

Table 1. EHRA/HRS/APHRS/LAHS 2022 Consensus Statement on genetic testing. Genes implicated in short QT syndrome (SQTS)

Gene	Locus	Phenotype—syndrome	Protein (functional effect)	Frequency	ClinGen classification
<i>KCNH2</i>	7q35-36	SQTS/AD	Increase in I_{Kr} channel function	<10%	Definite
<i>KCNQ1</i>	11p15.5	SQTS/AD	Increase in I_{Ks} channel function	5%	Strong
<i>KCNJ2</i>	17q23	SQTS/AD	Increase in I_{K1} channel function	$\pm 1\%$	Moderate
<i>SLC4A3</i>	2q35	SQTS/AD	pH ($\uparrow$) and Cl^- ($\downarrow$)	<1% ^a	Strong-moderate ^b

Functional effect: ($\downarrow$) loss-of-function or ($\uparrow$) gain-of-function at the cellular *in vitro* level.

BrS, Brugada syndrome; SQTS, short QT syndrome.

^aMight be significantly higher (personal communication AAMW and MG).

^bClassification discussed between members of the Clin Gen curation panel. Maybe become strong based on new data (personal communication AAMW and MG).

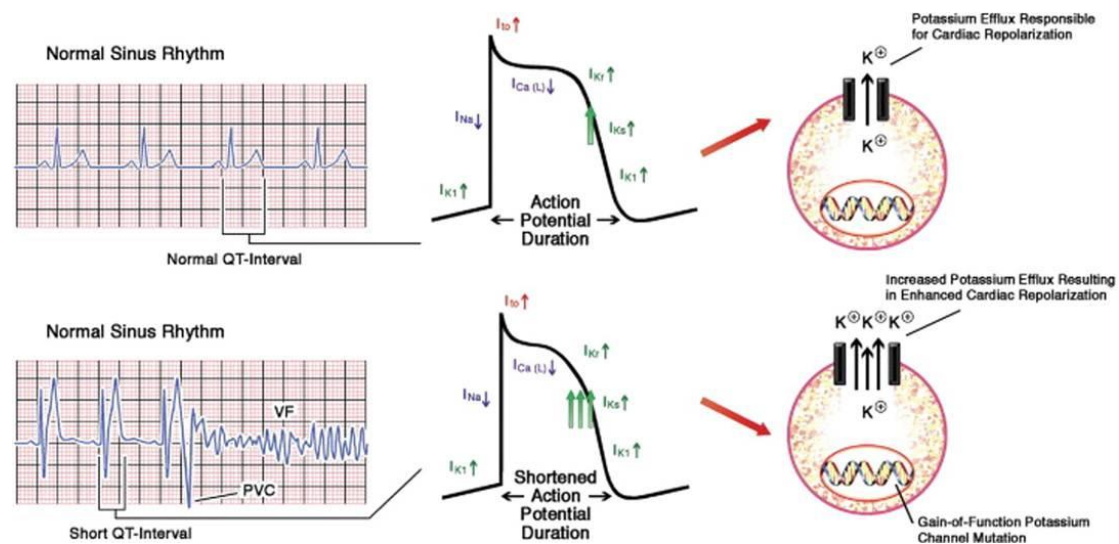


Figure 1. Cellular Mechanism of Short QT Interval.

A gain-of-function potassium channel mutation results in an increased efflux of potassium current from the cell resulting in an acceleration of cardiomyocyte repolarization and a shortened action potential duration. Additional cellular mechanisms, possibly due to nonpotassium channels, remain to be elucidated.

Gollob MH, et al. The short QT syndrome: proposed diagnostic criteria. *J Am Coll Cardiol.* 2011;57:802-12.

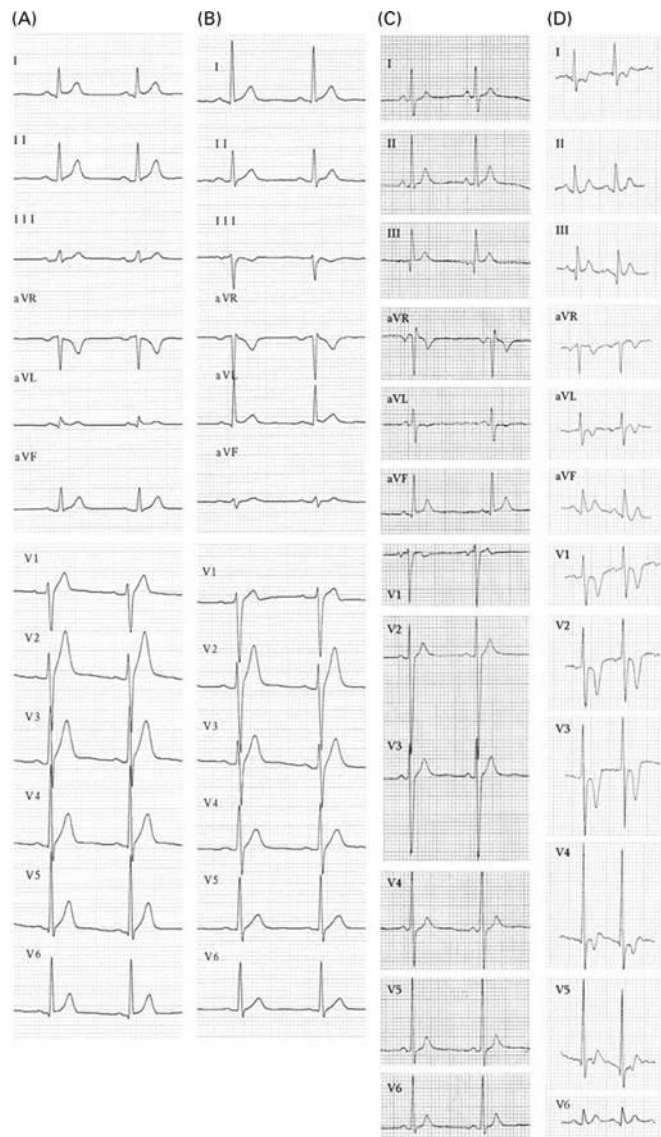


Figure 2. ECG of four patients with SQTS

A: 50 years, QTc 313 ms

B: 39 years, QTc 311 ms

C: 6 years, QTc 293 ms

D: 35 months, QTc 324 ms. Heart rate is 143 bpm. The deep negative T waves in leads V1–V3, are the equivalent of the high peaked T-waves in adult patients.

Giustetto C, et al. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. *Eur Heart J* 2006; 27: 2440–47.

Table 2. Diagnosis**ESC 2022 GL on VA and SCD. Recommendations for the management of patients with short QT syndrome****Diagnosis**

SQTS is diagnosed in the presence of a QTc ≤ 360 ms and one or more of the following: I C

(a) a pathogenic mutation,

(b) a family history of SQTS,

(c) survival from a VT/VF episode in the absence of heart disease

Genetic testing in patients diagnosed with SQTS I C

SQTS considered in the presence of a QTc ≤ 320 ms IIa C

SQTS considered in the presence of a QTc ≥ 320 ms and ≤ 360 ms and arrhythmic syncope. IIa C

SQTS considered in the presence of a QTc ≥ 320 ms and ≤ 360 ms and a family history of SD at age <40 years. IIb C

Table 3. Genetic testing**AHA/ACC/HRS 2017 GL on VA/SCD. SQTS**

Genetic counseling and mutation-specific genetic testing in first-degree relatives of patients who have a causative mutation for SQTS I-B-NR

In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives IIb-C-EO

EHRA/HRS/APHRS/LAQRS 2022 Consensus Statement on genetic testing.**Impact of genetic testing for the index case**

Disease	Diagnostic	Prognostic	Therapeutic
SQTS	+	+	+

Recommendations**Should do**

In any patient satisfying the diagnostic criteria for SQTS (such as Class 1 clinical diagnosis or SQTS diagnostic score >4), molecular genetic testing for the definitive disease associated genes (currently KCNH2, KCNQ1).

Variant-specific genetic testing for family members and appropriate relatives following the identification of the disease-causative variant.

May do

Testing of KCNJ2 and SLC4A3 in all index patients in whom a cardiologist has established with a high probability a diagnosis of SQTS, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline or during ECG Holter recording and exercise stress test (SQTS diagnostic score ≥ 4 *).

Predictive genetic testing in related children in specific settings.

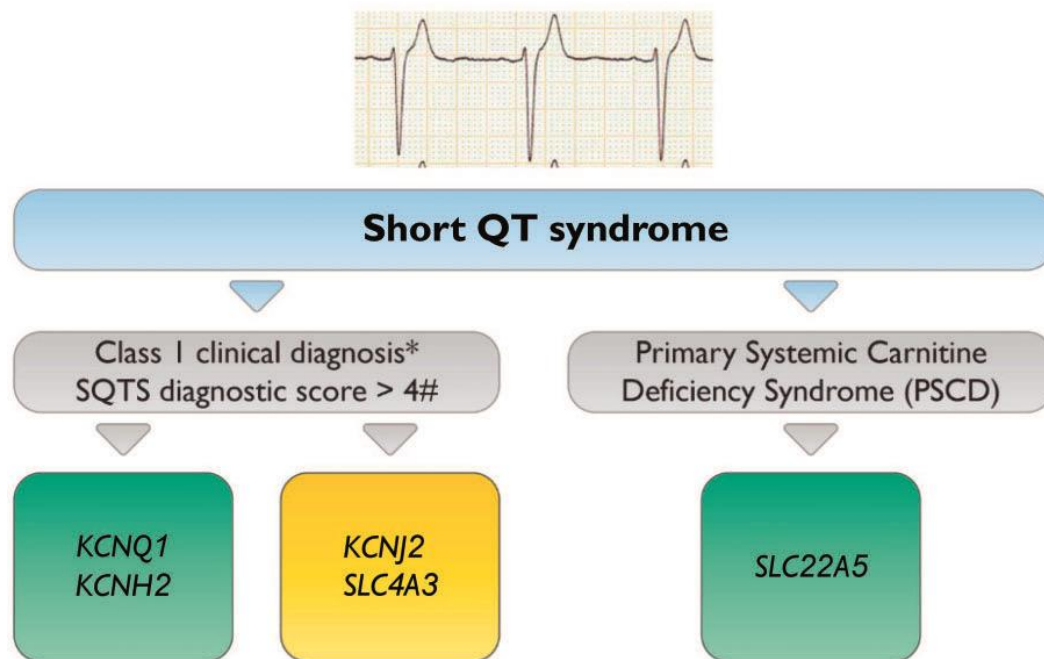


Figure 3. EHRA/HRS/APHRS/LAQRS 2022 Consensus Statement on genetic testing.
Clinical algorithm for genetic testing and family screening in short-QT syndrome

Table 4. Therapy of SQTS**AHA/ACC/HRS 2017 GL on VA/SCD. SQTS**

In asymptomatic patients with a short QTc interval, observation without treatment	I-B-NR
ICD in patients with a cardiac arrest or sustained VA	I-B-NR
Quinidine in patients with recurrent sustained VA	IIa-C-LD
Isoproterenol infusion in VT/VF storm	IIa-C-LD

ACC/AHA/HRS 2017 GL on syncope. SQTS

ICD in patients with short-QT pattern and syncope of suspected arrhythmic etiology.	IIb-C-EO
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ESC 2022 GL on VA and SCD. Recommendations for the management of patients with short QT syndrome***Risk stratification, SCD prevention and treatment of VA***

ICD in patients with a diagnosis of SQTS who: (a) are survivors of an aborted CA and/or (b) have documented spontaneous sustained VT.	I C
ILR in young SQTS patients.	IIa C
ICD implantation in SQTS patients with arrhythmic syncope.	IIa C
Quinidine in (a) SQTS patients who qualify for an ICD but present a contraindication to the ICD or refuse it, and (b) asymptomatic SQTS patients and a family history of SCD.	IIb C
Isoproterenol in SQTS patients with an electrical storm	IIb C
PES is not recommended for SCD risk stratification in SQTS patients.	III C

CA, cardiac arrest; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder, SCD, sudden cardiac death; SD, sudden death; SQTS, short QT syndrome; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia