ESC European Society of Cardiology

Europace (2018) **20**, f113–f121
doi:10.1093/europace/eux186

Multiple clinical profiles of families with the short QT syndrome

D. Akdis[1], A. M. Saguner[1], A. Medeiros-Domingo[2], A. Schaller[3], C. Balmer[4], J. Steffel[1], C. Brunckhorst[1], and F. Duru[1]*

[1]Department of Cardiology, University Heart Center Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland; [2]Department of Cardiology, Inselspital Bern, University Hospital Bern, Freiburgstrasse 8, CH-3010 Bern, Switzerland; [3]Division of Human Genetics, Department of Pediatrics, Inselspital Bern, University Hospital Bern, Freiburgstrasse 8, CH-3010 Bern, Switzerland; and [4]Department of Cardiology, University Children's Hospital Zurich, Steinwiesstrasse 75, CH-8032 Zürich, Switzerland

Received 18 December 2016; editorial decision 2 May 2017; accepted 3 June 2017; online publish-ahead-of-print 19 July 2017

Aims Short QT syndrome (SQTS) is a rare cardiac channelopathy characterized by a shortened corrected QT (QTc)-interval that can lead to ventricular arrhythmias and sudden cardiac death. The aim of this study was to investigate the clinical phenotypes and long-term outcomes of three families harbouring genetic mutations associated with the SQTS.

Methods and results Clinical data included medical history, physical examination, 12-lead ECG, 24-h Holter-ECG, and transthoracic echocardiography from three index patients and their first-degree relatives. Next generation clinical exome sequencing and genetic cascade screening were performed in index patients and their relatives, respectively. Two index patients experienced malignant ventricular arrhythmias and one patient suffered from arrhythmogenic syncope during a median follow-up period of 8 years. They all had genetic mutations associated with the SQTS. Two mutations were found in the *KCNH2* gene, and one in the *CACNA2D* gene. One patient had an additional *SCN10A* variant. Alive and mutation-positive family members had short QTc-intervals, but no further phenotypic manifestations. None of the mutation-negative family members had an abnormal ECG or any symptoms. In all patients with shortened QTc-intervals, the QTc-interval had a low long-term variability and QTc shortening always remained detectable by 12-lead ECG.

Conclusion This study shows the variety of phenotypic manifestations in different families with SQTS. It further emphasizes the importance of a 12-lead ECG for early diagnosis, and the utility of next generation sequencing for the identification of mutations associated with the SQTS.

Keywords Short QT • Channelopathy • Repolarization • Sudden cardiac death • Ventricular arrhythmia

Introduction

The short QT syndrome (SQTS) is a rare cardiac channelopathy with only about 100 reported cases that can lead to ventricular arrhythmias and sudden cardiac death (SCD).[1–3] The disease is diagnosed if there is a short corrected QT (QTc)-interval in the absence of secondary causes (hypercalcaemia, hyperkalaemia, sinus tachycardia, catecholamine/digitalis intake, acidosis). It is thought to be associated with accelerated repolarization and increased dispersion of refractoriness, which are known factors promoting ventricular tachyarrhythmias.[4] Multivariable analyses report a 2.6-fold increased risk of death in patients with a QTc ≤ 300 ms.[5] The diagnosis is based on an expert consensus statement of 2013.[1,6] It is recommended that SQTS is diagnosed in the presence of a QTc ≤ 330 ms or a QTc ≤ 360 ms with one additional criterion such as family history of SQTS, the presence of a genetic mutation being associated with the SQTS, family history of SCD at <40 years of age, or aborted SCD due to ventricular tachycardia/fibrillation without underlying structural heart disease.[6]

The inheritance is autosomal dominant with incomplete penetrance and the genetic background is heterogeneous.[1] Three genes encoding cardiac potassium channels are known to be affected in SQTS. Gain of function mutations of these potassium channels lead to a shortened

* Corresponding author. Tel: +41 44 255 20 99; fax: +41 44 255 44 01. *E-mail address*: firat.duru@usz.ch

What's new?

- Our study shows that during clinical long-term follow-up of index patients with the short QT syndrome (SQTS) there were no structural changes regarding the heart function.
- The corrected QT-interval of index patients remained short, showed a low variability during follow-up and was always recognizable by 12 lead ECG.
- Genetic analysis using next generation sequencing (NGS) methods revealed that all SQTS patients had SQTS-associated genetic mutations.
- This study describes the first SQTS case where a *KCNH2* p.Ser631Ala and a *SCN10A* p.Arg1869Cys missense variant was detected using NGS.

cardiomyocyte action potential duration and refractoriness, and therefore, to a shorter QTc-interval. These mutations involve the *potassium voltage-gated channel subfamily H member 2* (*KCNH2*) gene of the *human ether-à-go-go-related gene* (*hERG*) channel, which is responsible for the rapid-delayed outward rectifier potassium current causing SQTS1, the *potassium voltage-gated channel subfamily Q member 1* (*KCNQ1*) gene, which encodes a subunit of channels, mediating slow-delayed outward rectifier potassium channel causing the SQTS2, and the *potassium voltage-gated channel subfamily J member 2* (*KCNJ2*) gene, which contributes to inwardly rectifying potassium channel current, causing the SQTS3.[7–9] Furthermore, loss of function mutations have been described in the *calcium voltage-gated channel subunit alpha1 C* (*CACNA1C*), *calcium voltage-gated channel subunit beta 2 B* (*CACNB2B*), and recently in the *calcium voltage-gated channel auxiliary subunit alpha2delta 1* (*CACNA2D1*) gene, which encode for subunits of the L-type calcium channel and lead to shorter QTc-intervals by decreasing the amplitude of inward calcium current.[10,11]

Today, with the emerging role of rapid genetic screening tools such as next generation sequencing (NGS), there is a new possibility of identifying novel mutations and genetic modifiers that might change phenotypic expression and disease outcome.[1,12] Thus, the purpose of this study was to determine the genotype of three families with the SQTS by using NGS and to describe the clinical profile of this cohort during long-term follow-up.

Methods

Study population

Three unrelated index patients with the SQTS and their first- or second-degree family members were studied. Diagnosis of SQTS was made as described above. The heart rate QTc-interval was calculated using Bazett's equation ($QTc = QT/(\sqrt{RR})$). All patients signed an informed consent, which was in accordance with the standards of the Declaration of Helsinki and approved by the Ethics Committee of the Canton of Zurich (approval number KEK-ZH-Nr. 2014-0443).

Assessment of clinical data and genetic testing

Physical examination, 12-lead surface ECG, 24 to 48 h Holter ECG, stress testing and transthoracic echocardiography (TTE) were performed in all index patients. In first-degree family members, physical examination and 12-lead surface ECG were performed, while those with a QTc ≤ 360 ms additionally received a TTE and 24 h Holter ECG. Genetic analysis was performed in all first-degree family members of all index patients, and additionally in second-degree family members of family number 3.

In all index patients DNA was extracted from peripheral macrophages. A targeted clinical exome panel sequencing was performed by NGS using the TrueSight One Sequencing Panel (Illumina, San Diego, USA), which includes 4813 genes. The analysed cardiac panel consisted of 104 genes (see Supplementary material online, *Table S1*). All associated mutations were confirmed by direct Sanger sequencing. Read alignment and local realignment of indels was performed using CLC Workbench v7.5.1 (CLCBio, Aarhus, Denmark). Variant prediction was done using the tools Polyphen2, SIFT, and MutationTaster. The following databases were used to analyse the sequences in detail: Human Gene Mutation Database Professional (Biobase, Wolfenbuettel, Germany), 1000 Genomes Project (Massachusetts, USA), and Exome Aggregation Consortium browser (ExAC), as previously described by our group.[12] In index patient 3, the loss of function calcium channel mutation has been previously described by our group.[11] In this paper, we report the comprehensive genetic findings and extended clinical follow-up of this patient and cascade screening of her family members.

Results

Clinical characteristics and genetic analysis of the three families with the SQTS

SQTS family 1

The male index patient 1 (III1) was first screened at the age of 6 months after his father (II2) died of confirmed SCD due to ventricular fibrillation (VF). The 12-lead surface ECG of index patient (III1) revealed a shortened QTc < 320 ms at that time. The patient suffered from syncope at the age of 1 year. Although the electrophysiological study that was performed at a previous work-up did not induce tachyarrhythmia during programmed ventricular stimulation, an intravenous ICD was implanted at the age of 16 due to the strong family history of SCD. His latest adequate ICD discharge was at the age of 17 due to VF.[13,14] The device was changed 2 years later, in 2005, due to battery malfunction. During the same year, he had two inappropriate therapies due to T-wave oversensing. After adjustment of the sensing threshold and initiation of antiarrhythmic therapy with quinidine, there were no other episodes of inadequate shocks. In 2015, the intravenous ICD was replaced due to battery depletion. During follow-up, the patient had a lead fracture. A transvenous lead extraction was attempted, but was not successful due to severe adhesions in the superior vena cava. The lead was hence left in place and a subcutaneous ICD (S-ICD) was implanted. The patient had normal TTE findings. His most recent ECG at age 28 revealed a QTc of 304 ms. His father (II2) was 28 years old when he died of SCD. He never had an ECG, cardiac imaging, or genetic testing performed. It was reported that his paternal grandmother (I2) also had a shortened QTc. His father's siblings all received cardiovascular examinations including TTE, and none of them had shortened QTc-intervals or other pathological findings.

NGS in the index patient (III1) revealed a pathogenic missense mutation in *KCNH2* c.1764C>G (p.Asn588Lys). This mutation has been

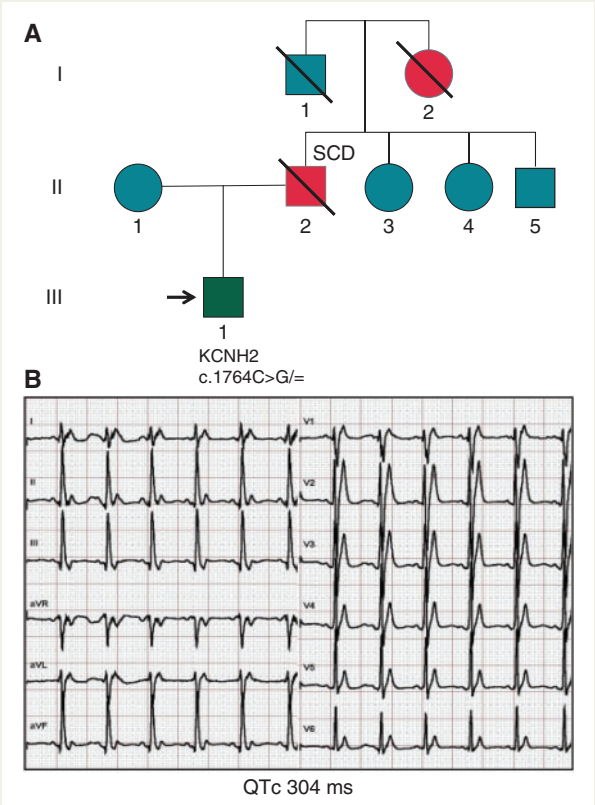

Figure 1 SQTS family 1. (*A*) Pedigree of the reported family. Roman number indicates each generation; Arabic number indicates each individual; black arrow indicates index patient; circle and box indicate female resp. male gender; green box indicates phenotypically affected family member; red boxes and circles are family members with suspected phenotypes; blue boxes and circles are family members without clinical phenotypes; slashed indicate deceased family members; each genetic variant is listed above; /= indicating heterozygous mutation; =/= indicating non-presence of variant/mutation; SCD, sudden cardiac death; (*B*) 12-lead surface ECG (25 mm/s, 10 mm/mV) of the index patient III1 with QTc interval.

predicted to be deleterious according to SIFT, probably damaging according to Polyphen 2, and it has been previously associated with SQTS-1. No other mutations in genes associated with SQTS or SCD were found. Of note, we found the KCNJ5 variant c.631C>T (p.Arg 211Trp) of unknown significance predicted to be deleterious by SIFT and probably damaging by Polyphen 2, so far not being associated with SQTS (*Figure 1*; *Tables 1 and 2*).

SQTS family 2

The female index patient (III1) of this family was screened when she was 6 years old, after one of her cousins died suddenly at the age of 17. Her ECG at that time revealed a QTc of <320 ms. She remained free of any symptoms until the age of 16 when she had two episodes of arrhythmic syncope during physical activity. Initially, an S-ICD was implanted at age 17. She underwent surgical revision due to persistent pain, which did not subside. As a result, the S-ICD had to be removed and a transvenous system was implanted. The patient did not receive any ICD therapies since implantation. Her most recent ECG at age 18 revealed a QTc of 323 ms. All performed TTEs were normal. The father (II2) of the index patient also had a shortened QTc of 324 ms. Due to his age (54 years) and complete lack of clinical symptoms, ICD therapy was not considered. His TTE was normal. A clinical assessment of the younger sister revealed a shortened QTc of 340 ms. TTE at age 12 showed a slightly reduced left ventricular ejection fraction of 49% that remained stable during follow-up. Cardiac magnetic resonance tomography showed a slightly enlarged left ventricle with an ejection fraction of 47%, but no signs of myocardial fibrosis or intramyocardial fat. There were no morphological abnormalities and the right ventricle was normal in volume and systolic function. She never complained of any cardiac symptoms and stress testing as well as 48-h ECG did not reveal any pathologies. Due to complete lack of symptoms and after assessing the individual risk-to-benefit ratio, an ICD was not implanted. Regular follow-up has been recommended, and she is currently doing well. The asymptomatic twin brother (III3) also underwent clinical examinations, and his ECG did not reveal a shortened QTc-interval. The father (II2) has 10 siblings; three brothers and seven sisters. One of the sisters (II3) had died suddenly at age 30. Another sister had two sons, one of them (III4) had died suddenly at the age of 4 months, the other one (III5) had died suddenly at the age of 17 years. No further information was obtainable since the father had not been in contact with any of his siblings for the past 10 years. According to the mother (II1), all her siblings were in good health (*Figure 2*, *Table 1*). Next generation sequencing in the index patient (III1) revealed a novel missense mutation in *KCNH2* c.1891T>G (p.Ser631Ala) that has not been previously associated with the SQTS, and additionally a missense variant in *SCN10A* c.5605C>T (p.Arg1869Cys). The KCNH2 variant was predicted to be tolerated according to SIFT, probably damaging according to Polyphen 2, and disease causing according to MutationTaster; the *SCN10A* variant was predicted to be deleterious according to SIFT, probably damaging according to Polyphen 2, and disease causing according to MutationTaster. The father (II2) of the index patient had the same *KCNH2* mutation, but did not harbour the *SCN10A* mutation. Her siblings were also screened for the SQTS-associated mutation. The younger sister (III2) harboured the same *KCNH2* mutation, whereas the dizygotic twin brother (III3) of the index patient did not (*Table 2*). Of note, the asymptomatic mother with a normal ECG harboured only the *SCN10A* variant.

SQTS family 3

The female index patient from this family (III1) was screened for SQTS after an out of-hospital arrest due to VF and aborted SCD at the age of 17 years. The first ECG at hospital admission showed a QTc of 329 ms. TTE was always normal. A transvenous ICD was implanted during this first admission and a beta-blocker therapy was initiated. Since then, no episodes of sustained arrhythmia were detected. Five years later, this patient started suffering from convulsive episodes without any arrhythmias recorded on the ICD. An electroencephalogram revealed epileptic potentials leading to the diagnosis of symptomatic complex-partial epilepsy. An anticonvulsive therapy with lamotrigine was initiated, and the patient did not have

Table 1 Clinical characteristics of index patients and first-degree family members of each index patient

Patient	Age at diagnosis (years)	Age at last follow-up (years)	Arrhythmic Event: 1 = sudden cardiac arrest, 2 = ventricular fibrillation, 3 = syncope	Gender (m = 0 f = 1)	Family history; 0 = no; 1 = yes	Systolic/ diastolic BP (mmHg)	ICD since	LVEF (%)	QTc-interval (ms)
SQTS family 1 Index: III1	0.5	28	2, 3	0	1	132/92	07.2.2003	55	304
SQTS family 2 Index: III1	6	18	3	1	0*	110/70	19.1.2015	60	323
SQTS family 3 Index: III1	17	25	1, 2, 3	1	0	132/84	05.8.2008	55	322
SQTS family 2 Member: II2	54	54	–	0	1	–	–	56	324
SQTS family 2 Member: III2	12	15	–	1	1	–	–	45	340
SQTS family 2 Member: III3	–	20	–	0	1	–	–	60	381
SQTS family 3 Member: II2	45	51	–	0	1	–	–	–	357
SQTS family 3 Member: III2	–	24	–	0	1	–	–	–	389

Roman number indicates each generation; Arabic number indicates each individual.
m, male; f, female; BP, blood pressure; family history, (survived) sudden cardiac death of first degree family member ≤ 40 years; QTc, corrected QT;
*, sudden cardiac death of second degree family member ≤ 40 years.

Table 2 List of genetic mutations of index patients and first degree family members

Patient	Gene	DNA change	Predicted aminoacid change	GenBank accession-number	Type	SIFT	Polyphen 2	MutationTaster	Consequence
SQTS family 1 index III1	*KCNH2*	c.1764C>G	p.Asn588Lys	NM_000238	Missense	Tolerated	Possibly damaging	Disease causing	Gain-of-function[18]
SQTS family 2 index III1	*KCNH2*	c.1891T>G	p.Ser631Ala	NM_000238	Missense	Tolerated	Possibly damaging	Disease causing	Gain-of-function[19]
	SCN10A	c.5605C>T	p.Arg1869Cys	NM_006514	Missense	Deleterious	Possibly damaging	Disease causing	Loss-of-function[20]
SQTS family 3 index III1	*CACNA2D1*	c.2264G>C	p.Ser755Thr	NM_000722	Missense	Tolerated	Benign	Disease causing	Loss-of-function[11]
SQTS family 2 member III2	*KCNH2*	c.1891T>G	p.Ser631Ala	NM_000238.3	Missense	Tolerated	Possibly damaging	Disease causing	Gain-of-function[19]
SQTS family 2 member II2	*KCNH2*	c.1891T>G	p.Ser631Ala	NM_000238.3	Missense	Tolerated	Possibly damaging	Disease causing	Gain-of-function[19]
SQTS family 3 member II2	*CACNA2D1*	c.2264G>C	p.Ser755Thr	NM_000722	Missense	Tolerated	Benign	Disease causing	Loss-of-function[11]

SIFT, Polyphen 2, and MutationTaster are algorithms that predict the pathogenic effect of a genetic variant. Roman number indicates each generation; Arabic number indicates each individual.
NM, GenBank accession number.

another epileptic episode. Her most recent ECG at age 25 showed a QTc of 322 ms. Screening of family members including her brother (III2), mother (II1) and father (II2), her father's siblings (II3/4), as well as her paternal grandparents (I1/2), and revealed that her asymptomatic father (II2) and asymptomatic grandmother (I2) both had relatively short QTc-intervals, but otherwise normal cardiovascular exams (*Figure 3*, *Table 1*). NGS in the index patient (III1) confirmed the loss of function *CACNA2D* mutation c.2264G>C (p.Ser755Thr) (SQTS-6), which has previously been described by our group.[11]

We did not find any other variants related with SQTS or SCD. Of note, we found a variant in dystrophin c.5010G>T (Trp1670Cys) of uncertain significance predicted to be deleterious by SIFT and probably damaging by Polyphen 2. Co-segregation analysis showed that her father (II2) (with a QTc of 357 ms at last follow-up in 2016) and her paternal grandmother (I2) were also carriers of the same *CACNA2D* variant (*Table 2*).

Long-term follow-up

The median follow-up period with yearly check-ups in our clinic was 8 years (IQR 6–10.5 years). During this period, there were no significant changes in ECG morphology nor QT-interval, no changes in LV/RV ejection fraction and no symptoms during stress testing in any of

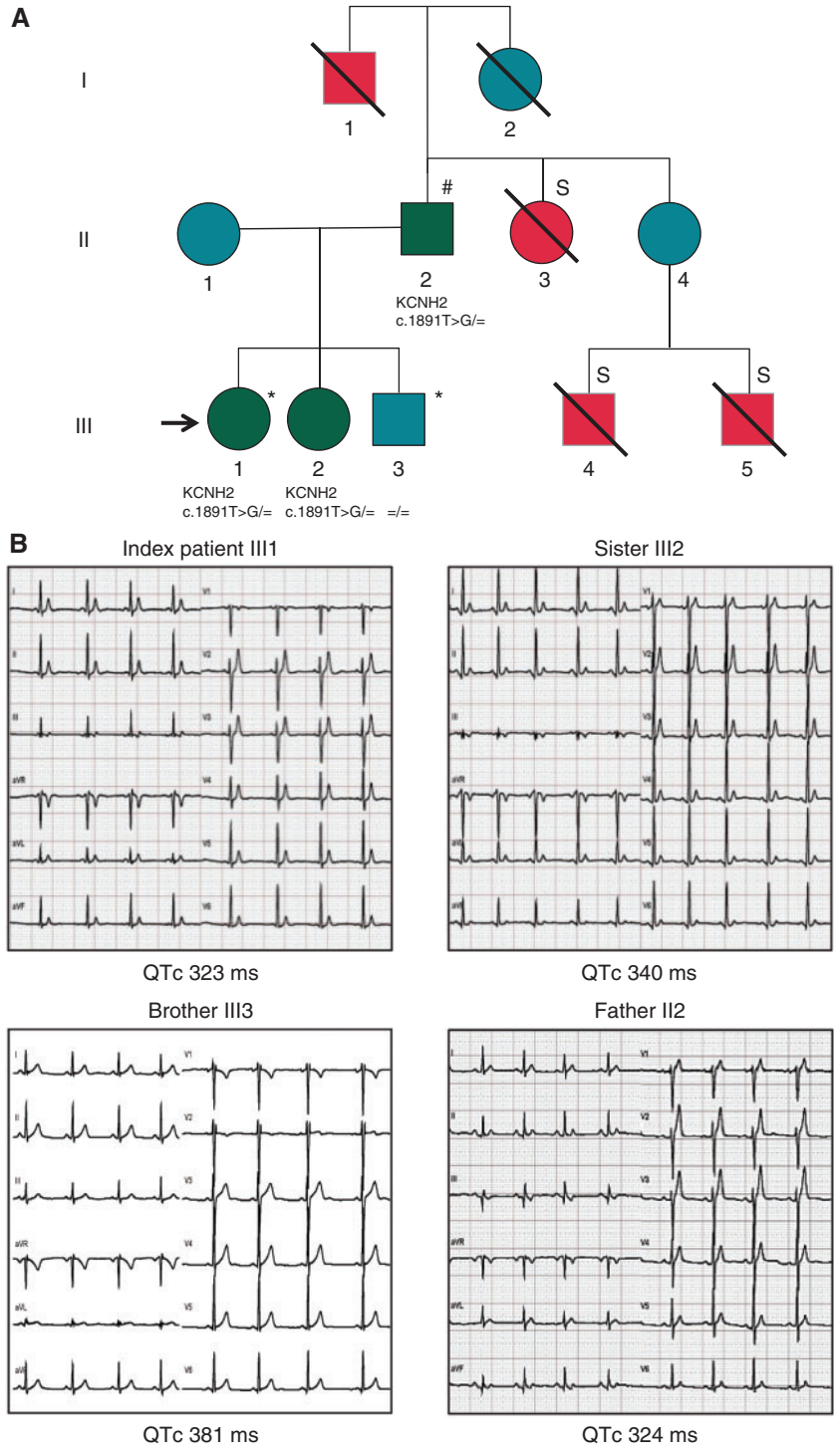

Figure 2 SQTS family 2. (*A*) Pedigree of the reported family. Roman number indicates each generation; Arabic number indicates each individual; black arrow indicates index patient, green boxes and circles are phenotypically affected family members; red boxes and circles are family members with suspected phenotypes; blue boxes and circles are family members without a clinical phenotype; slashed indicates deceased family members; each genetic variant is listed above; /= indicating heterozygous mutation; =/= indicating non-presence of variant; S, sudden death; * dizygotic twins; # the father has three brothers and five additional sisters. One brother died in a car accident at the age of 40 years. His other siblings are all healthy and had a clinical cardiovascular examination that was normal. (*B*) 12-lead surface ECG (25 mm/s, 10 mm/mV) of index patient III2, mutation positive first degree family members III2 and II2, and mutation negative first degree family member III3, with QTc intervals.

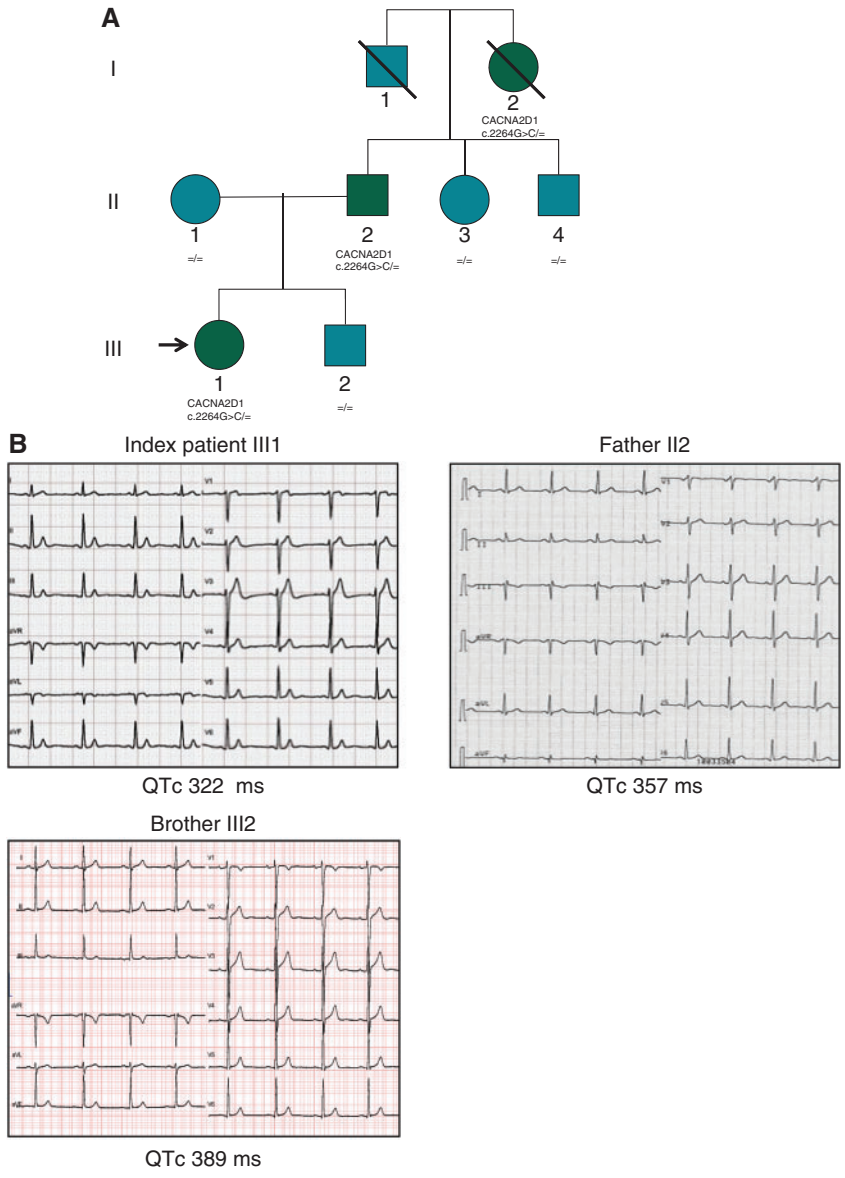

Figure 3 SQTS family 3. (*A*) Pedigree of the reported family. Roman number indicates each generation; Arabic number indicates each individual; black arrow indicates index patient, green boxes and circles are phenotypically affected family members and blue boxes and circles are family members without a clinical phenotype; slashed indicate deceased family members; each genetic variant is listed above; /= indicating heterozygous mutation; =/= indicating non-presence of variant; (*B*) 12-lead surface ECG (25 mm/s, 10 mm/mV) of index patient and mutation positive first degree family member II2, and mutation negative first degree family member III2, with QTc interval.

the index patients. Index patient 1 had a most recent episode of VF at age 17, which was not exercise-related. Index patient 2 never experienced an ICD therapy, and had a last episode of syncope at the age of 16 years during exercise prior to ICD implantation. Index patient 3 did not experience an ICD therapy either. Epileptic seizures were diagnosed in index patient 3 at age 22, but after the initiation of lamotrigine she remained seizure-free. In all index patients and family members with shortened QTc-intervals, the QTc-interval remained short and was always recognizable by 12-lead ECG during follow-up (*Table 3*). Symptomatic index patients had the shortest QTc-intervals, whereas asymptomatic gene carriers had a tendency towards longer QTc-intervals, and family members without a mutation did not have shortened QTc-intervals. (*Tables 1 and 3*) Other ECG parameters such as PQ-interval and QRS duration and morphology did not differ between symptomatic patients and asymptomatic family members.

Table 3 QTc variability assessed by 12-lead surface ECGs during follow-up of index patients and family members

Index patients and family members	Number of ECGs	Time between ECGs, months (median, IQR)	QTc-interval, ms (median, IQR)
SQTS family 1 (III1)	6	10 (8–28)	275 (261–287)
SQTS family 2 (III1)	5	4 (3–5)	304 (278–323)
SQTS family 3 (III1)	6	13 (12–16)	330 (329–335)
SQTS family 2 member II2	2	0.5	324 (312–326)
SQTS family 2 member III2	4	5 (5–7)	321 (304–331)
SQTS family 2 member III3	2	10	411 (396–426)
SQTS family 3 member II2	2	74	360 (358–361)
SQTS family 3 member III2	2	82	389 (389–389)

Data are presented as median (IQR).

Discussion

In this study we investigated the genotype and long-term clinical outcome of three unrelated index patients with SQTS and their family members. We assessed relevant clinical parameters and performed targeted clinical exome sequencing (NGS) and genetic cascade screening. Our study has the following main findings:

(1) Follow-up revealed no significant changes of the QTc-interval during the long-term.
(2) All index patients with the SQTS were genotype-positive and were symptomatic at a young age, either during childhood or during adolescence.
(3) Alive genotype-positive family members also had a short QTc, but were asymptomatic, whereas genotype-negative family members displayed normal QTc and were all asymptomatic.
(4) This study describes the first SQTS case harbouring *KCNH2* p.Ser631Ala and *SCN10A* p.Arg1869Cys missense variants using NGS.

Clinical outcome

Data on cohorts with the SQTS and their long-term outcomes are scarce. It was reported that SQTS can be lethal and that cardiac arrest may occur at a very young age. Mouse models have shown that an augmented transmural dispersion of repolarization could be the basis for arrhythmogenesis.[4] There is a high risk of recurrent cardiac arrest, and therefore, implantation of an ICD is justified in this population.[3] Previous studies have indicated that the age of disease manifestation can span from *in utero* to the 8th decade. Accordingly, our index patients all had an adverse arrhythmic event either during childhood or adolescence, and all of them had more than one arrhythmic event. Nonetheless, the arrhythmic event and age of onset were different in each patient.

A major observation of our study was that there were no significant changes in the QTc-interval in the index patients over time. The QTc-intervals consistently remained short on 12-lead ECG. This suggests a low variability of the QTc-interval and a high probability of detecting this channelopathy by 12-lead surface ECG as compared with the long QT syndrome or the Brugada syndrome. In the long QT syndrome, genotype-positive patients may have changing QTc-intervals, and from time to time even intervals within normal limits.[6]

Risk stratification

Clinical scores for risk stratification in this potentially life-threatening disease have been proposed,[3] but according to the expert consensus statement, the only established risk factors for recurrent malignant arrhythmias, and therefore class I indications for ICD implantation, are aborted SCD or sustained VT/VF.[6] Therefore, the use of Holter ECGs is important. Implantable ECG loop recorders in patients with a suspicious history may be useful. Another potential arrhythmogenic risk factor is the degree of QTc shortening.[3] In line with this, index patient 1 (SQTS famiy1, III1) had the shortest QTc-interval of all patients and was the one to develop symptoms and ventricular arrhythmias at a younger age as compared with the others. Furthermore, all index patients had shorter QTc-intervals compared with their genotype positive family members and asymptomatic genotype negative family members all had a normal QTc-interval. Moreover, being an index patient *per se* has been reported to confer an increased risk for ventricular arrhythmias as compared with family members in other inherited channelopathies and cardiomyopathies.[1] We made the same observation for SQTS in this study. However, this phenomenon may be caused by an ascertainment bias, indicating that index patients may present with more severe phenotypes because they are the ones being most symptomatic and presenting to the clinic.[2,3] Regarding asymptomatic family members with a short QTc-interval or those with positive genotypes, there are no therapy recommendations.[6] Nonetheless, it is suggested that first-degree family members of an index patient should all be genetically screened, especially if a pathogenic variant has been identified. Screening should also include more distant relatives if a suspicious clinical history is reported.[1,6]

Differential phenotypic expression

In the case of family 2, the sister (III2) of index patient 2 with the same *KCNH2* mutation did not display any arrhythmic symptoms, but presented with a slightly impaired LV ejection fraction. It has been speculated that SQTS may slightly influence LV ejection fraction through mechanical dispersion.[4,15] Indeed, it is known from other inherited cardiac diseases that a genetic mutation may present with ion-channel dysfunction and arrhythmias in some patients, but structural abnormalities in others.[16] It may be hypothesized that epigenetic factors and post-translational modification may cause this phenomenon.

Next generation sequencing (NGS)

The role of genetic testing for identifying the aetiology of SCD and its prevention is becoming increasingly important. NGS, a recently introduced technology that can yield a vast amount of genetic information within a short period of time, is emerging as a valuable diagnostic tool in SCD, channelopathies, and cardiomyopathies.[12] NGS can potentially help to identify the aetiology of overlap syndromes and differential phenotypic expression, where multiple mutations influence disease onset and severity.[17] Various *in silico* bioinformatic tools have been developed to predict the pathogenicity of missense variants such as SIFT, Polyphen 2, and MutationTaster. However, their predictions should be interpreted with caution, and further evidence regarding the pathogenicity of a variant should be sought.

In the present study, phenotypic expression and clinical outcomes were different in each index patient and family members suggesting that genetic modulators and disease modifiers may play an important role. The KCNH2 mutation of SQTS family 1 c.1764C>G has been described as a gain of function mutation of the hERG channel associated with SQTS-1,[18] whereas the KCNH2 c.1891T>G mutation of SQTS family 2 has never been described before. Early functional studies showed that this mutation affects the pore region of the *hERG* channel and confers a gain of function mutation comparable to the mutations already described in SQTS, even before the disease was first described.[18,19] Moreover, the *SCN10A c.5605C>T* variant of index patient III1 from SQTS family 2 was predicted to be deleterious according to SIFT, possibly damaging according to Polyphen 2 and disease causing according to MustationTaster. Co-segregation analysis showed that her father, presenting with a milder phenotype, did not harbour this SCN10A variant, but the asymptomatic mother with a normal ECG did harbour that variant. *SCN10A* c.5605C>T has been associated with a loss of function of the SCN10 sodium current and Brugada syndrome.[20] It may be speculated that this variant alone is not enough to cause SQTS, but acts as a modifier in our index patient. Index patient of SQTS family 3 III1 had a *CACNA2D1* c.2264G>C mutation, which was first discovered by our group in 2011.[11] Functional studies showed that a loss of function mutation in this gene, which encodes for subunits of the L-type calcium channel, leads to shorter QTc-intervals by decreasing the amplitude of inward calcium current. Our observations in the current study are in line with previous literature on SQTS showing that gain of function in *KCNH2* and loss of function mutations in *CACNA2D1* both lead to shorter QTc-intervals.

Treatment

In patients who have experienced an aborted SCD and/or documented spontaneous sustained VT/VF with or without syncope, ICD implantation is warranted. Appropriate programming of the ICD is essential in order to prevent inappropriate shocks due to T-wave oversensing, as seen in index patient III1 of SQTS family 1.[6] Regarding additional drug therapy, quinidine seems to be effective due to its QT-prolonging properties. However, this seems to be mainly prominent in SQTS-1.[21] This index patient (SQTS family 1) from our study remained free of symptoms after the initiation of quinidine. Other drugs, including class III antiarrhythmics, may be considered in other subtypes. Experimental studies also highlight the role of ranolazine as an inhibitor of the hERG potassium channel, thus representing a promising therapeutic agent.[22] Nonetheless, recommendations on antiarrhythmic drugs only rely on small observational cohorts.[6,21] There are no studies supporting ICD implantation in asymptomatic patients despite being genotype positive. Nevertheless, an ICD may be considered in SQTS patients without documented VT/VF/SCD, but with a strong family history of SCD.[3]

Limitations

Since this was an observational clinical study in SQTS families, data were acquired during regular visits to our clinic. In order to avoid 'genetic overdiagnosis', our search included 104 genes commonly associated with channelopathies/cardiomyopathies. Therefore, we cannot exclude to have missed novel mutations or modifiers in other genes. Since these are observations in a limited number of patients, our findings need to be verified in larger cohorts.

Conclusions

SQTS is a rare genetic condition, which is associated with a short QTc-interval and potentially life-threatening ventricular tachyarrhythmias. This long-term follow-up study shows low variability of the QTc-interval in each patient and different phenotypic outcomes in this disease. It also highlights the importance of NGS for early diagnosis, and the possibility to identify genetic disease modifiers. Nonetheless, our preliminary findings have to be confirmed in larger cohorts.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: Dr. Steffel has received consultant and/or speaker fees from Amgen, Astra-Zeneca, Articure, Bayer, Biosense-Webster, Biotronik, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cook Medical, Daiichi Sankyo, Medtronic, Novartis, Pfizer, Sanofi-Aventis, Sorin, St. Jude Medical and Zoll. Dr. Steffel is Co-director of CorXL. He has received grant support through bis iostitutioo trom Bayer Healthcare Biosense Webster Biotronik Boston Scientjfic Paiicbi sankyo Medtronic, und St. Jude Medical. The other authors have no conflict of interest to declare related to this study.

Funding

This study was funded by a research grant from the Georg and Bertha Schwyzer-Winiker Foundation and Baugarten Foundation in Zurich, Switzerland.

DA was funded by the Filling the Gap grant from the University of Zurich in Switzerland.

References

1. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H *et al.* HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace* 2011;**13**:1077–109.
2. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O *et al.* Long-term follow-up of patients with short QT syndrome. *J Am Coll Cardiol* 2011;**58**:587–95.

3. Villafañe J, Atallah J, Gollob MH, Maury P, Wolpert C, Gebauer R *et al*. Long-term follow-up of a pediatric cohort with short QT syndrome. *J Am Coll Cardiol* 2013;**61**:1183–91.
4. Extramiana F, Antzelevitch C. Amplified transmural dispersion of repolarization as the basis for arrhythmogenesis in a canine ventricular-wedge model of short-QT syndrome. *Circulation* 2004;**110**:3661–6.
5. Iribarren C, Round AD, Peng JA, Lu M, Klatsky AL, Zaroff JG *et al*. Short QT in a cohort of 1.7 million persons: prevalence, correlates, and prognosis. *Ann Noninvasive Electrocardiol* 2014;**19**:490–500.
6. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C *et al*. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;**15**:1389–406.
7. 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**:30–5.
8. Bellocq C, van Ginneken AC, Bezzina CR, Alders M, Escande D, Mannens MM *et al*. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. *Circulation* 2004;**109**:2394–7.
9. 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. *Circ Res* 2005;**96**:800–7.
10. 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**:442–9.
11. 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). *Eur Heart J* 2011;**32**:1077–88.
12. Medeiros-Domingo A, Saguner AM, Magyar I, Bahr A, Akdis D, Brunckhorst C *et al*. Arrhythmogenic right ventricular cardiomyopathy: implications of next-generation sequencing in appropriate diagnosis. *Europace* 2016; pii: euw098. [Epub ahead of print].
13. Schimpf R, Bauersfeld U, Gaita F, Wolpert C. Short QT syndrome: successful prevention of sudden cardiac death in an adolescent by implantable cardioverter-defibrillator treatment for primary prophylaxis. *Heart Rhythm* 2005;**2**:416–7.
14. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R *et al*. Short QT Syndrome: a familial cause of sudden death. *Circulation* 2003;**108**:965–70.
15. 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**:2096–105.
16. Cerrone M, Noujaim SF, Tolkacheva EG, Talkachou A, O'connell R, Berenfeld O *et al*. Arrhythmogenic mechanisms in a mouse model of catecholaminergic polymorphic ventricular tachycardia. *Circ Res* 2007;**101**:1039–48.
17. Harrell DT, Ashihara T, Ishikawa T, Tominaga I, Mazzanti A, Takahashi K *et al*. Genotype-dependent differences in age of manifestation and arrhythmia complications in short QT syndrome. *Int J Cardiol* 2015;**190**:393–402.
18. McPate MJ, Duncan RS, Hancox JC, Witchel HJ. Pharmacology of the short QT syndrome N588K-hERG K+ channel mutation: differential impact on selected class I and class III antiarrhythmic drugs. *Br J Pharmacol* 2008;**155**:957–66.
19. Zou A, Xu QP, Sanguinetti MC. A mutation in the pore region of HERG K+ channels expressed in *Xenopus* oocytes reduces rectification by shifting the voltage dependence of inactivation. *J Physiol* 1998;**509(Pt 1)**:129–37.
20. Hu D, Barajas-Martínez H, Pfeiffer R, Dezi F, Pfeiffer J, Buch T *et al*. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. *J Am Coll Cardiol* 2014;**64**:66–79.
21. Gaita F, Giustetto C, Bianchi F, Schimpf R, Haissaguerre M, Calò L *et al*. Short QT syndrome: pharmacological treatment. *J Am Coll Cardiol* 2004;**43**:1494–9.
22. Du C, Zhang Y, El Harchi A, Dempsey CE, Hancox JC. Ranolazine inhibition of hERG potassium channels: drug-pore interactions and reduced potency against inactivation mutants. *J Mol Cell Cardiol* 2014;**74**:220–30.