Short QT Syndrome

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11.1 Introduction

In 2000, Gussak et al. described an idiopathic short QT interval associated with atrial fibrillation in a family and sudden death in an unrelated individual.[1] Three years later, in 2003, Gaita et al. reported the association of a short QT interval and sudden cardiac death in two unrelated European families.[2] Within the following years, mutations in five different genes causative for the short QT interval were identified. The mutations either cause a gain of function of cardiac potassium channels I_{Kr}, $I_{Ks,}$ and I_{K1}, or a loss of function in the cardiac L-type calcium channel (I_{Ca}).[3–6]

The scope of this chapter is to provide a comprehensive description of the short QT syndrome (SQTS) including the clinical, genetic, and pathophysiologic aspects, as well as therapeutic consequences and treatment options.

11.2 Molecular and Genetic Background

The SQTS is a genetically heterogeneous disease just like the congenital long QT syndrome. By now, mutations in five different genes have been identified.[3–6] The mutations are located on chromosomes 7, 10, 11, 12, and 17 and encode for different cardiac ion channels. According to the chronology of their first description, the mutations are termed SQT1 to SQT5 (Table 11.1).

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The first mutation identified to be causative for the short QT syndrome (SQT1) was a gain of function mutation leading to an increase of the rapid component of the delayed rectifier potassium current (I_{Kr}).[7] Two different missense mutations were identified resulting in the same amino acid change in HERG (KCNH2). These mutations at nucleotide 1764 in the KCNH2 gene substitute the asparagine at codon 588 for a positively charged lysine (N588K). The residue is located in the S5-P loop region of HERG at the outer mouth of the channel. The N588K mutation causes a loss of the normal rectification of the current at plateau voltages, which results in a significant increase of I_{Kr} during phase 2 and 3 of the action potential leading to abbreviation of the action potential and both, atrial and ventricular refractoriness.

Genetic heterogeneity in SQTS was stressed by findings of Bellocq et al. in 2004 who identified a mutation in a single sporadic case of a 70-year-old patient with SQTS (QTc 302 ms) and sudden cardiac arrest. They identified a gain-of-function mutation (V307L) in the KCNQ1 gene, which encodes the slow component of the delayed rectifier potassium channel (I_{Ks}) (SQT2). The mutation causes a −20 mV shift of the half-activation potential and acceleration of the activation kinetics and activation of the mutant channels at more negative potentials. This results in a gain of function of I_{Ks} and abbreviation of the action potential. A further missense mutation in the same gene (V141M) was identified in a baby with bradycardia and atrial fibrillation in utero.[3] The ECG revealed a shortened QT interval and episodes of atrial fibrillation.

The third mutation responsible for SQTS was identified in 2005 by Priori and coworkers in two relatives without sudden cardiac arrest (SQT-3).[4] A gain of function in KCNJ2, encoding the inward rectifier potassium channel (I_{K1}), causes abbreviation of the QT

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Table 11.1 Short QT subtypes

SQT	Gene	Channel
SQT1	KCNH2	IKr
SQT2	KCNQ1	IKs
SQT3	KCNJ2	IK1
SQT4	CACNA1C	ICa
SQT5	CACNB2b	ICa

interval and asymmetrical T waves with a rapid terminal downslope.

Recently, novel mutations of the cardiac L-type calcium channel genes responsible for shortening of the QT interval in families characterized by sudden cardiac death, atrial fibrillation, and a Brugada type I ECG pattern have been reported.[5] Functional analyses revealed loss of function missense mutations of the CACNA1C (A39V and G490R) and CACNB2b (S481L) genes encoding the pore forming of $Ca_v1.2$ α1- and β2b-subunits of the cardiac L-type calcium channel. The decreased net current of the cardiac L-type calcium channels leads to an abbreviation of the plateau phase of the action potential and thus to a short QT interval.

11.3 Epidemiology and Prevalence

To date, there is no clear-cut definition of what a short QT syndrome is mainly because the lower cut-off for the normal has not been defined in a consensus. There have been some suggestions based on the distribution of QT intervals in large populations using, for example, two standard deviations as a cut-off. However, larger diseases populations will have to be awaited to draw conclusions regarding cut-offs. It can, however, be stated here that a short QT interval is not the same as a QT syndrome.

In the general population, QTc intervals follow a Gaussian normal distribution.[8–11] Normal QT intervals were proposed as QTc intervals within two standard deviations from the mean.[12] Thus, 95% of the QTc intervals of the general population are "normal." QTc shorter than the 2.5th percentile were defined as "short." Following this calculation, QTc of <350 ms for men and QTc < 360 ms for women are considered short. For children, no specific data is available or has been discussed so far with respect to lower limits of the normal. Schulze-Bahr proposed 310 ms as the lower limit for QT interval. In large population-based studies, the prevalence of a short QT interval was analysed. Within an Italian predominantly male cohort, the prevalence of a QTc <360 ms was 0.5%.[10] Anttonen et al. analysed a population of 10,822 subjects and found short QTc intervals of <340 ms in 0.4% of the subjects. Very short QTc intervals <320 ms were seen in 0.1% of the cases. Patients with both a short and a very short QTc interval had no cardiac events.[8] In a Japanese cohort of 12.149 subjects, 0.01% exhibited a QTc interval within the 2.5th percentile (men QTc < 354 ms; females <364 ms) and only three male subjects (0.03%) a QTc of <300 ms.[9] In another recent analysis of 19,153 subjects undergoing biannual health examinations in the follow-up program in Hiroshima and Nagasaki since 1958, the prevalence for a short QT interval (QTc < 350 ms) was 0.01%.[13] Recently, Kobza et al. found a similar low prevalence of 0.01% of QTc intervals <320 ms in 41,767 male army conscripts.[11]

We cannot give any explanation for the difference between the study groups. A short QT interval does not necessarily mean that it is per se pathological or that one deals with the short QT syndrome. By now approximately 50 patients have been diagnosed worldwide with the short QT syndrome. The QTc intervals of these patients are ranging from <300 ms up to <360 ms. This indicates that there is a large overlap of patients with short QT intervals and patients with the short QT syndrome, as no clear cut-off value exists.

In summary, a short QT interval on the 12-lead ECG does not predict a risk for life-threatening tachyarrhythmias per se. However, the rare finding of a short QT interval should initiate a diagnostic work-up, including among family members. In the case of a short QT interval together with episodes of atrial fibrillation, sustained palpitation, unexplained syncope, ventricular fibrillation, and/or a positive family history for premature sudden cardiac death, short QT syndrome should be suspected.

11.4 Pathophysiology

After the identification of the underlying mutations and affected cardiac ion channels, the cellular basis and arrhythmogenesis in SQTS was examined.

The first experiments in transmural left ventricular wedge preparations and Langendorff heart preparations were performed using pinacidil, an activator of $I_{K\text{-}ATP}$ as no specific I_{Kr}, $I_{Ks,}$ or I_{K1} agonists were available.[14, 15] Under pinacidil, QT interval was shortened and transmural dispersion of repolarization increased. The action potential was abbreviated heterogeneously among different cell types spanning the ventricular wall and thus open the window for the genesis for polymorphic ventricular tachycardia (phase 2 reentry). Transmural dispersion of repolarization was associated with the inducibility of ventricular tachyarrhythmias. Quinidine application was able to reduce monophasic action potential duration, and dispersion of repolarization.[15]

Recently, a specific agonist of I_{Kr} PD-118057 became available. In LV wedge preparations, this agent was able to abbreviate the QT interval significantly, increased T wave amplitude and transmural dispersion of repolarization. Furthermore, a shortening of the effective ventricular refractoriness as known from the SQTS patients was observed. Under PD-118057, polymorphic VT were inducible in 50% of the cases compared to none in the control group. Quinidine therapy was able to prolong QT interval and to suppress the inducibility of polymorphic VT. However, the transmural dispersion of repolarization remained unchanged. Presumably, the suppression of inducibility of ventricular tachyarrhythmias by quinidine is caused by the increase in action potential duration and ventricular effective refractory periods.

11.5 Clinical Aspects and Clinical Diagnosis

11.5.1 Clinical Presentation

The clinical presentation of patients with SQTS is heterogeneous.[15] The most comprehensive data were presented by Giustetto et al. including patients with SQTS from the EUROSHORT registry.[16] Patients may be asymptomatic or present with benign symptoms like recurrent palpitations. Other clinical manifestations are atrial fibrillation or unexplained syncope (Fig. 11.1). The most frequent initial symptom in patients with SQTS was sudden cardiac arrest/death.[16] The onset of symptoms is highly variable reaching from the age of 4 months up to the age of 62 years and distributed over all decades of life. Sudden deaths occurred in the youngest patient at the age of 4 months. Thus, SQTS represents an additional cause for the sudden infant death syndrome (SIDS).

The hallmark of diagnosis is short QT interval on baseline ECG. QTc intervals of < 350 ms for males and <360 ms for females should gain attention and warrants further clinical work-up. In coincidence with the clinical symptoms such as atrial fibrillation, sudden cardiac death, family history of SQTS, or sudden cardiac death, the diagnosis of SQTS is established.

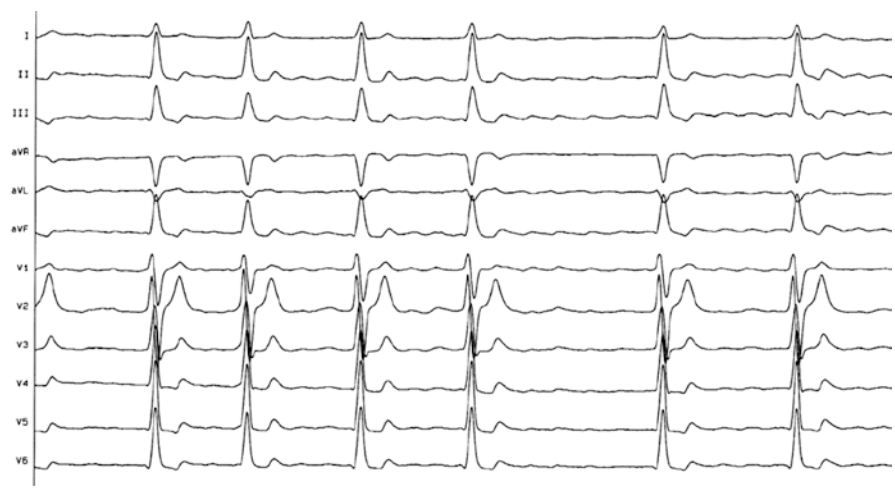

Fig. 11.1 This figure depicts the 12-channel ECG of a patient with SQT1 and atrial fibrillation

11.6 Diagnosis of Short QT Syndrome

The electrocardiogram of the first patients identified with a SQTS (SQT1) showed very short QT intervals and in addition short QT intervals corrected for heart rate (QTc <300 ms). The patients identified as SQT2 – SQT5 exhibited QTc of up to 360 ms. The ECG in SQT1-3 reveals tall, symmetrical, and asymmetrical peaked T wave especially in the precordial leads (Fig. 11.2). In SQT3, the T wave has a less steep ascending part and a steep downslope.[4] In most cases, a ST segment is absent with the T wave originating directly from the S wave. Another finding in SQTS is a prolonged $T_{peak} - T_{end}$ interval. Recently, Anttonen et al. compared the $J_{point} - T_{peak}$ interval in symptomatic patients with SQTS, probands with a short QT interval, and a control group of subjects with normal QT interval.[17] Symptomatic patients with SQTS had significantly shorter $J_{point} - T_{peak}$ intervals and higher corrected $T_{peak} - T_{end}$/QTc ratio compared to asymptomatic probands with a short QT interval and subjects with a normal QT interval. Patients diagnosed with SQT4 and SQT5 on the basis of a mutation in the cardiac calcium channel exhibit shorter than normal QT intervals of 330–360 ms, which is relatively longer than in SQT1–SQT3. These patients additionally show ST segment elevation diagnostic of Brugada syndrome either spontaneously or after the administration of intravenous ajmaline.[5]

Another important finding in SQT1 is the inappropriate adaptation of the QT interval to heart rate. In patients with SQTS the QT interval does not shorten adequately compared to normal controls.[18]

Quinidine was able to restore the QTc/heart rate ratio toward the normal range. A lack of adaptation of QT interval with heart rate may be one additional criterion for the diagnosis of SQTS.

A further diagnostic tool in SQTS is the electrophysiological study. Atrial and ventricular effective refractory periods are significantly shortened especially in SQT1. Atrial refractory period of 140 ms and ventricular effective refractory period of 150 ms or less are highly suspicious criteria of the SQTS. Another finding is the high inducibility of ventricular fibrillation during programmed ventricular stimulation in patients with SQTS (Fig. 11.3).[16]

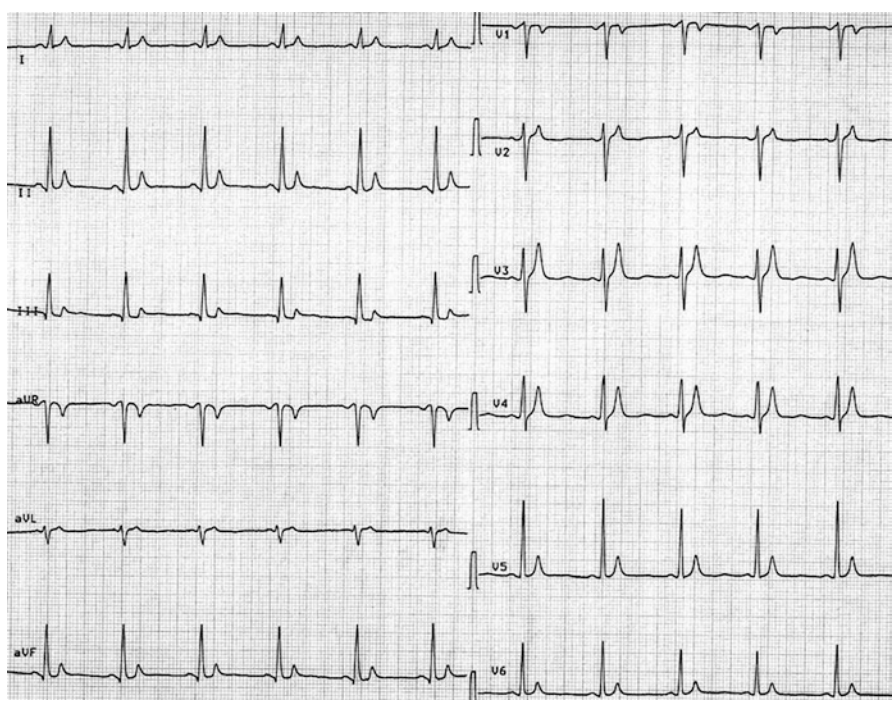

Fig. 11.2 In this ECG one can appreciate the typical T wave morphology of a patient with SQT1

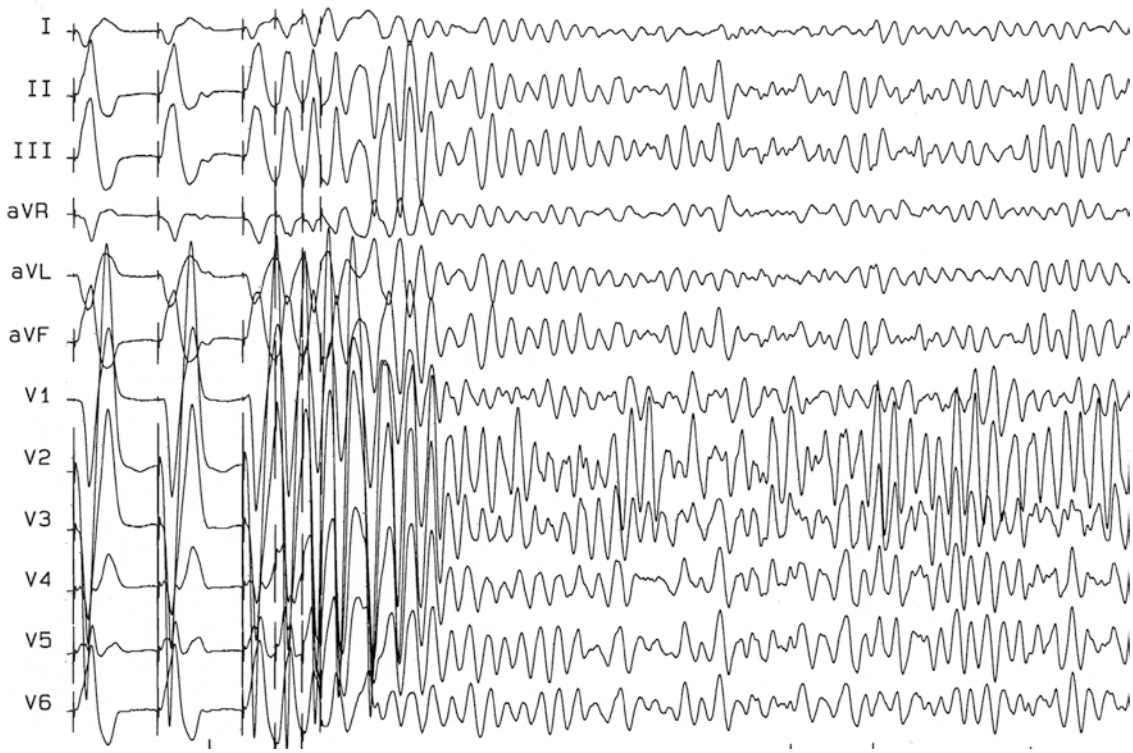

Fig. 11.3 This figure depicts the induction of ventricular fibrillation in a patient with SQT1 using triple extrastimuli with very short coupling intervals

11.7 Differential Diagnosis

The heritable SQTS should be differentiated from the acquired or secondary forms of QT shortening. Documentation of a short QT interval on the ECG should therefore lead to the exclusion of structural heart diseases and underlying conditions such as hyperkalemia, hypercalcemia, hyperthermia, the period immediately following VF, acidosis, and/or digitalis overdose.[19] Furthermore, structural heart disease, especially dilated cardiomyopathy, should be ruled out.[20]

11.8 Therapy, Follow-up, and Prognosis

11.8.1 Pharmacologic Therapy of Short QT Syndrome

After the identification of the genetic background and the cellular mechanisms of the SQTS clinical and experiment studies have been conducted with respect to the pharmacologic treatment. However, data on the pharmacology treatment of patients with SQTS are still limited with respect to the clinical use and long-term outcome because of the low number of patients diagnosed with SQTS at the moment.

Most of the experiences in vitro and in vivo are available for SQT1. Heterogeneous expression studies exhibited that the N588K mutation increased the density of I_{Kr} and reduced the affinity of I_{Kr} blockers like D-sotalol 20-fold.[7] Thus, in vitro experiments could proof the failure of D-sotalol restoring QT interval in vivo. McPate et al. could demonstrate that the effect of E-4031, a specific I_{Kr} blocker, was also significantly attenuated by the N588K mutation, whereas quinidine was less and disopyramide the least affected by N588K-HERG.[21] Cordeiro et al. could nicely show that these findings are based on the +90mV shift in the voltage-dependence of inactivation of the HERG channels. Most I_{Kr}-blockers interact with the HERG channels in the inactivated state. Thus, a failure of inactivation of the HERG channel leads to the inefficacy of the specific

I_{Kr} blockers.[22] Recently, McPate et al. could demonstrate that besides disopyramide and quinidine, propafenone and amiodarone also were only slightly inhibited by the mutant N588K.[21] Thus, these drugs may serve as an additional option in the pharamacologic treatmet of SQT1. For SQT3 El Harchi et al. could identify in in vitro experiments that chloroquine is an effective pharamcologic inhibitor of the SQT3 D172N mutant Kir2.1.[23]

In the clinical setting, several class I and III antiarrhythmic drugs have been tested in patients with the gain of function mutation in HERG (SQT1).[7,11,24] For class III antiarrhythmics, neither D-sotalol nor ibutilide were able to prolong QT interval. Flecainide, a Na+channel blocker, which has in addition a blocking effect on I_{Kr} and on the transient outward potassium current (I_{to}), led to an increase in ventricular effective refractory periods. However, acute administration of flecainide did cause prolongation of refractoriness and only slight prolongation of the QT interval.[24] In contrast, the class I antiarrhythmic agent quinidine, was able to normalize the QT interval and to prolong the ventricular effective refractory period in patients with a SQT1.[18] Additionally, quinidine restored the heart rate dependence of the QT interval toward the normal range and rendered ventricular tachyarrhythmias non-inducible in patients in whom baseline electrophysiological studies demonstrated reproducible inducibility of ventricular fibrillation.[18,24] Following the positive effects of disopyramide in in vitro experiments, disopyramide has also been shown to be effective in a pilot study in patients with a SQT1.[21,25] No patient on quinidine therapy suffered from ventricular fibrillation or a recurrence of atrial fibrillation during mid-term follow-up.[16,26] A subset of patients treated with propafenone is free of recurrences of atrial fibrillation without prolongation of the QT interval. Whether quinidine, propafenone, or disopyramide represent an alternative to ICD therapy in prevention of sudden cardiac death cannot be finally answered. Drugs may be an alternative in patients refusing ICD implantation or for those who are not eligible for ICD therapy. In addition, drugs can be given to ICD-bearing patients who experience recurrent electrical shocks.

Whether the effects of the investigated class I and III drugs can be translated to SQT2–SQT5 is not clear. However, in a patient with SQT4 quinidine was able to prolong QT interval and suppress paroxysms of atrial fibrillation.

Due to the electrophysiological and genetic heterogeneity of the SQTS, therapy may have very different effects depending on the type of mutation and the affected channel. Further studies of pharmacologic therapy are warranted to elucidate the potential long-term benefit of pharmacologic treatment. However, such studies are complicated by the low number of SQTS patients identified so far, especially in SQT2 and SQT3.

11.8.2 ICD Therapy

By now the only reliable treatment to prevent patients from sudden cardiac death is the implantation of an implantable cardioverter-defibrillator (ICD). In symptomatic patients with SQTS, the ICD is the therapy of choice, while antiarrhythmic drug therapy may represent an adjunct or an alternative therapy in children or in newborns where ICD implantation is technically challenging and often associated with high morbidity. The risk for inappropriate ICD discharges due to T wave oversensing is increased in patients with SQTS compared to other conditions with ICD implanted, since intracardiac T waves are high and closely coupled to the preceding R wave. This issue can be solved by individual ICD programming of the sensing parameters and selection of specific devices. Additionally, quinidine therapy helped to avoid T wave oversensing by increasing the QT interval.[27]

11.9 Risk Stratification and Indication for ICD

Since the number of patients with SQTS is still low, we are lacking reliable data and relevant follow-up duration for a conclusive statement on risk stratification. In patients with a short QT interval in the presence of syncope of unknown origin or aborted sudden cardiac death an implantation of an ICD is indicated. In asymptomatic patients the indication for primary prophylactic ICD implantation is not clear. In the families with SQT1 most of the asymptomatic relatives with SQTS underwent primary prophylactic ICD due to the high incidence of familiar sudden death and syncope. Whether the family history of sudden cardiac death

associated with a short QT interval serves as a risk factor is unknown. As stated above inducibility at programmed stimulation is high, which may be explained by the extremely short refractory periods. However, whether the inducibility of ventricular arrhythmias is predicting future cardiac events is doubtful. In the only patient with SQTS receiving an appropriate ICD shock so far, ventricular tachyarrhythmias were not inducible.[26] Whether the degree of QT interval shortening can be used as a marker of risk is still unknown.

11.10 Cardiogenetics Aspects

Because of the high genetic heterogeneity in SQTS and the low number of patients, a genotype–phenotype correlation cannot be established. Furthermore, only approximately 25% of patients diagnosed with SQTS were carriers of an underlying potassium or calcium channel mutation. This suggests that other, unknown, genetic defects may be involved. After the identification of a patient with SQTS, genetic analysis should be attempted and family screening initiated, irrespective of having a causal mutation found.

11.11 Summary

The SQTS is one of the primary electrical diseases of the heart with a high incidence of syncope and sudden cardiac death. The hallmark for the diagnosis is a short QT interval on the baseline ECG with a QTc <350 ms for males and a QTc < 360 ms for females, respectively-. Until now, approximately 50 patients have been identified worldwide. Because of the limited number of patients and the genetic heterogeneity of the disease, strong genotype–phenotype correlation and a conclusive risk stratification are not yet available. The class I antiarrhythmic drug quinidine was shown to prolong QT interval and refractoriness and rendered previously inducible ventricular tachyarrhythmias non-inducible. The only reliable treatment so far in the prevention of sudden cardiac death is the implantation of an ICD and anyone with the diagnosis of symptomatic SQTS should have an ICD implanted. In addition, patients with SQTS should be referred for genetic counseling, molecular genetic analysis, and initiation of family screening.

Take Home Message

- SQTS is a very rare but potentially highly malignant disease.
- SQTS should be considered in anyone with a QT < 350 ms without potential other causes.
- One always must think about SQTS in the following special cases:
  - Aborted cardiac arrest or sudden cardiac death of unknown origin
  - Atrial fibrillation at young age

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