Chapter

Short QT Syndrome: Update on Genetic Basis

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Abstract

Short QT syndrome (SQTS) is an extremely rare inherited arrhythmogenic entity. Nowadays, less than 200 families affected worldwide have been reported. This syndrome is characterized by the presence of a short QT interval leading to malignant ventricular tachyarrhythmias, syncope and sudden cardiac death. It is one of the most lethal heart diseases in children and young adults. Both incomplete penetrance and variable expressivity are hallmarks of this entity, making it difficult to diagnose and manage. Currently, rare variants in nine genes have been associated with SQTS (*CACNA1C*, *CACNA2D1*, *CACNB2*, *KCNH2*, *KCNJ2, KCNQ1*, *SLC22A5*, *SLC4A3* and *SCN5A*). However, only pathogenic variants in four genes (*KCNH2*, *KCNQ1*, *KCNJ2* and *SLC4A3*) have been found to definitively cause SQTS. The remaining genes lack a clear association with the disease, making clinical interpretation of the variants challenging. The diagnostic yield of genetic tests is currently less than 30%, leaving most families clinically diagnosed with SQTS without a conclusive genetic diagnosis. We reviewed and updated the main genetic features of SQTS, as well as recent evidence on increasingly targeted treatment.

Keywords: sudden cardiac death, arrhythmias, short QT syndrome, genetics, QT interval variability

1. Introduction

Short QT syndrome is a rare inherited cardiac channelopathy characterized by the presence of short QT intervals and a high risk of malignant arrhythmias in the context of a structurally normal heart. Described more than 20 years ago by Gussak et al. [1], it was not until 2004 when the first genetic variants associated with the disease were published in *KCNH2* [2] *KCNQ1* [3] and *KCNJ2* [4], named SQT1, SQT2 and SQT3, respectively. Since then, pathogenic variants have been described in six other genes associated with the disease, however, due to the low number of cases and the lack of a correct genotype-phenotype correlation, it is difficult to confirm the definitive pathogenic role of these genes as cause of SQTS. We aim to update current advances in SQTS, especially focused on genetics.

2. Prevalence

Today, it is difficult to establish the real prevalence of SQTS in the population, mainly due to the rarity of the disease and its possible underdiagnosis. The estimated prevalence is less than 1/10.000 in adults and about 1/2.000 in children and adolescents [5–8]. SQTS is potentially lethal for children in the first year of life, leading to a cardiac arrest rate close to 4%, making it one of the causes of sudden infant death syndrome (SIDS) [9].

3. Diagnosis

SQTS is diagnosed by the presence of a QTc ≤ 340 ms, or a QTc ≤ 360 ms when one of the following clinical criteria is met: detection of a clearly pathogenic genetic variant in one of the genes associated with the disease, family history of SQTS, family history of syncope or sudden cardiac death (SCD) before 40 years of age or survival of a ventricular tachycardia (VT) /ventricular fibrillation (VF) episode in the absence of heart disease [10]. However, its diagnosis can be challenging due to the large variability of the QT interval in healthy subjects.

Resting ECG should be performed at a normal heart rate when SQTS is suspected [11]. In addition, a stress test could be useful and a slope of the QT/HR ratio of less than −0.9 ms/beat/min could help distinguish affected subjects from healthy individuals [12]. Some studies support that QTc values should be adjusted in each population according to factors such as sex and age, and assessed in conjunction with other ECG criteria [13, 14]. For instance, a recent study in children and young adults demonstrated that a QTcB <316 ms, J-Tpeak cB < 181 ms (corrected by using Bazett's formula) and the presence of early repolarization (ER) could be indicative of SQTS in patients younger than 20 years of age [15]. Tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) could be part of the clinical evaluation, as systolic function may also be impaired and patients may present a dispersion of contraction in myocardium [16]. In contrast, invasive electrophysiological study (EPS) with programmed ventricular pacing is not recommended for SCD risk stratification [10] .

4. Clinical findings

SQTS is characterized by a short QT interval in the ECG, with an asymmetric and sharp T wave, especially in precordial leads. Short or absent ST segments and paroxysmal episodes of atrial or ventricular fibrillation (**Figures 1** and **2**). The most common symptoms are palpitations (30%), syncope (25%) and cardiac arrest (40%) [17]. Ventricular and atrial fibrillation is present in most patients [18]. Cardiac events usually occur in adrenergic situations (noise or exercise), although occasionally it can also occur at rest [19]. Despite no studies focused on diet, any food modifying significantly the potassium levels may affect the QT interval. Symptoms occur in all age groups, with an increasing rate of SCD between 14 and 40 years of age. The probability of presenting with SCD as the first symptom increases with age, reaching 41% at 40 years of age [5]. A slightly male predominance was suggested, but recent analysis showed that although males present syncope more frequently than females, they show a lower risk of arrhythmic events and/or SCD [20]. In addition,

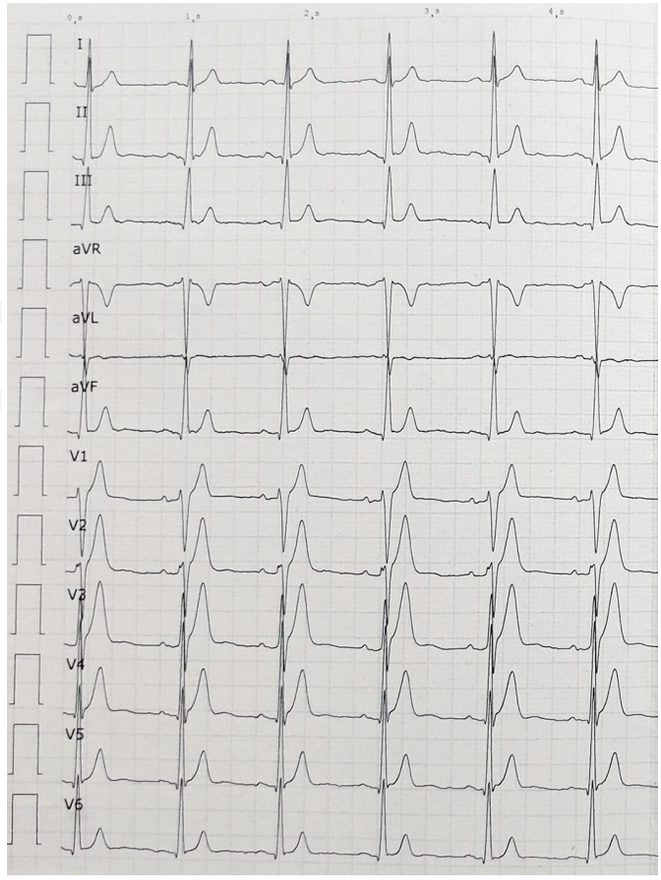

Figure 1.
ECG taken from a 39-year-old patient with SQTS; QT interval: 310 ms, QTc: 355 ms (corrected by using Bazett's formula).

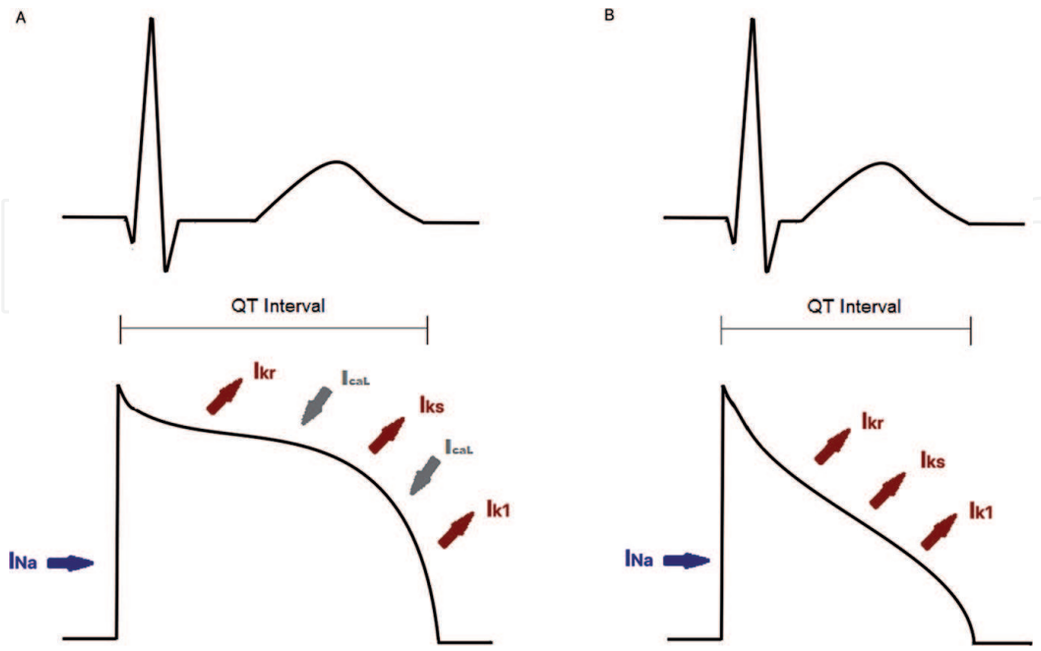

Figure 2.
ECG diagram and cellular ionic currents under normal conditions (A) and SQTS (B). Voltage-gated Na+ and K+ currents define the ventricular action potential and the QT interval of the ECG. The functional effect of IKs, IKr or IK1 gain-of-function or INa or CaL loss-of-function on the ventricular action potential results in the shortening of the action potential associated with SQTS.

some studies suggest that genes located on the X chromosome may be involved in the regulation of the QTc interval [21].

5. Genetic basis

Short QT syndrome occurs mainly in an autosomal dominant pattern of inheritance with high phenotypic and genetic heterogeneity. To date, potential deleterious rare variants located in nine genes (*CACNA1C*, *CACNA2D1*, *CACNB2*, *KCNH2*,

SQTS	Prevalence	Genes	Effect of variant	Current affected	Phenotypic overlap
SQT1	<15%	*KCNH2*	GOF	I_{Kr}	LQTS, BrS
SQT2	<5%	*KCNQ1*	GOF	I_{Ks}	LQTS
SQT3	<3%	*KCNJ2*	GOF	I_{K1}	LQTS, CPVT
SQT4	<1%	*CACNA1C*	LOF	I_{ca}	LQTS, BrS
SQT5	<1%	*CACNB2*	LOF	I_{ca}	LQTS, BrS
SQT6	<1%	*CACNA2D1*	LOF	I_{ca}	LQTS, BrS
SQT7	<1%	*SCN5A*	LOF	I_{Na}	LQTS, BrS
SQT8	<1%	*SLC4A3*	LOF	AE3	.
SQTS-mimic	<1%	*SLC22A5*	LOF	.	CDSP

AE3: Anion exchanger; BrS: Brugada syndrome; CDSP: Systemic primary carnitine deficiency; GOF: gain-of-function; ICa: Voltage-gated calcium currents; IKr: Rapidly activating potassium currents; IKs: Slowly activating potassium currents; IK1: Inward rectifier potassium currents; LOF: loss-of-function; LQTS: Long QT syndrome; SQTS: Short QT syndrome.

Table 1.
Genes associated with Short QT Syndrome or Shorter than normal QT interval and its phenotypic overlap with the main arrhythmogenic syndromes.

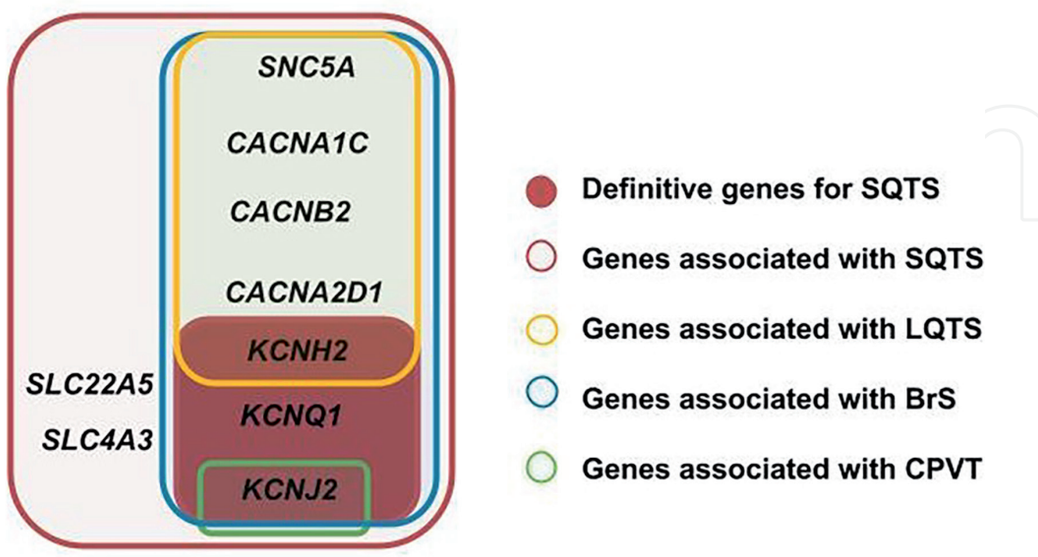

Figure 3.
Diagram of the overlap between the genes associated with the short QT syndrome (SQTS) and the main channelopathies: Brs: Brugada syndrome; LQTS: long QT syndrome and CPVT: catecholaminergic polymorphic ventricular tachycardia.

KCNJ2, *KCNQ1*, *SLC22A5*, *SLC4A3* and *SCN5A*) have been associated with SQTS (**Table 1**) [22]. However, only three genes (*KCNH2*, *KCNQ1* and *KCNJ2*) have been shown to cause SQTS definitively so far, and the *SLC4A3* gene presents moderate evidence [23]. The association of the other genes with SQTS remains controversial (**Figure 3**) [24].

6. Genes definitely associated with SQTS

Pathogenic variants in the *KCNH2*, *KCNQ1* and *KCNJ2* genes are responsible for SQTS type 1, 2 and 3 respectively. These variants are usually of the gain-of-function type and generate prolonged K^+ channel activation, accelerated cardiac repolarization with shorter refractory periods, resulting in the short QT phenotype [25].

The *KCNH2* gene (ID: 3757) encodes a voltage-activated potassium channel belonging to the eag family, subfamily H, member 2 (Kv 11.1 α/hERG subunit). It mediates the rapidly activating component of the delayed rectifying potassium current in the heart (I_{Kr}) [26–28]. Gain-of-function hERG variants lead to abbreviated ventricular repolarization and SQTS; in contrast, loss-of-function hERG variants are responsible for Long QT Syndrome (LQTS). The pathogenic variants p.Thr618Ile and p.Asn588Lys are the most frequently associated with SQTS [29]. Several functional studies have demonstrated the pathophysiological role of these variants, and their contribution to the SQTS phenotype seems clear [30]. Although other rare variants in the *KCHN2* gene associated with SQTS have been described, many of them require further functional or segregation studies to elucidate their definitive pathological role.

The *KCNQ1* gene (ID: 3784), encodes a voltage-activated potassium channel (Kv7.1 α-subunit) required for repolarization. This protein can form complexes associated with MinK (the *KCNE1* gene) and MiRP2 (the *KCNE3* gene) proteins, both potassium channel. When associated with *KCNE1*, it forms the I_{Ks} current, and induces rapid activation of the potassium-selective outward current. It can also associate with the MiRP2 protein and other associated proteins to form the potassium channel [3, 31]. Deleterious variants in this gene are associated with SQT2 and account for less than 5% of SQTS cases. In addition, some *de novo* variants in the *KCNQ1* gene have been associated with a particular phenotype *in utero* with clinical diagnosis of atrial fibrillation (AF), along with concomitant bradycardia and SQTS [32]. The rare variants p.Val141Met and p.Val307Leu have the clearest association with SQT2 to date [22], being potential targets for various therapeutic models. For example, functional and computational simulation studies identified channel-specific blockade of I_{K1} or I_{Ks} as a possible antiarrhythmic strategy in SQT2, depending on the identified deleterious variants (p.Val141Met and p.Val307Leu, respectively) [33, 34].

The *KCNJ2* gene (ID: 37591) encodes the integral membrane protein and an inward rectifier-type potassium channel, subfamily J, Member 2 (Kir2.1 α-subunit). Inward rectifier potassium channels are characterized by a greater tendency to allow potassium to flow into the cell rather than out of it (IK1 current) [4, 35]. Currently, pathogenic variants with the most evidence of causality for SQT3 are the variants p.Asp172Asn and p.Glu299Val [36, 37]. The *KCNJ2* gene has also been associated with other channelopathies, mainly catecholaminergic polymorphic ventricular tachycardia (CPVT) [38].

6.1 Gene moderately associated with SQTS

In 2017, the *SLC4A3* gene (Solute Carrier Family 4 Member 3, ID: 6508) was associated with SQTS, presenting an unusual mechanism for the development of malignant arrhythmia. *SLC4A3* encodes plasma membrane anion exchange protein 3 (AE3) and acts by mediating part of the Cl-/HCO3- exchange in cardiac myocytes. To date, only one rare variant in this gene has been identified in two families (p.Arg370His). This loss-of-function variant would cause an increase in pH_i and a decrease in $[Cl-]_i$, shortening the AP duration and reducing the QT interval [39]. This gene is associated with SQT type 8; however, further studies are needed to clarify the definitive role of this gene in SQTS.

6.2 Other genes associated with SQTS

Loss-of-function alterations in genes encoding different subunits of cardiac Ca^{2+} channels have been associated with SQTS syndrome with an autosomal dominant inheritance pattern, each accounting for less than 1% of all SQTS cases [40]. However, evidence-based review of this association (ClinGen) leaves the causation of SQTS by mutations in these genes currently in dispute [24].

The *CACNA1C* gene (ID: 775) encodes an alpha-1 subunit of a voltage-dependent calcium channel (calcium channel, voltage-dependent, L-type, alpha 1C subunit, Cav1.2 α subunit). Calcium channels mediate the influx of calcium ions into the cell upon membrane polarization. To date, all variants identified in *CACNA1C* decrease inward currents at early phases of cell repolarization (I_{CaL}) and induce transmural and epicardial dispersion of repolarization, leading to a combined phenotype of SBr and short QTc interval [41]. Currently, more than 10 rare variants in the *CACNA1C* gene have been potentially associated with SQTS, so-called SQT4. However, there is insufficient evidence to establish a definitive association and further studies are needed [22]. Gain-of-function variants in this gene have also been associated with LQTS.

The *CACNB2* gene (ID: 783) encodes a subunit of a voltage-dependent calcium channel protein, a member of the voltage-gated calcium channel superfamily (Cav1.2 β subunit). The beta subunit of voltage-dependent calcium channels contributes to the calcium channel function by increasing peak calcium current, shifting the voltage dependencies of activation and inactivation, modulating G protein inhibition and controlling the alpha-1 subunit membrane targeting. Only one rare variant in the *CACNB2* gene has been associated with SQTS (p.Ser481Leu) to date, known as SQT5. This variant is also found to be associated with BrS [40].

The *CACNA2D1* gene (ID: 781) encodes 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 calcium current density and activation/inactivation kinetics of the calcium channel (I_{CaL}) [40]. Only one variant has been identified in this gene (p.Ser755Thr), but its high frequency in the Ashkenazi population and conflicting evidence refutes its pathogenic role in SQTS [24]. It is associated with the so-called SQTS type 6. This gene has also been associated with other channelopathies, mainly LQTS.

The *SCN5*A gene (ID: 6331) encodes the alpha subunit of the type 5 sodium channel (Nav1.5) that mediates voltage-dependent sodium ion permeability in the cardiomyocyte. So far, only a rare variant in the *SCN5*A gene (p.R689H) has been described to be associated with SQTS (called SQT7). Carriers of this variant show a

characteristic BrS phenotype with concomitant shortened QT intervals, but without a conclusive clinical diagnosis of SQTS. Therefore, its association is in dispute.

6.3 Gene associated with a SQTS-mimic phenotype

The *SLC22A5* gene (ID: 6584) encodes a high-affinity sodium ion-dependent carnitine transporter protein (Solute Carrier Family 22 Member 5). So far, only the pathogenic variant p.Phe17Leu has been associated with SQTS, following an autosomal recessive inheritance pattern [42]. However, because the short QT phenotype is reversible with carnitine supplementation, the association of this gene with SQTS remains inconclusive [24].

7. Genetic counselling

Due to the low number of cases reported worldwide, the real penetrance and incidence of SQTS is difficult to estimate. Although some pathogenic variants exhibit 100% penetrance, approximately 40% of patients may remain asymptomatic [29]. Current guidelines recommend the analysis of four genes: *KCNH2*, *KCNQ1*, *KCNJ2* and *SLC4A3*, despite last gene need more conclusive data concerning definite role [23]. Despite controversial association data between calcium channel genes and SQTS, current guidelines recommend the analysis of *CACNA1C*, *CACNA2D1* and *CACNB2,* frequently associated with BrS. Genetic diagnosis of SQTS has a diagnostic yield of less than 30% [43] with the *KCNH2* gene as the most cost-effective option [10]. Familial genetic analysis is recommended, both to clarify the pathogenic role of newly identified variants and to identify family members at risk for SCD.

8. Risk stratification and management

Risk stratification is the main current challenge in the clinical setting, especially in asymptomatic patients carrying a pathogenic genetic alteration. In addition, patients with QTc intervals ≤340 ms should be considered at higher risk for SCD, despite the fact that no conclusive results have been published so far. ICD implantation is the treatment of choice for all patients with SQTS, especially for those who have survived aborted cardiac arrest or who have had spontaneous sustained VT [44]. However, there is also a significant risk of device-related complications, mainly due to inappropriate shocks from the over detection of T waves (high and narrow) seen in SQTS. Drugs that prolong the QT interval (quinidine and sotalol) should be considered for all patients at risk for SQTS in both asymptomatic and symptomatic patients who do not have an ICD, especially in young children [43]. Quinidine is currently the agent of choice, since in patients with SQT1, in addition to prolonging the QT interval and ventricular refractory period, it leads to the normalization of ST segments and T waves and the prevention of VF induction. However, the personalized use of drugs aimed at the treatment of patients carrying certain types of variants is becoming increasingly common. A study on human-induced, pluripotent stem cell-derived cardiomyocytes demonstrated that in addition to quinidine, ivabradine, ajmaline and mexiletine may be drug candidates for preventing tachyarrhythmias in patients carrying the p.Asn588Lys variant in the *KCNH2* gene [45]. In addition, modelling studies indicated that high-dose amiodarone may be a potential drug treatment for SQTS2,

especially those patients carrying the p.Val307Leu variant in the *KCNQ1* gene [46]. Recently, a study show that vernakalant (sodium and potassium channel blocker) can prolong action potential and reduce arrhythmias in human-induced pluripotent stem cell-derived cardiomyocytes from a patient diagnosed of SQTS type-1 due to p.Asn588Lys, suggesting an effective candidate drug for treating arrhythmias [47]. Although more studies are needed to confirm these findings, the development of personalized treatments for inherited arrhythmias is currently in expansion.

9. Conclusions

Currently, SQTS is still a relatively unknown disease. First described in 2000, the small number of families diagnosed with SQTS worldwide makes the establishment of a risk stratification scale difficult. Clarification of electrophysiological and clinical abnormalities associated with the disease and the genetic origin, has only been carried out in recent years. However, only four genes (*KCNH2*, *KCNQ1*, *KCNJ2, SLC4A3*) have been definitively associated with the disease and a comprehensive genetic analysis only identify the causative alteration in no more than 30% of diagnosed families. It is crucial to perform more genotype-phenotype analyses in diagnosed SQTS families as well as segregation studies and *in vitro/ion vivo* functional tests that will allow clarification of the pathophysiological mechanism involved this lethal arrhythmogenic syndrome. Survivors of SCD have a high recurrence rate of episodes, thus implantation of an ICD is recommended in this group of patients. The pharmacological approach may also be effective in some cases, especially in the pediatric population, and the use of personalized medicine is becoming increasingly feasible. Personalized clinical evaluation, genetic analysis and the adoption of effective therapeutic measures by specialists help to improve the evolution of diagnosed patients with an increasingly positive long-term outcome.

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] Gussak I, Brugada P, Brugada J, Wright RS, Kopecky SL, Chaitman BR, et al. Idiopathic short QT interval: A new clinical syndrome? Cardiology. 2000;**94**:99-102. DOI: 10.1159/000047299

[2] Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation. 2004;**109**:30-35. DOI: 10.1161/01.CIR.0000109482.92774.3A

[3] Bellocq C, Van Ginneken ACG, Bezzina CR, Alders M, Escande D, Mannens MMAM, et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation. 2004;**109**:2394-2397. DOI: 10.1161/01.CIR.0000130409.72142.FE

[4] Priori SG, Pandit SV, Rivolta I, Berenfeld O, Ronchetti E, Dhamoon A, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circulation Research. 2005;**96**:800-807. DOI: 10.1161/01.RES.0000162101.76263.8C

[5] Mazzanti A, Kanthan A, Monteforte N, Memmi M, Bloise R, Novelli V, et al. Novel insight into the natural history of short QT syndrome. Journal of the American College of Cardiology. 2014;**63**:1300-1308. DOI: 10.1016/J.JACC.2013.09.078

[6] Kobza R, Roos M, Niggli B, Abächerli R, Lupi GA, Frey F, et al. Prevalence of long and short QT in a young population of 41,767 predominantly male Swiss conscripts. Heart Rhythm. 2009;**6**:652-657. DOI: 10.1016/J.HRTHM.2009.01.009

[7] Funada A, Hayashi K, Ino H, Fujino N, Uchiyama K, Sakata K, et al. Assessment of QT intervals and prevalence of short QT syndrome in Japan. Clinical Cardiology. 2008;**31**:270-274. DOI: 10.1002/CLC.20208

[8] Anttonen O, Junttila MJ, Rissanen H, Reunanen A, Viitasalo M, Huikuri HV. Prevalence and prognostic significance of short QT interval in a middle-aged Finnish population. Circulation. 2007;**116**:714-720. DOI: 10.1161/CIRCULATIONAHA.106.676551

[9] Mazzanti A, Underwood K, Nevelev D, Kofman S, Priori SG. The new kids on the block of arrhythmogenic disorders: Short QT syndrome and early repolarization. Journal of Cardiovascular Electrophysiology. 2017;**28**:1226-1236. DOI: 10.1111/JCE.13265

[10] Priori SG, Blomström-Lundqvist C, Mazzanti A, Bloma N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eurospace. 2015;**17**:1601-1687

[11] Giustetto C, Di Monte F, Wolpert C, Borggrefe M, Schimpf R, Sbragia P, et al. Short QT syndrome: Clinical findings and diagnostic-therapeutic implications. European Heart Journal. 2006;**27**:2440-2447. DOI: 10.1093/EURHEARTJ/EHL185

[12] Giustetto C, Scrocco C, Schimpf R, Maury P, Mazzanti A, Levetto M, et al.

Usefulness of exercise test in the diagnosis of short QT syndrome. Europace. 2015;**17**:628-634. DOI: 10.1093/EUROPACE/EUU351

[13] Providência R, Karim N, Srinivasan N, Honarbakhsh S, Vidigal Ferreira MJ, Gonçalves L, et al. Impact of QTc formulae in the prevalence of short corrected QT interval and impact on probability and diagnosis of short QT syndrome. Heart. 2018;**104**:502-508. DOI: 10.1136/HEARTJNL-2017-311673

[14] Hazeki D, Ninomiya Y, Ueno K, Yoshinaga M. Tentative screening criteria for short QT interval in children and adolescents. Circulation Journal. 2018;**82**:2627-2633. DOI: 10.1253/CIRCJ.CJ-18-0213

[15] Suzuki H, Horie M, Ozawa J, Sumitomo N, Ohno S, Hoshino K, et al. Novel electrocardiographic criteria for short QT syndrome in children and adolescents. Europace. 2021;**23**:2029-2038. DOI: 10.1093/EUROPACE/EUAB097

[16] Frea S, Giustetto C, Capriolo M, Scrocco C, Fornengo C, Benedetto S, et al. New echocardiographic insights in short QT syndrome: More than a channelopathy? Heart Rhythm. 2015;**12**:2096-2105. DOI: 10.1016/J.HRTHM.2015.05.024

[17] Mazzanti A, O'Rourke S, Ng K, Miceli C, Borio G, Curcio A, et al. The usual suspects in sudden cardiac death of the young: A focus on inherited arrhythmogenic diseases. Expert Review of Cardiovascular Therapy. 2014;**12**:499-519. DOI: 10.1586/14779072.2014.894884

[18] Raschwitz LS, El-Battrawy I, Schlentrich K, Besler J, Veith M, Roterberg G, et al. Differences in Short QT Syndrome Subtypes: A systematic literature review and pooled analysis. Frontiers in Genetics. 2020 Jan 17;**10**:1312. DOI: 10.3389/fgene.2019.01312

[19] Viskin S, Zeltser D, Ish-Shalom M, Katz A, Glikson M, Justo D, et al. Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls. Heart Rhythm. 2004;**1**:587-591. DOI: 10.1016/J.HRTHM.2004.07.010

[20] El-Battrawy I, Schlentrich K, Besler J, Liebe V, Schimpf R, Lang S, et al. Sex-differences in short QT syndrome: A systematic literature review and pooled analysis. European Journal of Preventive Cardiology. 2020;**27**:1335-1338. DOI: 10.1177/2047487319850953

[21] El-Battrawy I, Besler J, Liebe V, Schimpf R, Tülümen E, Rudic B, et al. Long-term follow-up of patients with short QT syndrome: Clinical profile and outcome. Journal of the American Heart Association. 2018 Dec 4;**7**(23):e010073. DOI: 10.1161/JAHA.118.010073

[22] Campuzano O, Fernandez-Falgueras A, Lemus X, Sarquella-Brugada G, Cesar S, Coll M, et al. Short QT syndrome: A comprehensive genetic interpretation and clinical translation of rare variants. Journal of Clinical Medicine. 2019 Jul 16;**8**(7):1035. DOI: 10.3390/jcm8071035

[23] Wilde AAM, Semsarian C, Márquez MF, Sepehri Shamloo A, Ackerman MJ, Ashley EA, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. EP Europe. 2022;**2022**:1-61

[24] Walsh R, Adler A, Amin AS, Abiusi E, Care M, Bikker H, et al.

Evaluation of gene validity for CPVT and short QT syndrome in sudden arrhythmic death. European Heart Journal. 2022;**43**:1500-1510. DOI: 10.1093/EURHEARTJ/EHAB687

[25] Priya PK, Jayaraman S. Effect of Percentage Reduction in Action Potential Duration of M-cells on Re-entry in Short QT Syndrome. Annual International Conference on IEEE Engineering and Medical Science. 2020;**2020**:2585-2588. DOI: 10.1109/EMBC44109.2020.9175751

[26] Guasti L, Crociani O, Redaelli E, Pillozzi S, Polvani S, Masselli M, et al. Identification of a posttranslational mechanism for the regulation of hERG1 K+ channel expression and hERG1 current density in tumor cells. Molecular and Cellular Biology. 2008;**28**:5043-5060. DOI: 10.1128/MCB.00304-08

[27] Kang Y, Guo J, Yang T, Li W, Zhang S. Regulation of the human ether-a-go-go-related gene (hERG) potassium channel by Nedd4 family interacting proteins (Ndfips). The Biochemical Journal. 2015;**472**:71-82. DOI: 10.1042/BJ20141282

[28] Li K, Jiang Q, Bai X, Yang YF, Ruan MY, Cai SQ. Tetrameric assembly of K + channels requires ER-located chaperone proteins. Molecular Cell. 2017;**65**:52-65. DOI: 10.1016/J.MOLCEL.2016.10.027

[29] Hu D, Li Y, Zhang J, Pfeiffer R, Gollob MH, Healey J, et al. The phenotypic spectrum of a mutation hotspot responsible for the short QT syndrome. JACC Clinical Electrophysiology. 2017;**3**:727-743. DOI: 10.1016/J.JACEP.2016.11.013

[30] Du C, Zhang H, Harmer SC, Hancox JC. Identification through action potential clamp of proarrhythmic consequences of the short QT syndrome T618I hERG "hotspot" mutation. Biochemical and Biophysical Research Communications. 2022;**596**:49-55. DOI: 10.1016/J.BBRC.2022.01.057

[31] Oliveras A, Roura-Ferrer M, Solé L, De La Cruz A, Prieto A, Etxebarria A, et al. Functional assembly of Kv7.1/Kv7.5 channels with emerging properties on vascular muscle physiology. Arteriosclerosis, Thrombosis, and Vascular Biology. 2014;**34**:1522-1530. DOI: 10.1161/ATVBAHA.114.303801

[32] Hong K, Piper DR, Diaz-Valdecantos A, Brugada J, Oliva A, Burashnikov E, et al. De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. Cardiovascular Research. 2005;**68**:433-440. DOI: 10.1016/J.CARDIORES.2005.06.023

[33] Lee HC, Rudy Y, Liang H, Chen CC, Luo CH, Sheu SH, et al. Pro-arrhythmogenic eof the V141M KCNQ1 mutation in short QT syndrome and its potential therapeutic targets: Insights from modeling. Journal of Medical and Biological Engineering. 2017;**37**:780-789. DOI: 10.1007/S40846-017-0257-X

[34] Adeniran I, Whittaker DG, El Harchi A, Hancox JC, Zhang H. In silico investigation of a KCNQ1 mutation associated with short QT syndrome. Scientific Reports. 2017 Aug 16;**7**(1):8469. DOI: 10.1038/s41598-017-08367-2

[35] D'Avanzo N, Cheng WWL, Doyle DA, Nichols CG. Direct and specific activation of human inward rectifier K+ channels by membrane phosphatidylinositol 4,5-bisphosphate. The Journal of Biological Chemistry. 2010;**285**:37129-37132. DOI: 10.1074/JBC.C110.186692

[36] Jeong DU, Lee J, Lim KM. Computational study to identify the

effects of the KCNJ2 E299V mutation in cardiac pumping capacity. Computational and Mathematical Methods in Medicine. 2020 Mar 31;**2020**: 7194275. DOI: 10.1155/2020/7194275

[37] Du C, Rasmusson RL, Bett GC, Franks B, Zhang H, Hancox JC. Investigation of the effects of the short QT syndrome D172N Kir2.1 mutation on ventricular action potential profile using dynamic clamp. Frontiers in Pharmacology. 2022 Jan 18;**12**:794620. DOI: 10.3389/fphar.2021.794620

[38] Martínez-Barrios E, Cesar S, Cruzalegui J, Hernandez C, Arbelo E, Fiol V, et al. Clinical genetics of inherited arrhythmogenic disease in the pediatric population. Biomedicines. 2022 Jan 5;**10**(1):106. DOI: 10.3390/biomedicines10010106

[39] Thorsen K, Dam VS, Kjaer-Sorensen K, Pedersen LN, Skeberdis VA, Jurevičius J, et al. Loss-of-activity-mutation in the cardiac chloride-bicarbonate exchanger AE3 causes short QT syndrome. Nature Communications. 2017 Nov 22;**8**(1):1696. DOI: 10.1038/s41467-017-01630-0

[40] Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 2007;**115**:442-449. DOI: 10.1161/CIRCULATIONAHA.106.668392

[41] Templin C, Ghadri JR, Rougier JS, Baumer A, Kaplan V, Albesa M, et al. Identification of a novel loss-of-function calcium channel gene mutation in short QT syndrome (SQTS6). European Heart Journal. 2011;**32**:1077-1088. DOI: 10.1093/EURHEARTJ/EHR076

[42] Gélinas R, Leach E, Horvath G, Laksman Z. Molecular autopsy implicates primary carnitine deficiency in sudden unexplained death and reversible short QT syndrome. Canadian Journal of Cardiology. 2019;**35**:1256

[43] Bjerregaard P. Diagnosis and management of short QT syndrome. Heart Rhythm. 2018;**15**:1261-1267. DOI: 10.1016/j.hrthm.2018.02.034

[44] Dewi IP, Dharmadjati BB. Short QT syndrome: The current evidences of diagnosis and management. Journal of Arrhythmia. 2020;**36**:962-966. DOI: 10.1002/JOA3.12439

[45] Zhao Z, Li X, El-Battrawy I, Lan H, Zhong R, Xu Q, et al. Drug testing in human-induced pluripotent stem cell-derived cardiomyocytes from a patient with short QT syndrome Type 1. Clinical Pharmacology and Therapeutics. 2019;**106**:642-651. DOI: 10.1002/CPT.1449

[46] Luo C, Wang K, Zhang H. Modeling the effects of amiodarone on short QT syndrome variant 2 in the human ventricles. Annual International Conference on IEEE Engineering and Medical Biological Society. 2017;**2017**:4273-4276. DOI: 10.1109/EMBC.2017.8037800

[47] Xu Q, Huang X, Meng Z, Li Y, Zhong R, Li X, et al. Antiarrhythmic effects of Vernakalant in human-induced pluripotent stem cell-derived cardiomyocytes from a patient with short QT syndrome Type 1. Journal of Cardiovascular Developmental Diseases. 2022;**9**:112. DOI: 10.3390/JCDD9040112