



# Rare but lethal short QT syndrome: most recent understanding of the disease

## *Síndrome de QT corto, inusual con potencial letal: Revisión reciente de esta enfermedad*

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### ABSTRACT

Short QT syndrome (SQTS) is a rare genetic channelopathy that affects the repolarization of cardiac cells and is associated with cardiac arrhythmia and sudden cardiac death (SCD). "Abbreviated repolarization" is the hallmark of the disease, which is secondary to genetic defects; mutations in several genes that encode different cardiac ion channels have been identified in individuals with the disease. Presentations of the disease include syncope, atrial or ventricular arrhythmia and SCD. SQTS is diagnosed with a corrected-QT (QTc) interval of <340 milliseconds (ms) or a QTc of 340-360 ms and either personal or family history of SCD, family history of SQTS or an identified genetic mutation. Implantable cardioverter-defibrillator (ICD) is the main treatment used in the secondary prevention of SCD in patients with the disease who have experienced previous major arrhythmic events. Pharmacological treatment with quinidine is used as an adjuvant therapy to ICD in the setting of recurrent shocks or as an alternative treatment when ICD is not feasible. The goal of this review article is to describe this rare and under-studied condition, highlight steps to diagnosis and describe treatment modalities, particularly in South America where there is a lack of studies and understanding of this disease.

**Keywords:** genetic, electrocardiogram, sudden cardiac death, ventricular fibrillation, short QT syndrome

### RESUMEN

El síndrome de QT corto es una canalopatía genética que afecta la repolarización de las células cardíacas, asociado a arritmias cardíacas y a muerte súbita cardíaca. El concepto de "repolarización abreviada" es el mecanismo fisiopatológico de esta enfermedad, secundario a defectos genéticos en la codificación de diferentes canales iónicos cardíacos. Esta enfermedad se presenta usualmente con síncope, arritmias auriculares y ventriculares, y muerte súbita cardíaca. El síndrome de QT corto es diagnosticado al hallar un intervalo QT corregido (QTc) <340 milisegundos (ms) o un QTc de 340-360 ms con uno de los siguientes requisitos: historia personal o familiar de muerte súbita cardíaca, historia familiar de síndrome de QT corto o mutaciones genéticas previamente identificadas. El desfibrilador cardíaco implantable es el principal tratamiento utilizado para la prevención secundaria de muerte súbita cardíaca en pacientes diagnosticados con dicho síndrome quienes hayan experimentado episodios de arritmia previos. El tratamiento farmacológico con Quinidina se ha utilizado como terapia adyuvante al desfibrilador cardíaco implantable en el contexto de descargas recurrentes o como terapia alternativa en casos en los que el desfibrilador cardíaco implantable no pueda ser implantado o suponga altos riesgos para el paciente. El objetivo de este artículo de revisión consiste en describir esta infrecuente enfermedad, resaltar los pasos para llegar al diagnóstico y describir las modalidades terapéuticas, particularmente en Suramérica, en donde existen vacíos en el conocimiento en general de esta enfermedad.

**Palabras clave:** genética, electrocardiograma, muerte súbita cardíaca, fibrilación ventricular, síndrome de QT corto

### INTRODUCTION

Short QT Syndrome (SQTS) is a rare inherited condition that has only relatively newly been described; it is caused by a defect in cell membrane ion channels affecting the action potential of cardiac myocytes, and is associated with atrial and ventricular arrhythmias (1). To date, several different genes have been linked to SQTS. Prior the syndrome ever being initially characterized, it was discovered using longitudinal data that a corrected QT (QTc) <400 ms was associated with a 2.4-fold increase in SCD (2). It was only in the year 2000 that short QTc interval was postulated as an inherited arrhythmogenic syndrome after the case of a young female with atrial fibrillation, a QT of 280 ms, and a mother and

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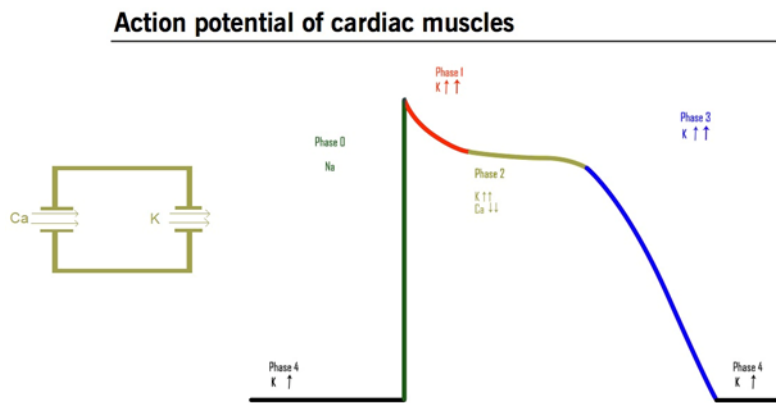
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**Figure 1:** Normal Action potential

Source: Elaborated by the authors

brother who likewise had shortened QT intervals was described (3). Since then, over a 100 cases of SQTS have been reported and awareness of the disease has risen. Despite this rise in awareness, our understanding of this rare syndrome remains limited.

## EPIDEMIOLOGY

Rare diseases in which death can be the initial presentation, such as SQTS, make the true prevalence of these diseases hard to determine. The prevalence of a short QTc interval (not necessarily short QT syndrome) also varies depending on the population and the defining cutoff, further complicating any determination of the prevalence of the disease. Most large cohorts use a QTc cutoff of less than 360 ms. In the United States, a QTc of <360 ms was found in 2% of 46,129 healthy subjects (4). A retrospective study of 486,014 primary care based patients in Brazil found a QTc of <370 ms in 2% of the population (5). Where as in Japan a QTc interval  $\leq 357$  ms in males and  $\leq 364$  ms in females was found in 0.37% of a large cohort (6). A Swiss cohort of 41,767 male army individuals reported a 1% prevalence of short QTc intervals (<347 ms) (7).

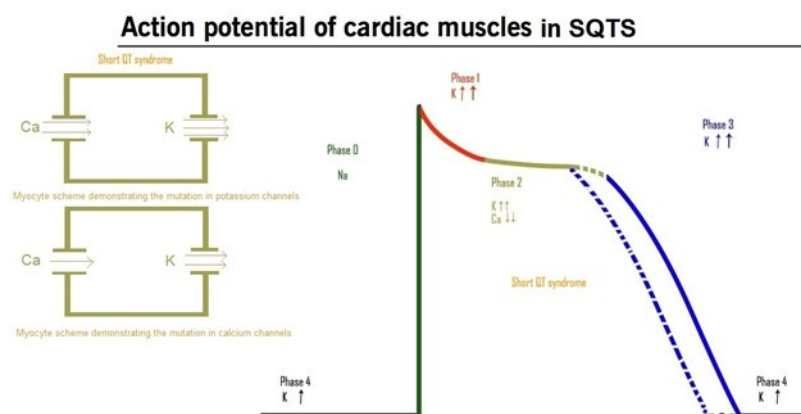
## PATHOPHYSIOLOGY

The "electrical" activity of cardiac myocytes is mainly generated by ion movements through ion channels, creating the cardiac action potential (AP) (8). The depolarizing current starts after the opening of fast sodium channels ( $I_{\text{Na}}$ ) which allow rapid influx of sodium into the cell (8). Repolarizing current is generated by potassium efflux from the cell through potassium channels ( $I_{\text{Kr}}$ ,  $I_{\text{Ks}}$ ,  $I_{\text{K1}}$ ) (8–10). Repolarization plateaus temporarily as a result of calcium ion influx (8,9). (**Figure 1**). The QT interval is a representation of the length of a whole AP cycle. A disturbance in the aforementioned ion channels will affect the length of AP and in turn the QT interval (9,10). Therefore, defects that decrease the function of sodium or calcium channels and/or increase the function of potassium channels would lead to shortening of the QT interval. Several genotypes of SQTS have been described and linked to specific ion channel defects (10); those are summarized in **Table 1**.

**Table 1: Genotypes identified for SQTS with their corresponding ion channelopathy**

SQT variant	Gene	Channel	Amino acid change	Original study	Length QTc (QT) interval
SQT1	KCNH2	I <sub>Kr</sub>	N588K	Brugada et al.	≤300
			T618I	Sun et al.	316±9
			E50D	Redpath et al.	366-381
			I560T	Harrell et al.	319
			R1135H	Itoh et al.	329
SQT2	KCNQ1	I <sub>Ks</sub>	S631A	Akdis et al.	<320
			V307L	Belloccq et al.	302
			V141M	Hong et al.	294
			I274V	Rhodes et al.	-
			F279I	Moreno et al.	356
SQT3	KCNJ2	I <sub>K1</sub>	R259H	Mazzanti et al.	316
			A287T	Rothenberg et al.	333
			D172N	Priori et al.	315-330
			M301K	Hattori et al.	194
			E299V	Deo et al.	200
SQT4	CACNA1C	I <sub>Ca</sub>	K346T	Ambrosini et al.	331
			A39V	Antzelevitch et al.	360
			G490R	Antzelevitch et al.	346-373
SQT5	CACNB2b	I <sub>Ca</sub>	S481L	Antzelevitch et al.	331-370
SQT6	CACNA2D1	I <sub>Ca</sub>	S755T	Templin et al.	330
SQT7	SCN5A	I <sub>Na</sub>	R689H	Hong et al.	320
SQT8	SLC4A3	Anion exchanger AE3 (Cl, HCO <sub>3</sub> -exchanger)	R370H	Thorsen et al.	322-358

Source: Adapted from Priori et al. (2005) (10), Brugada et al. (2004) (11), Sun et al. (2011) (12), Redpath et al. (2009) (13), Harrell et al. (2015) (14), Itoh et al. (2009) (15), Akdis et al. (2018) (16), Belloccq et al. (2004) (17), Hong et al. (2005) (18), Rhodes et al. (2008) (19), Moreno et al. (2015) (20), Mazzanti et al. (2014) (21), Rothenberg et al. (2016) (22), Hattori et al. (2012) (23), Deo et al. (2013) (24), Ambrosini et al. (2014) (25), Antzelevitch et al. (2007) (26), Templin et al. (2011) (27), Hong et al. (2012) (28), Thorsen et al. (2017) (29)

**Figure 2: Action potential in SQTS**

SQTS = Short QT Syndrome.

Source: Elaborated by the authors

Gain of function mutations of genes KCNH2, KCNQ1 and KCNJ2 increase the efflux of potassium (10,11,17). On the other hand, loss of function mutations in CACNB2b, CACNA1C and CACNA2D1 decrease the influx of calcium into the cell (26,27). These mutations and their effects on cellular ion movements decrease the duration of the AP by enhancing repolarization, as evidenced by the ECG finding of short J-point to T-peak interval noticed in some patients with SQTS [Figure 2] (26,27,30). Loss of function mutation in SCN5A causes a decrease in sodium influx thereby shortening the QTc (28). Less than 25% of SQTS cases are explained by cation channel mutations. Other classes of genes, therefore, are likely to be linked with the development of SQTS.(31). However, few other genes mutations have been identified in SQTS that don't directly affect the function of ion channels. Roussel et al. described three patients with SLC22A5 gene mutation, resulting in carnitine deficiency and SQTS, QTc was significantly shortened (282-340) in these individuals and was

corrected with carnitine supplementation. Carnitine deficiency in these individuals is thought to affect the rapid potassium channels (IKr) (30,32). Recently, a “loss of function” mutation in the SLC4A3 gene, which encodes the cardiac chloride-bicarbonate exchanger AE3, was reported by Thorsen et al. to be associated with SQTS. This mutation was associated with an increase in intracellular pH, causing a potential shortening in QTc (29).

## DIAGNOSIS

In 2013, the Heart Rhythm Society/European Heart Rhythm Association/Asian Pacific Heart Rhythm Society expert consensus statement defined a standalone QTc of <330 ms as sufficient to make the diagnosis of SQTS (33). However, since then, Mazzanti et al. (2014) described 73 patients with SQTS including 21 patients with a QTc > 330, supporting a previously published study by Giustetto on the presence of the disease in patients with a higher QTc (21,34). The European Society of Cardiology in 2015 suggested a QTc of <340 as diagnostic of SQTS (Class of recommendation I, Level of evidence C) (35). The diagnosis of SQTS in patients with QTc 340-360 ms is suggested by short QTc plus one of the following (Class of recommendation IIa, Level of evidence C) (35):

- A confirmed pathogenic mutation
- A family history of SQTS
- A family history of sudden death at age <40 years
- Survival from a VT/VF episode in the absence of heart disease

Another diagnostic criterion proposed by Giustetto et al. (2015) for patients with a QTc 340-360 ms is poor adaptation (poor expected shortening) of the QT interval to an increase in heart rate. In Giustetto et al. study, 21 individuals with SQTS were studied and noticed to have decreased QTc adaptation in response to exercise ( $\Delta$ QTc at rest—QT at peak was  $48 \pm 14$ ms in SQTS patients versus  $120 \pm 20$ ms in the normal control group) (36). This study was limited by fact that the control group was composed of healthy individuals with normal QTc rather than non-SQTS individuals with short QTc.

## ARRHYTHMOGENESIS IN SQTS

Net inward depolarization currents, outward repolarization currents or a combination of both explain the shortening of the action potential leading to SQTS. The most common depolarization channels involved are the  $I_{Na}$  and  $I_{Ca}$ . For repolarization channels,  $I_{to}$ ,  $I_{K1}$ ,  $I_{K-ATP}$ ,  $I_{ACh}$ ,  $I_{Kr}$ , or  $I_{Ks}$  represent the most commonly involved in SQTS. An increase in the transmural dispersion of repolarization caused by defective ion channels has been described as a cause for cardiac circuit reentry and arrhythmia, creating a unidirectional block and also shortening the action potential. This effect was first described in experimental studies involving canine models, where specific  $I_{kr}$  agonists were administered causing a shortening of the SQTS and leading to an increase in the transmural dispersion of repolarization (37). Factors such as the shortening of wave length can also explain the maintenance of the refractory period, as described by Patel, Yan and Antzelevitch (2010). Mutations involving a loss of function in inward  $I_{Ca-L}$  channels and gain of function in outward K channels may shorten the QT interval as well (37).

## SCREENING AND RISK STRATIFICATION

Identifying individuals with SQTS is essential for implementing adequate and appropriate treatment and prevention strategies. A proposed scoring system developed by Gollob, Redpath and Roberts (2011) is helpful for stratifying high-risk individuals (38). This system, however, remains difficult to validate due to the small number of people with SQTS but is a helpful tool in identifying high-risk patients. This scoring system was modified by Villafane et al. (2013) and validated in 25 patients (**Table 2**) (39).

ECG screening is recommended for newborns with a family history of SQTS (40). Genetic testing is only recommended for those subjects with a high suspicion of SQTS (1). Invasive strategies such as routine electrophysiological study are not recommended since they have not showed a clear benefit in both diagnostic yield and in risk stratification (1).

**Table 2:** Modified Gollob's score for identifying patients with high risk to develop symptoms

Criteria	Points
<b>QTc, milliseconds</b>	
<370	1
<350	2
<330	3
J-point to T-peak interval <120 milliseconds	1
<b>Family history*</b>	
First- or second-degree relative with high probability of SQTs	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
<b>Genotype*</b>	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

Individuals with a score of 5 or more were symptomatic.

Source: Adapted from Villafane et al. (2013) (39)

## MANAGEMENT

Management of SQTs is based on expert consensus recommendations due to the lack of clinical trials. Current guidelines do not support primary prevention for patients without a previous episode of SCD. However frequent follow-up and referral to an electrophysiology specialist may be recommended in those asymptomatic individuals (39). In patients with SQTs who survived cardiac arrest, ICD placement is always recommended for secondary prevention of SCD (Class I recommendation according to AHA/ACC/HRS, ESC, and HRS/EHRA/APHRs guidelines) (1,33,35). These patients have a high incidence of recurrence of SCD. In a small study published by Giusteto et al. (2011) and Villafane et al. (2018), 18% of patients with SQTs and ICD implantation experienced appropriate ICD treatment during short term follow-up (34,39,41). However, patients with SQTs are prone to inappropriate shocks with the conventional programming of the ICD due to double sensing of the QRS complex and the short, sharp and high amplitude T-wave. Revision of programming with reduced sensitivity levels and decay delays effectively limited T wave oversensing (42,43). Medical treatment is used as an adjuvant therapy to ICD for patients with recurrent shocks, those who refuse ICD placement or patients with contraindications to ICD. Quinidine has been described as the optimal medical treatment for SQTs. In fact, several small studies showed normalization or prolongation of the QTc interval with quinidine (1,34,44–46). In addition, it has been shown to decrease the frequency of shocks in those with ICDs (1,34,45,46). Isoproterenol infusion can be effective in terminating electrical storm with refractory ventricular arrhythmia and restoring normal rhythm (Class II recommendation for this according to AHA/ACC/HRS guidelines) (1). In a small cohort of patients evaluated by Hong et al. (2005) (47), propafenone was found to be effective in treating atrial fibrillation in patients with SQTs (10). Multiple other medications (amiodarone, ibutilide, sotalol, flecainide, and metoprolol) have been described in individual case reports or in vitro studies but have not been replicated (12,31,34,48–50).

## CONCLUSIONS

Short QT syndrome is a rare genetic channelopathy that can manifest at any age. Affected individuals might be asymptomatic or might suffer from syncope or atrial or ventricular arrhythmias. Several genetic mutations have been identified and linked to SQTs. Diagnostic criteria for the disease have evolved over the years since the syndrome was discovered as new studies and research continue to emerge. Diagnosis is made in an asymptomatic individual with a QTc of <340 ms or an individual with a QTc of 340-360 and a positive gene mutation or a family history of SCD or SQTs or a personal history of SCD. ICD implantation and/or quinidine are recommended for secondary prevention of SCD. Primary prevention of SCD is controversial. Our understanding of the disease is very limited and mainly based on case series and small studies primarily done in Europe and the USA; very few cases have been reported in Latin American populations. Increased awareness of the syndrome is crucial to allow for the identification of a larger cohort needed for the conduction of bigger studies to increase our understanding of this deadly syndrome; this is especially true in Latin America where there is a lack of information regarding the diagnosis and treatment of this severe condition.

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