation, which encodes the pore-forming subunit of voltage-gated I_{ks} (slow delayed rectifier) potassium channels [26,27] when it is combined with *KCNE1*. It responsible of closely 5% of all SQTS cases. Currently, 6 rare variants have been identified as being potentially associated with SQT2, including: (1) V307L, a pore-helix (P-loop) of *KCNQ1* mutation [26]; (2) V141M, in the potassium channel (*KCNQ1* gene) [28,29]; (3) R259H, another *KCNQ1* mutation first discovered in Chinese [30]; (4) F279I, in the S5 segment of *KCNQ1* [31]; (5) F279C, impacting *KCNQ1* functionality by shifting the voltage dependence of activation in the hyperpolarizing direction [32]; and (6) A287T, the A287 residue (at the top of S5) forming a hydrogen bond with the hydroxyl group of residue T322 (at the top of S6), which may accelerated activation time-course [33].

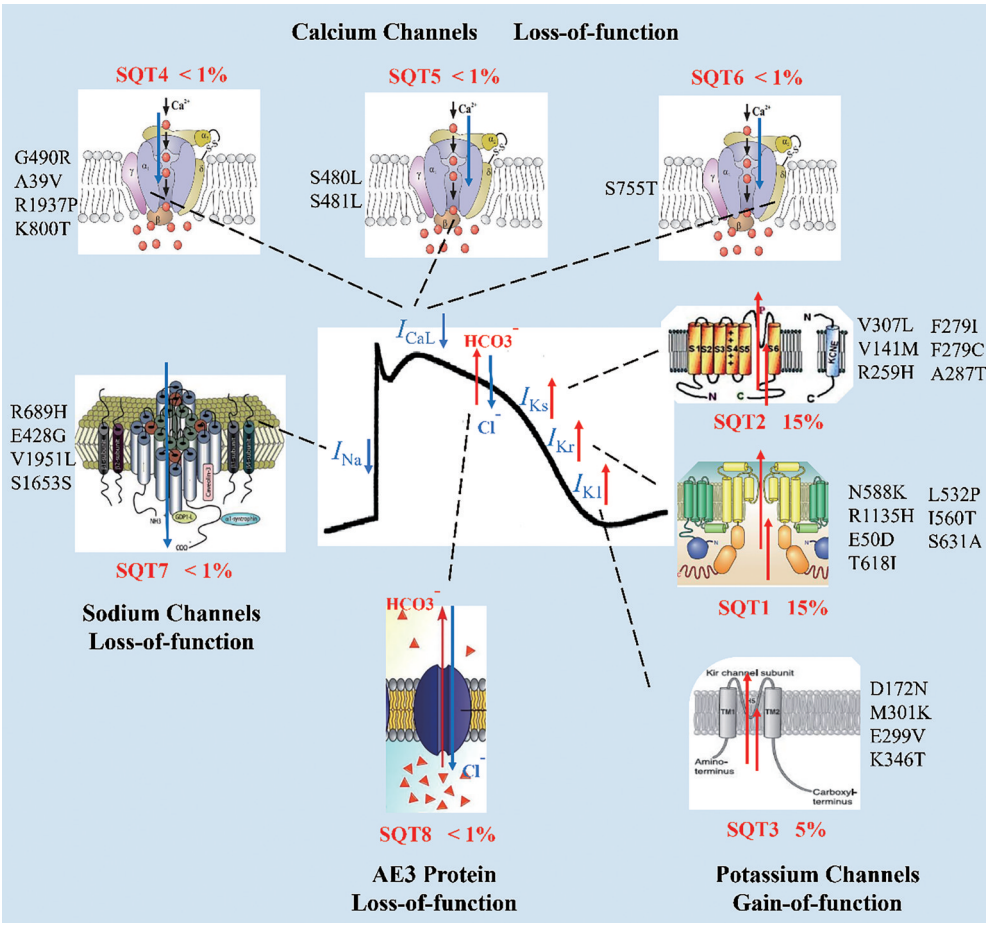

Figure 4. Summary of the molecular and cellular mechanisms of congenital SQTS. Red arrows represent for the ionic efflux, blue ones for ionic influx. Text in red word indicates the type of SQTS and the proportion of that type in all SQTS cases. The figure is based on modifications of Hancox, et al [40].

Variabt-3 type of SQTS (SQT3) is related to gene mutations *of KCNJ2* encoding the inwardly rectifying Kir2.1 (I_{K1}) channel. it is responsible of nearly 5% of all SQTS cases and has a unique ECG phenotype characterized by asymmetrical T waves [34]. Currently, 4 rare variants have been identified as being potentially associated with SQT3, including: (1) D172N, causing augmentation of outward but not inward current [35, 36]; (2) M301K, impairing the inward rectification of the channel under the heterozygous condition, resulting in a larger outward currents that predisposes SQTS [37]; (3) E299V, resulting a profound reduction of the inward rectification of Kir2.1 current [38]; and (4) K346T, resulting an increase in both inward and outward currents for Kir2.1 channels as shown in mammalian cell line [39].

3.3.2. Calcium Channels

Variant 4 – 6 types of SQTS (SQT4-SQT6) are associated with gene mutation of calcium channels, including *CACNA1C*, *CACNB2b* and *CACNA2D1*. SQT4 is related to *CACNA1C* gene mutation, encoding the alpha-1C subunit of a voltage-dependent calcium channel (Cav1.2 α subunit). All variants identified so far decrease the inward L-type Ca^{2+} channel current ($I_{Ca\text{-}L}$) at early phases of cellular repolarization, inducing altered epicardial and transmural dispersion of repolarization of ventricles, leading to a mixed phenotype of short QT_c interval and BrS. It is responsible for <1% of all SQTS cases [41]. Currently, 4 rare variants associated with SQT4 have been reported, including: (1) G490R, which is associated with a poor rate dependence and ST segment elevation in the ECG [41]; (2) A39V, which is associated with apparent ST elevation in V1 and saddleback ST elevation in V2 [41]; (3) R1937P, which is associated with an obstructive hypertrophic cardiomyopathy (HCM), early-repolarization pattern of ECG and an QT_C interval of 356 ms [23]; and (4) K800T, which is associated with a prominent reduction in the current density of I_{CaL} without

altering the gating behavior of the Cav1.2 channel, most likely due to the trafficking defect [42]. Other rare variants (p. Val2014Ile, p. Asp2130Asn, p. Asn547Ser, p. Arg632Arg, p. E1829_Q1833dup, p. Glu1115Lys, p. Arg1780His and p.Arg1880Gln) have also been identified in SQT4 patients despite further studies are needed to confirm their potential pathogenic role.

Varant 5 type of SQTS (SQT5) is related to gene mutation *of CACNB2*, encoding beta subunit of a voltage-dependent calcium channel (Cav1.2 β subunit). The β-subunit of voltage-dependent calcium channels promotes the function of calcium channel by increasing peak value of calcium currents, shifting the voltage-dependent activation and inactivation curves, regulating the G-protein inhibition and controlling the α-1 subunit membrane targeting. SQT5 is responsible for <1% of all SQTS cases. So far, 2 rare variants have been reported to be associated with SQT5: (1) S480L, resulting in a decreased L-type Ca^{2+} current by upregulation of DNA methyltransferases and enhanced methylation in the promoter region of the *CACNB2* gene [43]; (2) S481L, which is associated with coved ST-segment elevation in V1- and V2-lead ECGs [41]. Variant 6 type of SQTS (SQT6) is related to gene mutation in *CACNA2D1*, encoding a member of the alpha-2/delta subunit family, a protein in the voltage-dependent calcium channel complex (Cav1.2 α2/δ1 subunit). The protein regulates activation/inactivation kinetics and calcium current density of the L-type calcium channel ($I_{Ca\text{-}L}$). It responsible for <1% of all SQTS cases [41]. Only one rare variant has been reported related with SQT6 at present: S755T, with a short QT_c interval (329ms) and tall, narrow ECG T-waves [44]. But no conclusive data exist about the association of this gene and SQTS.

3.3.3. Sodium Channels

Variant 7 type of SQTS (SQT7) is associated with gene mutation of sodium channels, *SCN5A*, encoding sodium channel protein type 5-subunit alpha ($Na_v1.5$), which mediates voltage-dependent sodium ion permeability of myocyte membranes. Pathogenic mutations in the cardiac sodium channel gene, *SCN5A*, lead to approximately 20% of BrS, 10% of LQT3, and 5% of sudden infant death syndrome [45]. It potentially responsible of <1% of all SQTS cases. Currently, 4 rare variants associated with SQT7 have been reported, including: (1) R689H, with a Brugada-like ECG, accompanied by a short QT interval [46]; (2) E428G, located in $Na_v1.5$ channel-protein domain I-domain II intracellular connection region [46]; (3) V1951L, a relatively race-specific polymorphism (healthy Spanish population, with an incidence of 6.7%; non-Hispanic ethnic healthy population, not found) [45]. However, there was no significant difference in the biological function of sodium channel caused by V1951L mutation [47]; (4) S1653S, the first reported in the world that synonymous polymorphism regulates the biological function of *SCN5A* gene mutation, leading to hereditary arrhythmias syndrome [47]. However, no conclusive data exist concerning the association of this variant with SQTS. Objectively, the genetic translation of SCN5A variants in SQTS patients should be cautious, as its potential role is still ambiguous.

3.3.4. The SLC4A3 Gene

In 2011, Gollob MH et al. established diagnostic criteria for SQTS to facilitate clinical evaluation of suspected cases and showed that candidate ion channel screening resulted in genotype positive in less than 30% of SQTS cases [48]. Exome or genome sequencing thus can be predicted to uncover novel, unexpected genetic associations with SQTS. In 2017, a missense mutation in the plasma membrane anion exchange protein 3 (AE3)-encoding *SLC4A3* gene in two unrelated families with SQTS was identified. And the AE3 protein mediates a part of the Cl^-/HCO_3^- exchange in cardiac myocytes [49]. Although normal gene screening showed no mutation in the candidate ion channels, a missense mutation was found in SLC4A3 by exome screening of 6 SQTS individuals and 5 healthy controls, and a R370H mutation of a conserved motif in the SLC4 family was found [49]. The pathogenic variant resulted in a trafficking defect, decrease of Cl-HCO_3 exchange across the cell membrane and increase of intracellular pH, and shortening of the APD and QT interval. Recently, genetic testing was performed in a multicenter study and the pathogenicity of SLC4A3 variants was verified in the zebrafish embryo heart model. The result suggested that in about one-quarter of the SQTS patients, a potentially variant can be identified and non-synonymous variants in SLC4A3 were the most common cause of SQTS [50]. However, this variant has not been identified in global databases, reinforcing its potential impairing role. And no conclusive data exist concerning the association of this variant

with SQTS. It is associated with the so-called SQTS type 8, and responsible, so far, for <1% of all SQTS case. It also follows an autosomal dominant pattern of inheritance. But in line with *SCN5A* gene mutation, the genetic translation of *SLC4A3* variants in SQTS patients should be cautious.

3.4. Arrhythmia Mechanisms

Currently, the mechanism of arrhythmogenesis in SQTS is not well understood, especially in non-SQT1-SQT3 [51]. Several pre-clinical studies have been reported focused on reveal the pathophysiological mechanism involved in SQTS. In vivo approaches, mostly transgenic animal models, have been also carried focused on selected variants diagnosed in SQT families showing highly malignant phenotypes, even SCD, among most relatives. Unfortunately, there are few genotypically accurate mammalian models of the SQTS at present. Learning from the electrophysiological characteristics of action potential (AP) of myocardial cells, or any changes in current density, ion channel properties of outward channels; or anything that decreases the current density of inward ion channel currents may result in the shortening of APD, effective refractory period (ERP) in myocardium, leading to short QT interval on ECG. Therefore, the information on the underlying arrhythmia mechanism of the syndrome is mainly from the use of in vitro preparations such as ion channel activators or inhibitors and computer modeling based on changes in ion channel characteristics in the recombinant channel experiments, using algorithms reproducing biological systems associated with SQTS. And the study of SQTS mechanism based on multi-scale mathematical model has become a link between molecular dysfunction and arrhythmogenesis (Figure 5).

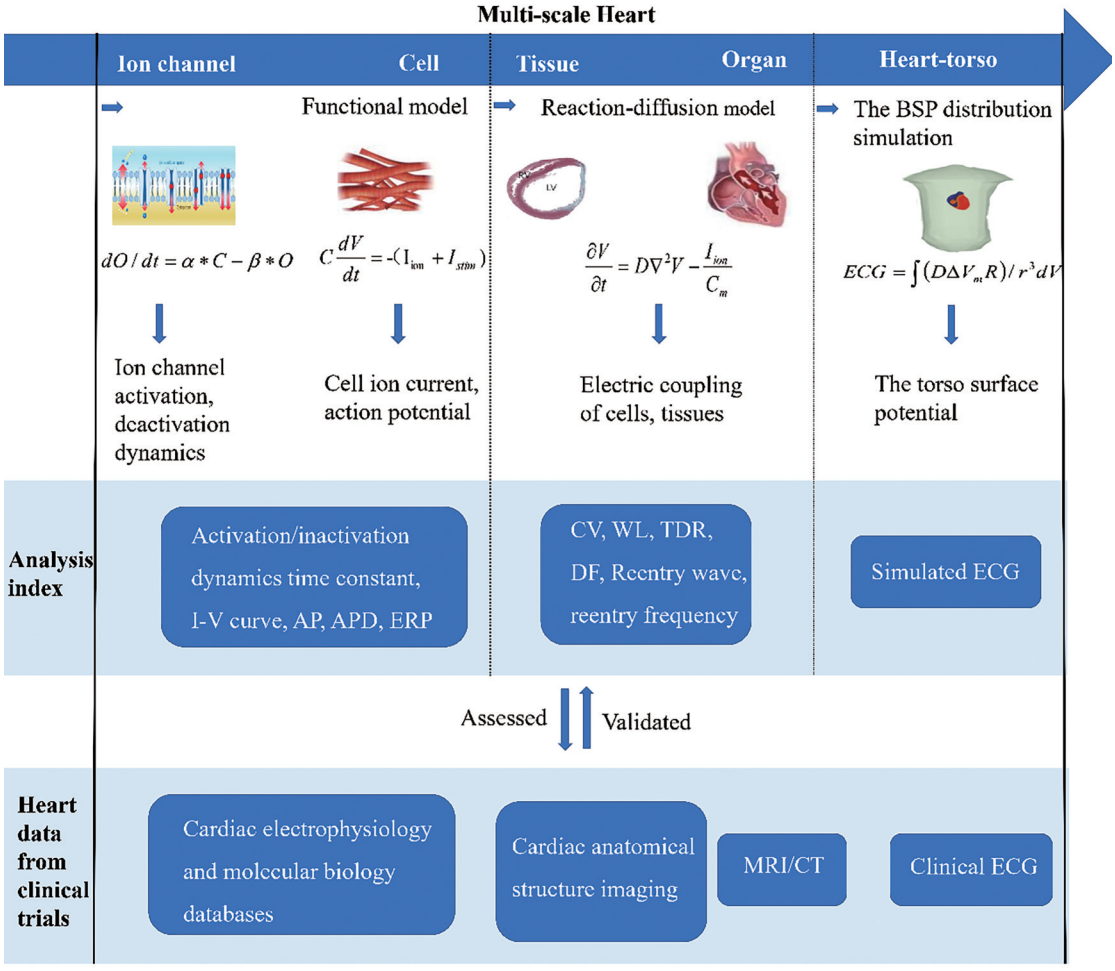

Figure 5. Schematic illustration of virtual heart as a platform of hereditary SQTS mechanism. AP: action potential; APD: action potential duration; ERP: effective refractory period; CV: conduction velocity; WL: wavelength; VW: vulnerable window; TDR: transmural dispersion of repolarization; DF: dominant frequency.

3.4.1. SQT1

In 2015, Giustetto C et al. first reported the in vivo effects of sotalol in SQTS patients carrying the T618I mutation in the *KCNH2* gene, but their data did not explain a clinical efficiency in these patients, neither in prolonging the QT interval to normal levels nor in preventing ventricular arrhythmias [52]. Therefore, there has been research on SQT1 mechanism also based on transgenic animal models. Zebrafish offers the possibility of studying genetic alterations in a short period of time, but essential anatomical and functional differences may limit the translation of results to humans. In 2008, Hassel et al. reported the first animal model of human SQTS represented by zebrafish reggae mutants, which displayed the clinical characteristics of malignant human SQTS associated with accelerated cardiac repolarization accompanied by cardiac fibrillation [53]. Transgenic rabbits models associated with SQT1 constructed by oocyte-microinjection of β -myosin-heavy-chain-promoter-*KCNH2*/*hERG*-N588K was to simulate the human disease phenotype on all levels with shortened QT/APD and increased ventricular tachycardia/ventricular fibrillation (VT/VF)-inducibility and show similar beneficial responses to quinidine [54]. And in vitro, El Harchi et al. reported the first AP voltage-clamp comparison between wild-type (WT) and V307L *KCNQ1* (co-expressed with *KCNE1* to recapitulate I_{Ks}) by perforated-patch voltage-clamp recordings at 37 °C. Compared with WT, *KCNQ1* V307L also showed a significant (−36 mv) shift in the middle-voltage of the activation curve, and slow down in the inactivation process obviously [55]. They also measured the characteristics of hERG current expressed in HEK 293 cells at 37 °C. f N588K-hERG variant 1 SQTS previously reported [56]. Patel and Antzelevitch seeked to examine the cellular basis for arrhythmogenesis in an experimental model of SQT1 created using PD-118057, a novel I_{Kr} agonist. It was applicated to canine left ventricular wedge preparations to mimic SQT1 abbreviated QT interval, ERP, augmented TDR and arrhythmia susceptibility. The results suggested that a combination of ERP abbreviation and TDR amplification underlie the development of Polymorphic ventricular tachycardia (PMVT) in SQT1 [57]. But recently, El-Battrawy et al. established a cellular model of SQTS using human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from skin fibroblasts on a SQTS patient carrying a N588K mutation in *KCNH2*, which further confirmed the mutation-induced increased I_{Kr} and AP shortening [58]. And using hiPSC-CMs of a SQT1-patient carrying the N588K mutation and a healthy donor, the result of patch clamp showed the deactivation-slowing effects and window current-reducing may be important for the antiarrhythmic effect [59].

Computer simulations recapitulated the repolarization shortening and created an arrhythmogenic substrate for VF so that SQTS patients may exhibit different clinical manifestations depending upon their genotype was proposed [24]. It was used to investigate the effects of the selective loss of voltage-dependent inactivation of I_{kr} upon ventricular AP and on the QT interval of the ECG by Zhang et al [60]. They substantiated the notion that selective loss of I_{kr} inactivation produces a gain in I_{kr} function that causes QT interval shortening. In 2005, using a biophysically detailed model of cellular electrophysiology, the behaviour of cells affected by the SQTS also was emulated. Simulates indicated that the activity of the repolarizing outward potassium current I_{Kr} was increased and the heterogeneous abbreviation of the APD decreased the dispersion of repolarization in heterogeneous tissue in conditions of SQTS, which consisted with experimental findings [61]. In 2006, the mechanism how the hERG channel gating defects causes life-threatening arrhythmia in the SQTS was reported, using a simulation model of ventricular APs. Unexpectedly, discovering 1 parameter change alone (βi and ββ), which caused gain of function, could shorten the APD but failed to induce early after-depolarizations (EADs) [62]. In 2011, a simulation study identified arrhythmogenic mechanisms in the rapid delayed rectifier K^+ current (I_{kr})-linked SQT1 variant. They explicated the N588K-*hERG* mutation contributes to initiation and maintenance of ventricular reentry, increasing the lifespan of reentrant spiral waves and the stability of scroll waves in 3D tissue [63]. In 2014, the different arrhythmogenic mechanisms of *hERG* missense mutations, N588K and L532P, on the cellular and tissue level were assessed, utilizing a computational model of human atrial myocytes. Both mutations showed an increase in arrhythmias due to the shortening of the refractory period and the prolongation of the linear repolarization period. However, the spiral wave of the L532P mutation had higher stability and regularity than that of the N588K mutation [64].

3.4.2. SQT2

The V307L mutation was incorporated into the simulations to reproduced defined characteristics of the SQTS: the abbreviation for QT interval, and the increases of T_{peak}-T_{end} duration and T wave amplitude [65]. In addition, a Markov chain (MC) model recapitulating WT and V307L mutant I_{ks} kinetics was incorporated into a model of the human ventricular AP for investigation of QT interval changes, arrhythmia substrates, the degree of simulated I_{ks} inhibition necessary to normalize the QT interval and terminate reentry in SQT2 conditions [66]. Simulation study investigated arrhythmia dynamics in multi-scale human ventricle models associated with the SQT2-related V307L *KCNQ1* 'gain-of-function' mutation. The results accurately showed that under the condition of homozygous (V307L) and heterozygote (WT-V307L) mutations, the modified I_{Ks} kinetic reproduction AP shortened and ERP decreased, the lifespan and dominant frequency (DF) of reentry increased in the 3D human ventricular models and the I_{Ks} reduced by 58% and 65% was sufficient to terminate the reentry under WT-V307L and V307L conditions, respectively. This may explain the partial inhibition of I_{Ks} as a potential antiarrhythmic strategy under SQT2 conditions [66]. Utilizing human AP computational models, the pro-arrhythmogenic effects of the V141M *KCNQ1* mutation in SQTS was studied and suggested that gain-of-function in I_{Ks} was characterized by increased current density, faster activation, and slower deactivation, resulting in I_{Ks} accumulation, explained how mutant I_{Ks} channels cause SQTS. The study had shown oocytes injected with cDNA encoding V141M *KCNQ1* + *KCNE1* subunits exhibited an instantaneous and voltage-independent K^+-selective current, and then computer modeling showed that the mutation would shorten APD of human ventricular myocytes and abolish pacemaker activity of the sinoatrial node cells [28]. Using computational modelling, Whittaker et al. elucidated the mechanism underlying the increased atrial arrhythmogenesis and impaired cardiac pace-making activity arising from increased I_{Ks} in KCNQ1 mutations, V141M and V307LV. Both mutations shortened APD through distinct I_{Ks} 'gain-of-function' mechanisms, whereas sinus node cells pace-making rate were slowed markedly only by the V141M mutation [67].

3.4.3. SQT3

The study identified D172N-Kir2.1-linked SQTS consequently lead to augmentation of outward but not inward current. Computer simulations using a human ventricular myocyte model indicated that the changes to I_{K1} consequent to this mutation accelerated the final stages of ventricular repolarization and abbreviate APD, though a lesser extent compare to the V307L *KCNQ1* or N588K *hERG* mutations [35]. Adeniran et al. used the modified human ventricular AP model by incorporating changes to I_{K1} based on experimentally observed changes to Kir2.1 function, and simulation results showed that D172N 'mutant' I_{K1} led to abbreviated APD and ERP, as well as steeper restitution curves of APD (APD-R), ERP (ERP-R). SQT3 'mutant' I_{K1} also stabilized and accelerated reentrant excitation waves, leading to sustained rapid reentry [68]. The study of Whittaker et al. showed that simulations of the D172N and E299V SQT3 Kir2.1 mutation found both to decrease reentry wavelength (WL) through reducing ERP and conduction velocity (CV). However, the two mutations, which produce qualitatively different effects on I_{K1} affected spatial dispersion of APD (with D172N producing increased spatial heterogeneities in some regions and E299V reducing global dispersion of repolarization), with consequences for stability of reentry in the two situations (D172N resulting in greater reentry stability) [69].

3.4.4. Others

In 2004, I_{KATP} channel activator was used to accelerate the AP repolarization of myocardial cells in dogs, and the arrhythmias model of SQTS was established for the first time. The results suggested that there was an uneven distribution of ion channels among the myocardial cells in each layer, which led to an significant heterogeneity in the shortening of APD, resulting in an increase in the degree of myocardial transmural dispersion of repolarization (TDR) and become the basis of reentrant arrhythmias [70]. In the canine ventricular wedge model, Extramiana and Antzelevitch confirmed the heterogeneous abbreviations of APD in different cell types across the ventricular wall, which laid the foundation for the occurrence of VT under SQTS-related conditions [70]. Computer simulations of ventricular excitation and propagation using both the homozygous and heterozygous conditions at three different levels of integration (single cell, 2D, and 3D)

accurately reproduced the ECG phenotype of the proband, including an exceedingly short QT interval with merging of the QRS and the T wave, absence of ST segment and peaked T waves. Simulations showed it to produce a much more marked AP abbreviation compared to the D172N mutation [71]. More simulation data have further substantiated a causal link between the mutation and QT interval/APD shortening/TDR increased and susceptibility to ventricular arrhythmia. Based on the previous results of Schimpf et al., electromechanical consequences of the SQTS were explored, utilizing electromechanically coupled human ventricle models incorporated by validated K^+ channel formulations for SQT variants 1 and 3. Simulations reconfirmed that there was a considerable attenuation of the effects of SQTS-associated action potential shortening on Ca^{2+} transients, sarcomere shortening and contractile force When stretch-activated channel current (I_{sac}) was incorporated.

3.5. Therapeutic Drug Research

3.5.1. Potassium Channel

I_{Kr} block is mainly responsible for delayed repolarization of class I and III antiarrhythmic drugs [72]. In the study of Brugada et al. that identified N588K-*hERG* linked SQT1, sotalol was administered, but the QT_c interval did not return to the normal value [18]. A great deal of antiarrhythmic drugs was tested in subsequent study but only hydroquinidine was found to be successful at prolonging QT_c interval, ventricular ERP and preventing from VF [73]. Using the multi-scale human ventricle model, they simulated the actions of quinidine at various physiological levels, but also elucidated why the sotalol failed in *KCNH2* T618I-associated SQT1 patients through profoundly analyzing its mutation-dependent actions [74]. The basis for this difference is likely to quinidine restored the heart rate dependence of the QT interval toward a range of adaptation reported for normal subjects. Evidence in support of this comes from the observation that heterologous expression of WT and mutant *hERG* genes indicated the mutation causes a ~5.8-fold increase in IC_{50} of quinidine compared to ~20-fold increase of sotalol [75]. Consistent with quinidine, the class I_a drug disopyramide was also comparatively less dependent on inactivation to bind to hERG and has been found to exert beneficial effects in SQT1 patients on QT_c interval, rate dependence and ventricular ERP [76]. Antiarrhythmic properties of ivabradine by pharmacologically simulated SQTS were reported. Using human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from a patient with SQT1, the antiarrhythmic effects of ivabradine, mexiletine, ajmaline [77] and disopyramide [78] have been reported. Utilizing a mathematical model of human ventricular electrophysiology, the potential effects of E-4031, disopyramide and quinidine on SQT1 were further assessed. Simulates reconfirmed that quinidine exhibited significantly better therapeutic effects on SQT1 than E-4031 and disopyramide as it caused QT prolongation and decrease in the T-wave amplitude, and increased ERP and decreased temporal susceptibility of the tissue to the initiation of reentry and increased the minimum substrate size necessary to prevent reentry [16]. In addition to QT interval shortening and ventricular arrhythmias, SQT1 is associated with increased risk of AF, which is often the only clinical presentation. Recently, according to computational modeling, class I drugs-disopyramide, quinidine, and propafenone were used to estimate pharmacotherapeutic effects and investigate mechanisms of human atrial arrhythmogenesis consequent to a SQT1 mutation. The results showed that heterozygous and homozygous formulations of the N588K-*hERG* mutation shortening the APD, which abbreviated the ERP and excitation WV in tissues, increasing the lifespan and DF of scroll waves in the 3D anatomical human atria. It reconfirmed that quinidine was the most effective in prolonged APD and ERP in the setting of SQT1 [79]. From the important role of I_{Kr} in repolarization, as well as the kinetics and drug binding, the possible effect of I_{Kr} block in the form of non-SQT1 forms can be inferred. Indeed, comparison of SQT1 and non-SQT1 forms of the syndrome suggests efficacy of quinidine in both settings, but with greater effects in SQT1 patients [12].

I_{Ks} inhibition is predicted to be an effective strategy in SQT2, with the efficacy in practice depending on the location of SQT2 mutations relative to drug binding sites. The V307L residue is located in a region of the KCNQ1 protein, which has been considered to be the interaction site of I_{Ks} inhibitors (based on chromanol), while the primary of V307L SQT2 mutation significantly reduces potency of inhibition by chromanol 293B [80]. Contrarily, mefloquine, a quinoline antimalarial drug, may not actually require channel gating for binding to inhibit recombinant I_{Ks} channels [81]. By contrast with V307L, the enhanced sensitivity of

KCNQ1-V141M gain-of-function mutations for I_{Ks} selective blocker HMR-1556 suggests the possibility of selective therapeutic targeting. It has justified the hypothesized that gain-of-function KCNQ1 mutations have obvious pharmacological properties associated with familial AF, which may cause targeted inhibition [82]. Moreover, An et al. found that $Mg\cdot(NH_2CH_2CH_2SO_3)_2\cdot H_2O$, a taurine-magnesium coordination compound (TMCC), exerted anti-arrhythmic effects with low toxicity and perfusion of TMCC (1–4 mmol/L) increased the QT interval and QT peak dose-dependently in Langendorff perfused guinea hearts. It provided obviously evidence that TMCC can prolonging repolarization period and suppressing repolarization current (I_{Ks}) [83]. Based on recently silico simulations, arrhythmia dynamics in multi-scale human ventricle models related with the *KCNQ1*-V307L 'gain-of-function' mutation were investigated. 58% and 65% inhibition of I_{Ks} were sufficient to terminate the lifespan of reentry in WT-V307L and V307L conditions compared to WT condition, respectively [66]. In principle, the overall importance of I_{Ks} to repolarization reserve might suggest that I_{Ks} block is used in the treatment of SQT2 and non-SQT2 forms of the SQTS variants.

For SQTS variants with a mixed SQTS/Brugada phenotype, selective I_{to} (transient outward potassium current) block could be useful in correcting early repolarization while selective I_{to} inhibitors are not clinically available [84]. Differences from the I_{Kr} and I_{Ks} channels, I_{K1} usually carries a small amount of current during the ventricular APs plateau phase, and the major repolarization contribution of I_{K1} is terminal repolarization process. Therefore, it is possible that I_{K1} block might not be an optimal select for APD/QT interval prolongation in non-SQT3 forms. In 2016, styrax, a kind of natural compound selected from traditional Chinese medicine, was identified as a novel blocker of Kir2.1. It has shown that styrax can abolish the inward and outward currents of Kir2.1 and can serve as a novel blocker for SQT3 [85]. Subsequently, pentamidine-Analogue 6 (PA-6), an efficient and specific I_{K1} inhibitor associated with V93I and D172N mutations, was reported [86]. Using biophysically-detailed human ventricular computer models, the potential effects of quinidine, disopyramide, and E-4031 on SQT3 have been investigated. All simulation data indicated that quinidine was more effective in preventing and terminating reentry in the heterozygous WT-D172N condition [87]. Recently, the effects of chloroquine and amiodarone on *KCNJ2*-linked SQT3 were also investigated. It was shown that both caused a dose-dependent reduction in I_{K1}, prolonged APD, and decreased the maximum voltage heterogeneity. They have provided further evidence that chloroquine or amiodarone [88] may be a potential pharmacological agent for preventing arrhythmogenesis in patients with SQT3.

3.5.2. L-Type Calcium Channel

The shortened repolarization in SQT4-6 involves the reduction of $I_{Ca,L}$, which can be regulated by pharmacological augmentation of $I_{Ca,L}$ [42]. But there are still the following defects: selective agonists of $I_{Ca,L}$ are not available in clinical, as $I_{Ca,L}$ agonists may cause extra-cardiac side effects, and increased $I_{Ca,L}$ levels may be proarrhythmic. In addition, both atrial electro-mechanical coupling and the ventricular consequences of such a large increase in $I_{Ca,L}$ must also be taken into account.

3.5.3. Sodium Channel

There have been reports of treatment of SQTS with class I and III antiarrhythmic drugs in the past, but most of them target SQTS caused by potassium channel mutations. Propafenone, a class of I_C antiarrhythmic drugs, inhibits the current of wild sodium channels by transferring the steady state inactivation (SSI) curve of sodium channels to hyperpolarization (accelerated inactivation), and prolonging the activation after inactivation. Thus, the depolarization velocity of AP was decreased, the APD and ERP were prolonged, and the spontaneous activation of myocardium was decreased. Studies have shown that propafenone blocks sodium channels by binding to the inactivated conformation of sodium channels [89]. Mexiletine, a class of I_B antiarrhythmic drugs, can block fast sodium channels, slow down the depolarization velocity of AP, increase the proportion of ERP, and has little effect on cardiac electrical conduction velocity [90]. It was more likely to combine with sodium channel inactivation and play a blocking role. Amiodarone, a class of III antiarrhythmic drugs, blocks a variety of ion channels and plays a mild role in blocking sodium channels by combine with inactivation of sodium channels [91]. Three different antiarrhythmic drugs, Propafenone, Mexiletine, Amiodarone, were used to intervene the E428G mutated sodium channel to observe the effect of the drug on the mutated sodium channel. However, only propafenone significantly increased E428G channel,

suggesting that propafenone may be a new, potential drug for the treatment of SQTS caused by E428G mutation.

3.5.4. Multichannel

For broad-spectrum antiarrhythmic drugs, they play a role in multiple ion channels associated with SQTS. Bjerregaard et al. showed that propafenone, a class of I_C antiarrhythmic drugs, has a significant effect on AF in patients with SQTS caused by potassium channel mutation, but has no effect on QT intervals [92]. The silico modelling suggested that combined block of I_{Kr} and I_{K1} was effective for terminating reentry in heterozygous D172N conditions, whereas I_{Kr} block alone might be a safer alternative for the E299V mutation. However, combined inhibition of I_{Kr} and I_{Kur} produced a synergistic antiarrhythmic effect in both forms of SQT3 [69]. In simulations of atrial effects of SQT3 mutations, increasing $I_{Ca,L}$ by 100% decreased the DF of atrial reentrant excitation but failed to terminate reentry but increasing to 250% was sufficient to terminate atrial reentry [69]. At present, quinidine is one of the most effective antiarrhythmic drugs in the treatment of SQTS, as an I_a antiarrhythmic drug with multi-channel binding sites. The effective has been proved in many types of SQTS. In 2017, Mazzanti A et al. investigated whether long-term use of Hydroquinidine (HQ) could reduce the occurrence of life-threatening arrhythmic events (LAE) (cardiac arrest or SCD) in patients with SQTS. Their studies suggested that the annual incidence of LAE in 16 patients with previous cardiac arrest decreased from 12% before HQ to 0 after therapy [16]. Recently, we also provided the theoretical basis for the antiarrhythmic effect of quinidine in SQTS silico model [93]. Therefore, the choice of therapeutic drugs in patients with hereditary arrhythmias cannot be solely based on the theoretical effects of drugs on wild channels, nor on the effects of ion channel gene mutations on anti-arrhythmias pharmacodynamics. It suggests that genotype individualized drug therapy is the future research direction for inherited arrhythmias, such as SQTS.

4. Discussion

4.1. Conclusion

The study systematic reviewed the clinical findings, genetic basis, drug therapy and underlying mechanism of malignant arrhythmias based on the retrieval result of PRISMA guidelines. We believe that with the improvement of computational models of human cardiac cell/tissues, the application of parallel computing and visualization techniques, the study of electrophysiological modeling of SQTS will be further advanced, which will be helpful to the early diagnosis and improve the diagnostic accuracy of SQTS. At the same time, it is helpful to the development of SQTS therapy, reducing the risk or side effects of new drugs. A recent literature has systematic reviewed the impact of potassium channel gene mutations (SQT1-3) on the electrophysiological properties of I_{Kr}, I_{Ks} and I_{K1} and the mechanism of increased arrhythmia susceptibility [40]. Both we have considered the experimental and simulation studies. We further review the cellular mechanisms of all congenital SQTS (SQT 1-8) and associated with drug treatment, and the arrhythmia mechanisms mainly in SQT1-3.

4.2. Limitations

In this study, the latest studies on arrhythmogenic mechanisms of the SQTS and possible drug therapy have been analyzed from a knowledge graph perspective to disclose the hotspots in this area. However, for some research hotspots, such as the general overview of the diagnosis, risk stratification and management of SQTS, it is shown on the development of clinical application scenarios, while its details are not being presented visually. Furthermore, the bibliometric analysis was used on English literature from five major database in this study, which may lead to the omission of information on non-English publications related to SQTS. In addition, with the citation changing over time, the literature data used in this study could only show the study status at the time of data collection, while the research content could not be tracked in real time.

4.3. Future Directions

For nearly 20 years, SQTS has been reported as a familial arrhythmogenic entity [94−96]. In fact, low

number of families have been reported but with a high lethality. SCD is usually the first manifestation of SQTS, where nearly 30% of SCD cases still have no defined cause of death. [97]. Currently, implantation of an ICDs remains the most effective preventive measure after aborted SCD and malignant ventricular arrhythmia although pharmacological therapies may be used in certain cases, especially in children [98]. Despite these observations, modulators of SQTS disease severity and expressivity are yet unknown, and arrhythmia risk prediction is elusive. This suggests that there is much to be learned in terms of the genetics of primary electrical diseases. Currently, the main development directions of SQTS in clinical and experimental were included as follows: (1) cellular models of SQTS. Human pluripotent stem cell (hiPSC) technology is gaining attention in addressing the major clinical problems related to channelopathies [99]. Therefore, disease modeling using the hiPSC from SQTS patients with inherited diseases is a powerful approach to explore the pathological mechanisms of arrhythmia and drug discovery. (2) genotype-phenotype research. As with other hereditary arrhythmias, the genotype-phenotype relationship of SQTS is significant [100]. However, the study of genotype-phenotype relationship of SQTS is limited due to the few cases reported in the literature. Therefore, more cases are needed to study and to provide genotype-phenotype-guided risk stratification associated with SQTS. (3) Implantable cardioverter defibrillator (ICD) is the only way to prevent SCD and effective therapeutic preparations are still lacked. Especially, the use of ICDs devices in young patients was a challenge [15]. (4) Actively searching for individualized therapeutic drugs for genotype is an important preface subject from the world. Currently, drugs are mainly targeted at SQT1-3 caused by potassium channel mutations. Due to the small number of SQTS patients, the effectiveness and safety of drug therapy, and whether individualized treatment should be taken according to the different types of SQTS remains to be studied. Hence, studies linking electrophysiological alterations at the level of the cardiomyocyte, the whole heart, and the intact animal, primarily in human are required in order to gain essential mechanistic insight. Among them, computer model is one of the most effective and useful tools to solve this difficulty. The primary task of virtual cardiologist is to establish an accurate and real cell model, based on which the pathogenesis of various SQTS types is simulated and analyzed on multiple physical scales.

At present, the main development directions of SQTS electrophysiological modeling and simulation were included as follows: (1) The effect of SQTS gene mutation on heart and the induction of pathogenesis of AF and VF from multiple physical scales can be analyzed. Using subcellular or cellular models, the relationship between functional changes in ion channels induced by mutations and the shortening of the APD/ERP/QT interval in atrial/ventricular myocytes were studied. Tissue models can be used to study the relationship between SQTS mutation and a specific augment of transmural refractory period in atrial/ventricular tissue and the effect of cardiac signal on the possibility of myocardial conduction and the generation of reentry wave. The indicators that can be analyzed in this mathematical model are action potential spatial heterogeneity, conduction excitability, VW, minimum wavelength and so on. And three-dimensional organ models can be used to study the effect of the dynamics of reentry wave induced by SQTS mutations, and the analyzable indexes are as follows: simulation ECG morphology and characteristic, reentry wave self-maintenance time and rotating track, frequency analysis. In addition to set up a multi-physical scale model by computational cardiologists, it is also necessary to compare the standard value under normal conditions with the abnormal value in the case of a mutation by means of a model simulation data analysis, to explain the mechanism that SQTS causes the pathogenesis of a malignant arrhythmia or even SCD. (2) Tracking the latest clinical data of SQTS mutation gene, fitting the current formula of isolated channel mutation, and integrating it into 1D-3D tissue model, then simulating some characteristic indexes to explore the pathogenesis of arrhythmia caused by gene mutation association with SQTS. Currently, a limited number of rare variants have been affirmed in eight genes, accounting for nearly 20–30% of the SQTS family. As mentioned earlier, only partial mutation subtype of SQT1-SQT3 have been studied by computer simulation. Modeling and analyzing the pathogenesis of SQT4 (*CACNA1C* mutation), SQT5 (*CACNB2b* mutation), SQT6 (*CACNA2D1* mutation), SQT7 (*SCN5A* mutation), SQT8 (*SLC4A3* mutation) are also the research contents in the future. (3) A more simplified SQTS cell model is developed. Large-scale organizational simulation can involve millions of grid points, in which case the cost of time is greatly reduced by using a simplified SQTS cell model. There are generally three types of simplified SQTS modules: models that directly reduce detail, general models and phenomenon models. (4) Drug simulation of SQTS. According to the eight subtypes of SQTS which have been found at present, the specific drug simulation is carried out, and

the results of drug simulation are compared with those of the normal parameters, or "generic" drugs that treat two or more SQTS subtypes can be found. Moreover, the integrated modeling and simulation of electrophysiology and mechanical contraction can better reflect the real mechanism of heart operation. Combining the two models to seek the pathogenesis of SQTS, the development of targeted drugs will be the focus of future research.

Author Contributions: For research articles with multiple authors, a concise paragraph detailing each author's specific contributions must be included. Authorship should be restricted to individuals who have made significant contributions to the reported research. The following statements should be used "A.A.: conceptualization, methodology, software; B.B.: data curation, writing—original draft preparation; C.C.: visualization, investigation; D.D.: supervision; E.E.: software, validation; F.F.: writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript." Please refer to the CRediT (Contributor Roles Taxonomy) for detailed definitions of each contribution role. Only those who have substantially contributed to the research should be listed as authors.

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