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The Short QT Syndrome

Proposed Diagnostic Criteria

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Objectives We aimed to develop diagnostic criteria for the short QT syndrome (SQTS) to facilitate clinical evaluation of suspected cases.

Background The SQTS is a cardiac channelopathy associated with atrial fibrillation and sudden cardiac death. Ten years after its original description, a consensus regarding an appropriate QT interval cutoff and specific diagnostic criteria have yet to be established.

Methods The MEDLINE database was searched for all reported cases of SQTS in the English language, and all relevant data were extracted. The distribution of QT intervals and electrocardiographic (ECG) features in affected cases were analyzed and compared to data derived from ECG analysis from general population studies.

Results A total of 61 reported cases of SQTS were identified. Index events, including sudden cardiac death, aborted cardiac arrest, syncope, and/or atrial fibrillation occurred in 35 of 61 (57.4%) cases. The cohort was predominantly male (75.4%) and had a mean QT_c value of 306.7 ms with values ranging from 248 to 381 ms in symptomatic cases. In reference to the ECG characteristics of the general population, and in consideration of clinical presentation, family history, and genetic findings, a highly sensitive diagnostic scoring system was developed.

Conclusions Based on a comprehensive review of 61 reported cases of the SQTS, formal diagnostic criteria have been proposed that will facilitate diagnostic evaluation in suspected cases of SQTS. Diagnostic criteria may lead to a greater recognition of this condition and provoke screening of at-risk family members. (J Am Coll Cardiol 2011;57:802–12) © 2011 by the American College of Cardiology Foundation

The short QT syndrome (SQTS) is a cardiac channelopathy associated with a predisposition to atrial fibrillation and sudden cardiac death. The arrhythmogenic potential of a short QT interval was first suggested by Gussak et al. (1) in 2000 when they reported an isolated case of sudden cardiac death in a young female, and the presence of early onset atrial fibrillation in a separate family. Cardiac workup in both instances revealed structurally normal hearts; however, electrocardiography (ECG) was notable for markedly abbreviated QT intervals ranging from 260 to 280 ms (Bazett corrected QT interval [QT_c] values ranging from 248 to 300 ms) in affected subjects. Similar findings were reported a few years later in a detailed description of 2 additional unrelated families with short QT intervals who suffered from a high incidence of sudden cardiac death in the absence of structural heart disease (2). These initial reports led to the recognition of SQTS as a distinct clinical entity and have been followed by numerous additional case descriptions within the past decade that have furthered our insight into this condition. To date, 3 separate genes encoding ion channels involved in the cardiomyocyte action potential have been implicated in the pathogenesis of SQTS, and further genetic culprits are suspected (3–5). The diagnostic hallmark of the condition remains a short ECG QT interval; however, consensus on an appropriate cutoff value and diagnostic criteria sufficient to establish a diagnosis of SQTS have yet to emerge in the literature.

The diagnosis of SQTS is further complicated by the presence of an overlapping range of QT intervals between affected cases and apparently healthy subjects. This concept is highlighted in a long-term follow-up study of healthy Finnish individuals with short (<340 ms) and very short (<320 ms) QT_c values who had no documented arrhythmic events after an average follow-up of 29 years (6). Additional studies examining subjects with short QT intervals from the general population have revealed similarly benign outcomes with no evidence of increased arrhythmic risk (7–9). These findings suggest that the presence of a short QT interval in isolation is not always predictive of an increased arrhythmic risk and therefore should not invariably lead to a diagnosis of SQTS.

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The prevalence and distribution pattern of short QT intervals in the general population have been examined in an effort to clarify the definition of a short QT interval. In a middle-aged Finnish population involving 10,822 men and women, 97.5% of males had a QT_c value greater than 348 ms, whereas a value of 364 ms was identified for females (6). Other large studies involving American, Japanese, and Swiss subjects have produced similar findings, with the mean QT_c value generally in the range of 400 to 410 ms, and values 2 standard deviations below the mean approximating 350 ms in males and 365 ms in females (7,10,11).

In the congenital long-QT syndrome (LQTS), the presence of an overlapping range of QT intervals in affected individuals and the general population is well recognized (12). To overcome the diagnostic limitations associated with relying on a single ECG parameter in LQTS, a scoring system involving multiple clinical and ECG features was developed (13,14). Recognition of an analogous scenario in SQTS emphasizes the need for a similar approach. Accordingly, we systematically reviewed the literature for reported cases of SQTS in an effort to develop diagnostic criteria designed to facilitate accurate clinical recognition of the disorder.

Methods

The MEDLINE electronic database was searched for relevant articles in the English language published before May 2010 using the medical subject heading or text word "short QT." Articles identified using this search strategy were individually reviewed for the presence of reported cases of SQTS. Published cases were considered eligible for inclusion in the study if the report provided details regarding the age, sex, clinical history, and QT interval of the affected patient. In order to limit the study to cases of isolated SQTS, subjects with structural heart disease and other cardiac manifestations including complete heart block were excluded. Clinical cases describing a coved-shape ST-segment elevation pattern in leads V_1 and V_2, and associated with abbreviated QT intervals and genetic mutations within *CACNA1c* or *CACNB2b*, were not included in the analysis (15). These cases have a recognizable ECG pattern consistent with the Brugada syndrome (15), and consideration of an additional diagnosis of SQTS is of limited clinical value.

The following clinical variables were extracted, when available, from each reported SQTS case: age at clinical presentation; sex; QT interval; QT_c value; the causative gene and specific mutation; clinical history of sudden cardiac death, aborted cardiac arrest, syncope, or atrial fibrillation; and family history of SQTS or sudden cardiac death. When multiple QT intervals were reported for a patient, the overall range was recorded and the shortest QT interval was used for analysis. A patient was defined as symptomatic following an episode of sudden cardiac death, aborted cardiac arrest, syncope, or atrial fibrillation.

Use of QT/predicted QT interval (QT_p) for heart rate correction was included given the poor performance of the QT_c value at extremes of heart rate (16). The QT_p was calculated using the formula developed by Rautaharju et al. (17): [QT_p = 656/(1 + heart rate/100)]. Dividing the measured QT interval by the QT_p results in a percentage predicted QT interval referred to as the QT index; a QT index value less than 88% is considered 2 standard deviations below the mean (17).

Abbreviations and Acronyms

ECG = electrocardiographic/electrocardiogram
IQR = interquartile range
IVF = idiopathic ventricular fibrillation
LQTS = long QT syndrome
QT_c = Bazett corrected QT interval
QT_p = predicted QT interval
SQTS = short QT syndrome
VT = ventricular tachycardia

When 12-lead surface ECGs were provided, the interval extending from the J-point to the peak of the T-wave (Jpoint-Tpeak) was measured. The J-point was taken as the point of inflection between the S-wave and the ST-segment, whereas the peak of the T-wave corresponded to the highest point of the waveform. The Jpoint-Tpeak interval was measured using the precordial lead with the largest amplitude T-wave.

Categorical variables were analyzed as percentages, whereas mean ± SD and median (interquartile range [IQR]) values were calculated from continuous variables.

Results

The search strategy yielded 197 articles that were reviewed for reported cases of SQTS. A total of 15 articles described unique cases of SQTS with inclusion of relevant clinical details. From these articles, 61 separate SQTS cases were reviewed. A subset of patients were reported in multiple articles; however, care was taken to ensure that these subjects were only included once in the study. A detailed listing of the clinical, electrocardiographic, and genetic details of the 61 evaluated cases is provided in Table 1.

Clinical features. A total of 46 (75.4%) patients from the overall cohort were male (Table 2). The presence of symptoms associated with SQTS, including sudden cardiac death, aborted cardiac arrest, syncope, and atrial fibrillation, occurred in 35 of the 61 (57.4%) subjects. There were 5 cases of sudden cardiac death and 15 of aborted cardiac arrest, whereas an isolated, unexplained syncopal event occurred in an additional 9 subjects. Atrial fibrillation was experienced in 18.0% (11 of 61) of cases within the cohort. Analysis on the basis of sex revealed that 8 of the 15 (53.3%) females had experienced symptoms in comparison with 27 of the 46 (58.7%) males.

Amongst the 35 symptomatic patients, the age at clinical presentation was available in 28 separate subjects. The overall median age at clinical presentation was 21 years (IQR: 17 to 31.8 years) with a value of 20 years (IQR: 17 to 29 years) in males and 30 years (IQR: 19 to 44 years) in

Table 1 Clinical and Genetic Features of the Reported Cases of SQTS

SQTS Case # (Ref. #)	Family	Presentation	Gender	QT (ms)	QT_c (ms)	QT/QT_p (%)	Jp-Tp (ms)	Gene	Mutation	SCD	ACA	Syncope	AF	Other	Family History
1 (1,18)	1	17 yrs	Female	225 (225–280)	300	71	100	*KCNH2*	N558K	Absent	Absent	Absent	Present		SQTS
2 (1,18)	1	51 yrs	Female	230 (230–260)	289	69	110	*KCNH2*	N558K	Absent	Absent	Absent	Present		SQTS
3 (1,18)	1	21 yrs	Male	240 (240–272)	267	66	90	*KCNH2*	N558K	Absent	Absent	Absent	Present		SQTS
4 (1)	2	37 yrs	Female	266	248	62	85	Not screened	—	Present	—	—	Absent		Negative
5 (2,3,19)	3	Not reported	Female	270	295	71	120	*KCNH2*	N558K	Absent	Absent	Absent	Present	Palpitations	SQTS
6 (2,3,19)	3	8 months	Male	260	300	71	70	*KCNH2*	N558K	Absent	Absent	Present	Absent		SQTS
7 (2,3,19)	3	Asymptomatic	Female	240	268	64	100	*KCNH2*	N558K	Absent	Absent	Absent	Absent		SQTS
8 (2,3,19)	3	62 yrs	Female	210	250	59	110	*KCNH2*	N558K	Present	—	—	Present		SQTS
9 (2,3,19)	4	18 yrs	Male	240 (240–270)	280	68	90	*KCNH2*	N558K	Absent	Absent	Present	Present		SQTS
10 (2,3,19)	4	Asymptomatic	Female	220 (220–250)	299	71	100	*KCNH2*	N558K	Absent	Absent	Vasovagal	Absent	Palpitations	SQTS
11 (2,3,19)	4	8 months	Male	240 (240–260)	290	70	120	*KCNH2*	N558K	Absent	Present	—	Absent		SQTS
12 (3)	5	51 yrs	Male	294	288	73	95	Negative*	—	Absent	Present	—	Absent		SQTS
13 (3)	5	Asymptomatic	Male	Not reported	293	Unavailable	Unavailable	Negative*	—	Absent	Absent	Absent	Absent		SQTS
14 (4)	6	70 yrs	Male	290	302	73	110	*KCNQ1*	V307L	Absent	Present	—	Absent		Negative
15 (5)	7	Asymptomatic	Female	Not reported	315	Unavailable	Unavailable	*KCNJ2*	D172N	Absent	Absent	Absent	Absent		SQTS
16 (5)	7	Asymptomatic	Male	Not reported	320	Unavailable	Unavailable	*KCNJ2*	D172N	Absent	Absent	Absent	Absent	Presyncope	SQTS
17 (19)	8	Asymptomatic	Male	275	303	73	Unavailable	Negative†	—	Absent	Absent	Absent	Absent		SQTS
18 (19)	8	29 yrs	Male	290	311	75	110	Negative†	—	Absent	Absent	Present	Absent		SQTS
19 (19)	8	50 yrs	Male	280	313	75	120	Negative†	—	Absent	Absent	Present	Present		SQTS
20 (19)	8	Asymptomatic	Male	300	310	75	Unavailable	Negative†	—	Absent	Absent	Absent	Absent		SQTS
21 (19,20,21)	9	Not reported	Male	280	302	73	Unavailable	Negative†	—	Absent	Absent	Absent	Present		SQTS
22 (19,20,21)	9	Asymptomatic	Male	300	315	76	Unavailable	Negative†	—	Absent	Absent	Absent	Absent	PMVT on ETT	SQTS
23 (19,20,21)	9	18 yrs	Male	270	308	73	110	Negative†	—	Absent	Present	—	Absent		SQTS
24 (19)	10	Asymptomatic	Female	320	317	78	Unavailable	Negative†	—	Absent	Absent	Absent	Absent		SQTS
25 (19)	10	14 yrs	Male	240	282	67	Unavailable	Negative†	—	Absent	Absent	Present	Absent		SQTS
26 (19)	10	Asymptomatic	Female	300	333	80	Unavailable	Negative**	—	Absent	Absent	Absent	Absent		SQTS
27 (19)	11	Asymptomatic	Male	290	338	80	Unavailable	Negative†	—	Absent	Absent	Absent	Absent		SQTS
28 (19)	11	17 yrs	Male	210	291	69	Unavailable	Negative†	—	Absent	Present	—	Absent		SQTS
29 (19)	12	16 yrs	Male	280	317	76	Unavailable	Negative†	—	Absent	Present	—	Absent		SQTS
30(19)	12	Asymptomatic	Male	294	324	78	Unavailable	Negative†	—	Absent	Absent	Absent	Absent		SQTS
31 (19)	12	Asymptomatic	Male	320	333	80	Unavailable	Negative†	—	Absent	Absent	Absent	Absent		SQTS
32 (19)	13	Asymptomatic	Female	310	327	79	Unavailable	Ongoing at report	—	Absent	Absent	Absent	Absent		SQTS
33 (19)	13	30 yrs	Male	315	302	74	Unavailable	Ongoing at report	—	Present	—	—	Absent		SQTS
34 (19)	13	Asymptomatic	Male	315	323	78	Unavailable	Ongoing at report	—	Absent	Absent	Absent	Absent		SQTS
35 (19)	14	19 yrs	Male	300	317	76	Unavailable	Negative†	—	Absent	Present	—	Absent		SCD

Continued on next page

Table 1 Continued

SQTS Case # (Ref. #)	Family	Presentation	Gender	QT (ms)	QT_c (ms)	QT/QT_p (%)	Jp-Tp (ms)	Gene	Mutation	SCD	ACA	Syncope	AF	Other	Family History
36 (19)	15	4 months	Female	210	307	73	80	Not screened	—	Absent	Present	—	Absent		SCD
37 (19,22,23)	16	62 yrs	Male	240	294	70	80	Negative†	—	Absent	Absent	Present	Present		SCD
38 (19,23)	17	27 yrs	Male	300	312	75	Unavailable	Not screened	—	Present	—	—	Present		Unknown
39 (24)	18	18 yrs	Male	280	310	74	110	Negative‡	—	Present	—	—	Absent		SQTS
40 (24)	18	Asymptomatic	Male	320	328	80	160	Negative‡	—	Absent	Absent	Absent	Absent		SQTS
41 (24)	18	Asymptomatic	Male	280	298	72	120	Negative‡	—	Absent	Absent	Absent	Absent		SQTS
42 (24)	18	Asymptomatic	Male	290	326	78	120	Negative‡	—	Absent	Absent	Absent	Absent		SQTS
43 (25)	19	20 yrs	Male	308 (308–340)	257 (257–302)	67	110	Ongoing at report	—	Absent	Absent	Absent	Present		Negative
44 (26)	20	30 yrs	Female	270	292	70	110	Not screened	—	Absent	Present	—	Absent		Negative
45 (27)	21	24 yrs	Male	313	308	75	170	Negative†	—	Absent	Absent	Present	Inducible at EPS		SCD
46 (28)	22	22 yrs	Male	334 (334–376)	349 (349–381)	85	140	*KCNH2*	E50D	Absent	Present	—	Absent		Negative
47 (29)	23	13 yrs	Male	300	283 (283-319)	77	80	Negative‡	—	Absent	Present	—	Absent		Negative
48 (29)	24	Not reported	Male	248	252	61	Unavailable	Not reported	—	Absent	Present	—	Absent		SQTS
49 (29)	25	Not reported	Male	280	313	75	Unavailable	Not reported	—	Absent	Present	—	Absent		SQTS
50 (29)	26	Not reported	Male	320	320	78	Unavailable	Not reported	—	Absent	Absent	Present	Absent		Negative
51 (29)	27	Not reported	Male	300	312	75	Unavailable	Not reported	—	Absent	Absent	Present	Inducible at EPS		Negative
52 (29)	28	Not reported	Male	245	315	74	Unavailable	Not reported	—	Absent	Present	—	Inducible at EPS		SQTS
53 (29)	29	Asymptomatic	Male	295	310	75	Unavailable	Not reported	—	Absent	Absent	Absent	Absent		SQTS
54 (29)	30	Asymptomatic	Male	280	262	65	Unavailable	Not reported	—	Absent	Absent	Absent	Absent		SQTS
55 (29)	30	Asymptomatic	Male	295	335	80	Unavailable	Not reported	—	Absent	Absent	Absent	Inducible at EPS		SQTS
56 (29)	30	Asymptomatic	Male	300	355	84	Unavailable	Not reported	—	Absent	Absent	Absent	Inducible at EPS		SQTS
57 (30)	31	21 yrs	Female	280	315	75	90	Not screened	—	Absent	Present	—	Absent		Negative
58 (31)	32	Asymptomatic	Male	276	298	72	110	Not screened	—	Absent	Absent	Absent	Absent		SCD
59 (32)	33	Asymptomatic	Male	322	329	80	Unavailable	*KCNH2*	R1135H	Absent	Absent	Absent	Absent	NSVT on Holter monitor	SQTS
60 (32)	33	Asymptomatic	Male	345	377	90	Unavailable	*KCNH2*	R1135H	Absent	Absent	Absent	Absent		SQTS
61 (32)	33	Asymptomatic	Female	401	379	93	Unavailable	*KCNH2*	R1135H	Absent	Absent	Absent	Absent		SQTS

Negative genotype: *Genes screened: *KCNH2*, *KCNQ1*, *KCNJ2*, *KCNE1*, *SCN5A*, *KCNE2*, *KCNJ3*, *KCNJ6*, *KCNJ11*, *KCND3*, *KCND2*, *KCNA5*, *KCNIP2*, *KCHAP*, *KCNIP1*, *ABCC8*, *ANKB*, *CHRM1*, *CHRM4*, and *CHRM5*. †Genes screened: *KCNH2*, *KCNQ1*, and *KNCJ2*. ‡Details not provided.

ACA = aborted cardiac arrest; AF = atrial fibrillation; EPS = electrophysiology study; ETT = exercise treadmill test; Jp-Tp = Jpoint-Tpeak interval; NSVT = nonsustained ventricular tachycardia; PMVT = polymorphic ventricular tachycardia; QT_c = Bazett corrected QT interval; QTp = predicted QT-interval; SCD = sudden cardiac death; SQTS = short QT syndrome.

Table 2 Analysis of Age, Sex, and QT Interval Characteristics of the SQTS Cohort

Characteristics		Overall	Male	Female
Presentation (yrs)	n	28	21	7
	Mean ± SD	27.1 ± 18.6	25.7 ± 18.1	31.2 ± 21.0
	Median (IQR)	21 (17–31.8)	20 (17–29)	30 (19–44)
	Overall range	4 months to 70 yrs	8 months to 70 yrs	4 months to 62 yrs
QT, ms	n	58	44	14
	Mean ± SD	281.8 ± 36.5	286.2 ± 29.0	268 ± 52.9
	Median (IQR)	285 (261.5–300)	290 (275.8–300)	268 (226.3–295)
	Overall range	210–401	210–345	210–401
QT_c, ms	n	61	46	15
	Mean ± SD	306.7 ± 26.5	308.1 ± 24.3	302.3 ± 33.0
	Median (IQR)	310 (293–320)	310 (295–320)	300 (290.5–316)
	Overall range	248–381	252–381	248–379
QT/QT_p, %	n	58	44	14
	Mean ± SD	74.1 ± 6.3	74.6 ± 5.4	72.5 ± 8.5
	Median (IQR)	74.5 (71–78)	75 (72–78)	71 (69.3–77.3)
	Overall range	59–93	61–90	59–93

Abbreviations as in Table 1.

females (Table 2). Although the majority of individuals came to clinical attention during late adolescence and early adulthood, there were notable exceptions, including cases that presented during infancy and a male patient (Subject #14; *KCNQ1* V307L) who remained asymptomatic until 70 years of age when he presented with an aborted cardiac arrest (Table 1).

The remaining 26 subjects, all asymptomatic, had been classified as SQTS on the basis of gene carrier status or the presence of a short QT interval in the context of a first-degree relative with a diagnosis of SQTS. Of the individuals considered asymptomatic, 2 had reported experiencing either palpitations or a pre-syncopal event (Subjects #10 and #16). These complaints were not considered sufficient to be classified as symptomatic given their relatively high prevalence in the general population and nonspecific nature. An additional 2 patients were found to have abnormal findings on clinical diagnostic testing, including an episode of polymorphic ventricular tachycardia during exercise treadmill testing (Subject #22) and a period of nonsustained ventricular tachycardia (not specified if polymorphic) observed on Holter monitoring at night (Subject #59; *KCNH2* R1135H).

ECG parameters. QT VALUES. Analysis of QT and QT_c values was performed using the shortest values recorded for each individual patient; in many cases, significant variability of QT values was observed when subjects underwent multiple ECGs (Table 1). Examples include Subject #43, a 20-year-old male from Turkey referred for evaluation of new-onset atrial fibrillation, whose QT_c values ranged from 257 to 302 ms. Similarly, variable QT_c values extending from 283 to 319 ms were noted in Subject #47, a 13-year-old male who presented with an aborted cardiac arrest. Finally, Subject #46 (*KCNH2* E50D) was a 22-year-old male reported by our group with an aborted cardiac arrest whose QT_c values ranged from 349 to 381 ms. Interestingly, Subject #46 first presented with a QT_c value (381 ms) that would generally be considered within the normal range.

The mean, median, interquartile, and overall ranges for the QT, QT_c, and QT/QT_p values were calculated for the overall cohort and then re-evaluated on the basis of sex and symptoms (Tables 2 and 3). The QT values for the entire group extended from 210 to 401 ms when uncorrected for heart rate, and ranged from 248 to 381 ms when adjusted with the Bazett correction formula. The mean and median QT_c values of the overall cohort were 306.7 ± 26.5 ms and 310 ms (IQR: 293 to 320 ms), respectively. The QT index (QT/QT_p) was below 88%, or 2 SDs below the mean, in all but 2 SQTS cases (17). QT parameters are summarized in Tables 2 and 3.

Examination of QT intervals on the basis of sex revealed similar values in both males and females. The QT_c values in males had a mean of 308.1 ± 24.3 ms and a median of 310 ms (IQR: 295 to 320 ms) compared with a mean of 302.3 ± 33.0 ms and median of 300 ms (IQR: 290.5 to 316 ms) in females. Findings for both the uncorrected QT intervals and QT/QT_p values based on sex are shown in Table 2.

When analysis was restricted to subjects classified as symptomatic, the mean and median QT_c values were 296.9 ± 22.1 ms and 302 ms (IQR: 288.5 to 312 ms). In comparison, the QT_c values tended to be longer in asymptomatic subjects, with a mean of 319.8 ± 26.7 ms and median of 321.5 ms (IQR: 304.8 to 332 ms). The longest recorded QT_c value (381 ms) in a symptomatic patient belonged to a 22-year-old male who presented with an aborted cardiac arrest (Subject #46; *KCNH2* E50D), whereas an asymptomatic gene carrier of the *KCNH2* R1135H mutation (Subject #61) was responsible for the longest QT_c (379 ms) in asymptomatic subjects. Table 3 contains results for the uncorrected QT and the QT/QT_p values for symptomatic and asymptomatic SQTS patients.

Table 3 QT Interval Parameters in Symptomatic and Asymptomatic SQTS Cases

Characteristics		Symptomatic	Asymptomatic
QT, ms	n	35	23
	Mean ± SD	270.2 ± 33.3	299.5 ± 34.7
	Median (IQR)	280 (240–297)	300 (285–317.5)
	Overall range	210–334	240–401
QT_c, ms	n	35	26
	Mean ± SD	296.9 ± 22.1	319.8 ± 26.7
	Median (IQR)	302 (288.5–312)	321.5 (304.8–332)
	Overall range	248–381	262–379
QT/QT_p, %	n	35	23
	Mean ± SD	71.9 ± 5.0	77.4 ± 6.6
	Median (IQR)	73 (69.5–75)	78 (74–80)
	Overall range	59–85	64–93

Abbreviations as in Table 1.

Finally, although the numbers were relatively low, the QT_c values associated with the 3 reported *KCNH2* missense mutations were examined. The calculated mean and median of the 10 reported cases of SQTS secondary to the *KCNH2* N588K mutation were 283.8 ± 17.1 ms and 289.5 ms (IQR: 271 to 298 ms), respectively. In contrast, the single case of SQTS associated with the *KCNH2* E50D mutation (Subject #46) had QT_c values that ranged between 349 and 381 ms, whereas the QT_c values associated with the R1135H *KCNH2* mutation ranged from 329 to 379 ms (Subjects #59 to #61). The single case containing the *KCNQ1* V307L mutation (Subject #14) had a QT_c value of 302 ms, whereas the 2 members of the family carrying the *KCNJ2* D172N mutation had QT_c values of 315 ms (Subject #15) and 320 ms (Subject #16).

Jpoint-Tpeak. Measurement of the Jpoint-Tpeak interval when the 12-lead ECG accompanied the report was possible in 30 separate cases. The mean Jpoint-Tpeak interval was 107.6 ± 22.3 ms with values that ranged from 70 to 170 ms (Table 4). The 20 male subjects had a mean Jpoint-Tpeak interval of 111.3 ± 25.6 ms, whereas the corresponding mean value for the 10 female cases was 100.5 ± 12.6 ms. When analyzed on the basis of symptoms, the mean Jpoint-Tpeak interval of the 24 symptomatic subjects was 104.8 ± 22.0 ms, in comparison with a value of 118.3 ± 22.3 ms in the 6 asymptomatic cases.

QT INTERVAL RESPONSE TO EXERCISE. The normal physiologic response of the QT interval to an increasing heart rate is to shorten and can be evaluated using the QT/heart rate (QT/HR) ratio during accelerating heart rate (33). In normal individuals, the QT/HR ratio generally exhibits a linear relationship in response to exercise, and slopes have been shown to typically range from −1.20 to −1.50 ms/beats/min (33). The driving force of the measured slope reflects the progressive shortening of the QT interval relative to increasing heart rate. The presence of a markedly blunted slope of the QT/HR relationship during exercise was observed in 4 cases of SQTS with QT/HR slopes in the range of −0.22 to −0.59 ms/beats/min (28,34). This finding suggests a lesser degree of QT shortening response with accelerating heart rate, possibly reflecting a lack of repolarization reserve due to already enhanced repolarizing currents in the setting of SQTS.

Genetics and family history. The presence of a positive family history for either SQTS or sudden cardiac death was reported in 23 of 32 index cases (71.9%) (family history could not be verified in 1 index case). Review of the genetics underlying the SQTS cohort revealed that 7 of 33 index cases had been found to possess a gain-of-function mutation in 1 of the 3 known culprit voltage-gated potassium channel genes: *KCNH2*, *KCNQ1*, and *KCNJ2* (Table 5, Fig. 1). A total of 14 patients within 5 different families have been found to have a mutation in *KCNH2*. The *KCNH2* N588K mutation was found in 3 of these families and until recently had been the only known *KCNH2* causative mutation (3,18). In 2009, our group reported an E50D mutant in Subject #46 (28), whereas the R1135H mutant was identified in a Japanese family (Subjects #59 to #61) (32).

The remaining 2 genes implicated in SQTS have, to date, only been identified in single index cases. The V307L *KCNQ1* mutation was found in an apparently sporadic case

Table 4 Analysis of the Jpoint-Tpeak Interval in SQTS Cases

Characteristics Jp-Tp, ms	Overall (n = 30)	Male (n = 20)	Female (n = 10)	Symptomatic (n = 24)	Asymptomatic (n = 6)
Mean ± SD	107.6 ± 22.3	111.3 ± 25.6	100.5 ± 12.6	104.8 ± 22.0	118.3 ± 22.3
Median (IQR)	110 (90–120)	110 (92.5–120)	100 (92.5–110)	110 (90–110)	115 (102.5–120)
Overall range	70–170	70–170	80–120	70–170	100–160

Abbrevations as in Table 1.

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Table 5 The Genetic Subtypes of SQTS and Frequency of Culprit Genetic Mutations

SQTS Subtype	Culprit Gene	Reported Mutation(s)	Number of Cases (Families)
SQT1	*KCNH2*	N558K	10 (3)
		E50D	1 (1)
		R1135H	3 (1)
SQT2	*KCNQ1*	V307L	1 (1)
		V141M*	1 (1)
SQT3	*KCNJ2*	D172N	2 (1)
Genotype unknown	—	—	44 (26)

*V141M was identified in a case of reported short QT syndrome (SQTS) identified in utero in association with complete heart block; the patient was not included in our cohort due to the additional presence of complete heart block (35).

of SQTS in a 70-year-old man (Subject #14) who suffered a cardiac arrest in the absence of structural heart disease (4). Following resuscitation, clinical evaluation was unremarkable aside from a QT_c of 302 ms on ECG. In contrast, the D172N *KCNJ2* mutation has not been reported to have been associated with adverse clinical events. It was identified in a single family following referral of a 5-year-old girl (Subject #15) for evaluation due to a short QT_c value (315 ms) (5). The ECG of the 35-year-old father (Subject #16) was also notable for a short QT interval (320 ms) and, although he had not experienced any definitive clinical events, he did report symptoms of palpitations and presyncope since the age of 15.

Of the remaining 26 index cases, 9 had no mutations identified in *KCNH2*, *KCNQ1*, and *KCNJ2*, indicating that other genetic culprits remain to be identified. Two index cases were reported as genotype negative; however, the specific genes screened were not cited. Genetic testing was ongoing in 2 further index cases, 6 other index cases were reportedly not screened, and it was unclear whether genetic testing had been performed in the remaining 7.

Discussion

The SQTS is characterized by a short QT interval on ECG; however, there remains a lack of consensus regarding an appropriate QT interval cutoff warranting diagnostic consideration. Furthermore, the existence of a range of QT_c values that overlap between reported cases of SQTS and the general population complicates clinical assessment. In the case of LQTS, a formalized diagnostic scoring system was developed in an effort to facilitate evaluation of suspected cases (13,14). Following a systematic review of all cases of SQTS reported in the literature, we have developed a similar diagnostic approach for SQTS (Table 6).

The SQTS diagnostic criteria have been divided into 4 different components including ECG, clinical history, family history, and genotype. In order to be eligible to receive points in the latter 3 sections, a minimum of 1 point must be received from the ECG criteria. An overall score of 4 points or greater indicates a high-probability diagnosis of SQTS, whereas 2 points or less makes a diagnosis of SQTS low probability. Patients with a score of 3 points are considered to have an intermediate probability of having SQTS. Given the significant QT interval variation docu-

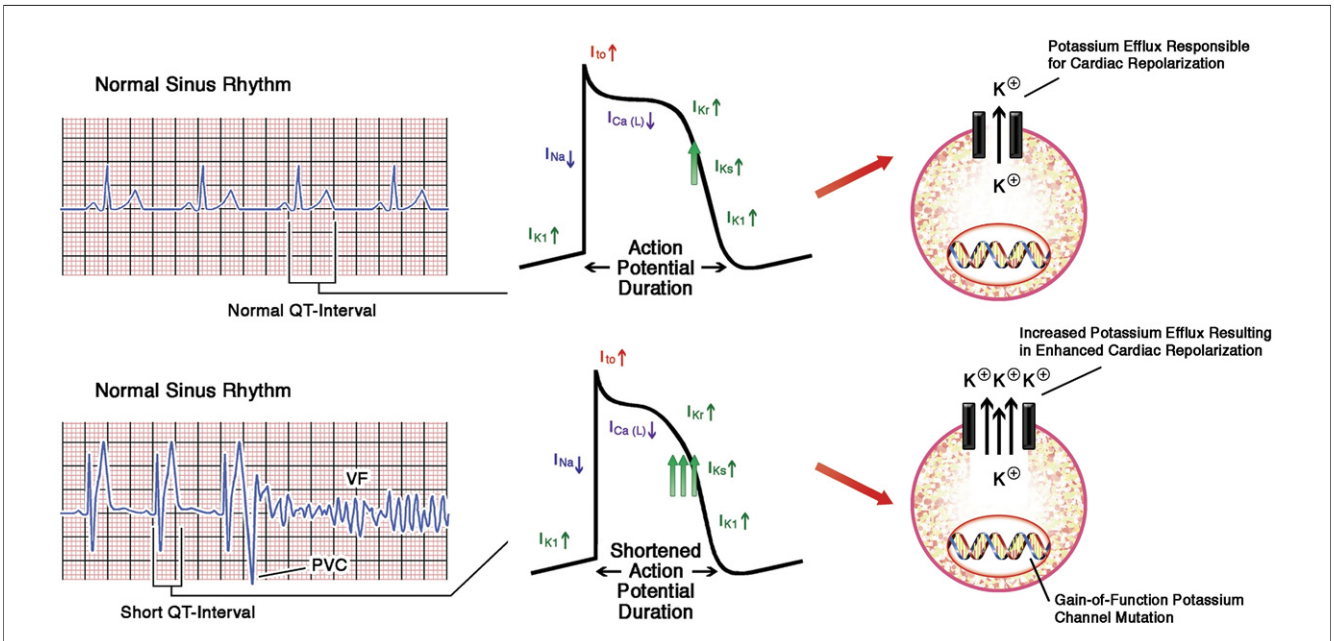

Figure 1 Cellular Mechanism of Short QT Interval

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. Illustration designed by authors with the assistance of Craig Skaggs. PVC = premature ventricular contraction; VF = ventricular fibrillation.

Table 6 SQTS Diagnostic Criteria

	Points
QT_c, ms	
<370	1
<350	2
<330	3
Jpoint-Tpeak interval <120 ms	1
Clinical history*	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

High-probability SQTS: ≥4 points, intermediate-probability SQTS: 3 points, low-probability SQTS: ≤2 points. Electrocardiogram: must be recorded in the absence of modifiers known to shorten the QT. Jpoint-Tpeak interval must be measured in the precordial lead with the greatest amplitude T-wave. Clinical history: events must occur in the absence of an identifiable etiology, including structural heart disease. Points can only be received for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope. Family history: points can only be received once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section in order to obtain additional points.

VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

mented in individual patients from our cohort, continued medical surveillance and serial electrocardiographic monitoring may serve to clarify the diagnosis in patients with intermediate probability. This approach, coupled with obtaining ECGs from first-degree relatives, has previously proven helpful in the context of the LQTS (36).

ECG criteria. The ECG component of the diagnostic criteria relies on the Bazett correction formula (QT_c) to account for changes in the QT interval associated with heart rate (37). Although this formula has important limitations during bradycardia and tachycardia (16), it remains the most commonly used heart rate correction factor in clinical practice. Our definition of a short corrected QT interval relied in part on data from large epidemiologic studies that reported the distribution of corrected QT intervals in the general population (6,7,10,11). These studies suggested that a QT_c value of approximately 350 ms in males and 365 ms in females corresponded to values 2 standard deviations below the mean (6,7,10,11). In over 90% of SQTS cases, both the measured QT_c value and QT index demonstrated values well below 2 SDs from the mean (QT_c <350 ms and QT index <88%) of healthy subjects (Table 1). The mean QT_c value for our SQTS cohort was substantially lower at 306.7 ± 26.5 ms with a relatively narrow IQR that stretched from 293 to 320 ms. However, despite the apparent contrast between QT_c values in SQTS and the general population, the standard deviation in SQTS cases was broad, and exceptional cases were observed. The longest QT_c value in the SQTS cohort was observed in a 22-year-old male (Subject #46) who presented with an aborted cardiac arrest. His initial QT_c value was 381 ms, and lowest subsequent QT_c was 349 ms. This patient was identified to have a novel E50D missense mutation in the *KCNH2* gene (28).

The range of short QT_c intervals that may be associated with event risk is further highlighted in a reported series of patients with "idiopathic ventricular fibrillation" (IVF), who were noted to have a mean QT_c value of 371 ms, significantly below the QT_c value of healthy, sex- and age-matched controls (38). Although speculative, these findings suggest that a proportion of patients previously classified as IVF may actually suffer from a pathology consistent with the SQTS. Diagnostic consideration of SQTS in such patients and subsequent screening of culprit genes may prove beneficial. In light of the range of QT_c intervals in documented cases of SQTS and in previously diagnosed IVF cases, we have chosen a QT_c value of 370 ms as an initial cutoff for diagnostic consideration of this condition. Although a QT_c upper limit of 370 ms will include a proportion of normal individuals, the diagnostic criteria require an association with multiple different clinical or genetic details in order to avoid an inappropriate diagnosis on the basis of QT_c value alone.

Individuals with a recorded QT_c value of less than 370 ms receive a minimum of 1 point from the scoring system. Although QT duration has been observed to be greater in females, a phenomenon also observed at the lower limit of normal QT values, we have not chosen a separate cutoff value for females in view of similar QT_c values being observed in diagnosed males and females (Table 2) (6,7,10). Additional points are assigned for increasingly abbreviated QT_c intervals, based on observations suggesting that very short QT intervals are exceedingly rare in the general population. In the large Finnish population study, a QT_c value <340 ms was observed in 0.4% of the population, whereas a QT_c value <320 ms was found in just 0.1% (6). This low frequency of extremely short QT intervals was further corroborated by multiple additional studies that demonstrated similar findings (7–9,11,39). Accordingly, patients with a QT_c value less than 350 ms receive 2 points, whereas 3 points are assigned for a QT_c value <330 ms. Of note, patients should not receive points in the presence of modifiable factors known to abbreviate the QT interval such as hypercalcemia, digoxin administration, and androgen use (40–42).

In addition to the QT interval, other distinctive features associated with the ECGs of SQTS patients have been reported, including the relative absence of an ST-segment. Data suggest that extreme abbreviation of the Jpoint-Tpeak interval may help distinguish patients with the SQTS from healthy subjects with an apparent abbreviation of the ST-segment and shortened QT intervals. Reported analyses of 10 symptomatic SQTS patients indicated a markedly shortened mean Jpoint-Tpeak interval (101 ms, range 80 to 120 ms) in comparison with 12 healthy subjects with QT_c values <320 ms (184 ms, range 150 to 240 ms) who had remained

arrhythmia-free over an average follow-up of 29 years (43). A separate ECG study involving 500 healthy subjects identified mean Jpoint-Tpeak values of 188 ± 11 ms and 214 ± 15 ms in males and females, respectively (44). These findings suggest that a shortened Jpoint-Tpeak interval may permit ECG discrimination between individuals with a pathologic substrate consistent with the SQTS and those individuals who possess a benign form of abbreviated QT intervals. Measurement of the Jpoint-Tpeak interval in 30 SQTS cases from our cohort using the precordial lead with the greatest T-wave amplitude, consistent with the previous studies, identified a mean value of 107.6 ± 22.3 ms, providing further support for the presence of a markedly abbreviated Jpoint-Tpeak interval in SQTS cases (Table 5). From these findings, the presence of a Jpoint-Tpeak interval <120 ms in the precordial lead with the greatest T-wave amplitude is allocated 1 point. The cutoff of 120 ms provides high specificity for the SQTS based on current data while remaining readily recognizable on visual ECG inspection in clinical practice.

The presence of high-amplitude, peaked T waves, which are frequently observed on ECG in SQTS subjects, was considered for inclusion in the diagnostic scorecard. However, in contrast to measures of Jpoint-Tpeak, high-amplitude T waves have not been shown to distinguish SQTS patients from healthy individuals with short QT intervals and no clinical events (43). Another morphological T-wave feature, the total cosine of the angle between the main vectors of the QRS and T-wave loops, has also been reported to be abnormal in SQTS patients (45). However, this parameter requires specific software for analysis, is not used routinely in clinical practice, and was not considered practical for use in diagnostic criteria. Finally, a high prevalence of early repolarization has been observed in SQTS patients; however, this observation in the diagnosis of SQTS is limited, given its high frequency in the general population (46).

The QT response to exercise was also considered for use in the diagnostic critieria. At present, analysis of QT response to accelerating heart rate has only been formally reported in 4 cases of diagnosed SQTS (28,34). Analyses of the QT/HR relation through exercise appears to demonstrate a blunting of the slope with increasing heart rates. However, in the absence of validation of these observations in a larger cohort of patients, and given the challenges of measuring QT intervals during rapid heart rates, the diagnostic value of this test was deemed to be minimal and is not included in the diagnostic criteria.

Clinical history. Upon receiving a minimum of 1 point from the ECG section, cases are subsequently eligible to receive points from the other components of the SQTS diagnostic criteria scorecard. Diagnostic points are provided for a documented history of cardiac arrest (either aborted or resulting in death), observed nonsustained polymorphic ventricular tachycardia (VT) or VF, unexplained syncope, and/or atrial fibrillation. Events must occur in the absence of other identified clinical pathologies. The events of a cardiac arrest or nonsustained VT/VF result in 2 points, whereas unexplained syncope and atrial fibrillation are only assigned a single point, given their relatively high prevalence in the general population. Points can only be received for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope.

Family history and genotype. The final 2 components of the diagnostic scoring system relate to heritability of the syndrome. The importance of heritability is illustrated by the finding that 23 of the 32 (71.9%) index cases reviewed had a family history of SQTS or sudden cardiac death. A positive family history for SQTS has been assigned 2 points and requires a high-probability diagnosis of SQTS (4 points or greater) in a first- or second-degree relative. In contrast, a positive family history for sudden cardiac death with a negative autopsy or sudden infant death syndrome in a first- or second-degree relative in the absence of a high-probability diagnosis of SQTS yields 1 point.

Genetic studies have implicated 5 separate genes in the etiology of a proportion of patients with diagnosed SQTS, although the majority of diagnosed cases do not have reported genetic associations (3–5,15). The initial 3 genes identified were voltage-gated potassium channels whose gain-of-function mutations accounted for the SQTS phenotype secondary to accelerated repolarization resulting from increased potassium efflux (Table 5, Fig. 1) (3–5). In contrast, the most recent genes reported are loss-of-function mutations in the *CACNA1c* and *CACNB2b* genes, which encode subunits of L-type calcium channels (15). However, the 3 patients reported to harbor these mutations had clear ECG findings consistent with a Brugada type 1 pattern, albeit with abbreviated QT intervals. To most clinicians, these cases would be readily recognized as Brugada syndrome. Thus, in its purest form, the SQTS has 3 known genetic culprits at the present time: *KCNH2*, *KCNQ1*, and *KCNJ2*. It is expected that further genes will be identified and novel cellular mechanisms of QT-interval shortening elucidated.

The presence of a suspected disease-causing genetic mutation for the SQTS has been assigned a score of 2 points. Identification of a novel mutation of undetermined significance in a known gene associated with SQTS has been assigned a single point. This is to acknowledge that the interpretation of genetic variations as disease causing may be uncertain, especially in the context of novel genes that may be identified in the future with little history in regard to known disease-causing variants or polymorphisms.

Clinical application of the SQTS diagnostic criteria scorecard. The proposed SQTS diagnostic criteria were evaluated using the 61 symptomatic and asymptomatic cases that were systematically reviewed from the literature. Of these cases, 58 of 61 (95%) would receive a diagnostic score indicating high-probability SQTS. Although the diagnostic criteria provide a systematic diagnostic approach for SQTS in suspected index cases, the value of the scorecard for

evaluation of family members is not expected to be highly sensitive due to the common phenomena of incomplete disease penetrance observed for inherited cardiac syndromes. In addition, clinicians are encouraged to remain cognizant of benign variants of QTc abbreviation, analogous to the challenges of evaluating prolonged QT intervals in consideration of LQTS. Treatment consideration should be reserved for those cases receiving a high-probability score, whereas medical surveillance or expert opinion considered for intermediate- or low-probability cases.

Conclusions

The absence of formalized diagnostic criteria for the SQTS is associated with a lack of consensus regarding an appropriate QT interval cutoff suitable for diagnostic consideration of this condition. This has been further complicated by the recognition of an overlap of short QT_c intervals in previously diagnosed cases and apparently healthy individuals from the general population. The proposed diagnostic criteria will facilitate evaluation in suspected cases and may lead to the reclassification of previously considered IVF patients as having SQTS. A universal diagnostic approach should enhance recognition of SQTS patients and facilitate clinical evaluation of family members who may be at risk of events from this genetically-mediated arrhythmia syndrome.

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