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Journal Pre-proof



Type 3 long QT syndrome: is the effectiveness of treatment with beta-blockers population-specific?

Alexis Hermida, MD, Jean-Baptiste Gourraud, MD, Isabelle Denjoy, MD, Véronique Fressart, MD, Florence Kyndt, PharmD, PhD, Alice Maltret, MD, Diala Khraiche, MD, Didier Klug, MD, PhD, Philippe Mabo, MD, Frédéric Sacher, MD, PhD, Philippe Maury, MD, PhD, Pierre Winum, MD, Pascal Defaye, MD, Gael Clerici, MD, Dominique Babuty, MD, Yedid Elbez, MSc, Charles Morgat, MD, Elodie Surget, MD, Anne Messali, MD, Patrick De Jode, MD, Aurélien Clédel, MD, Damien Minois, MD, Pierre Maison-Blanche, MD, Adrien Bloch, MD, Antoine Leenhardt, MD, Vincent Probst, MD, PhD, Fabrice Extramiana, MD, PhD

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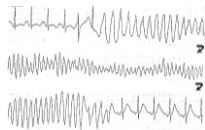
141 patients with LQT3

β -blockers initiation
N=61 patients (43.3%)



20.5% [14.2-29.0]
probability of
CE (syncope/SCD/ACA/
appropriate ICD shock)
at the age of 40

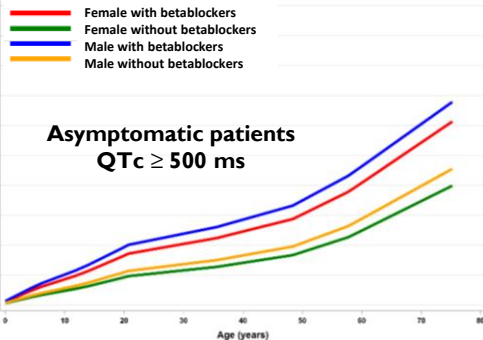
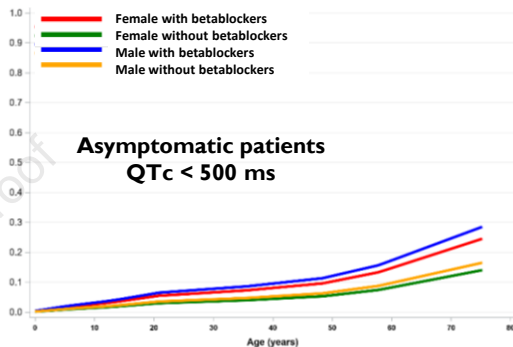
9.9% [5.5-17.5]
probability of
SCE (SCD/ACA/
appropriate ICD
shock) at the age of 40



CEs predictors
(HR [95%CI]):
-Proband status: 4.07
[1.9-8.9]; $p < 0.001$
-QTc prolongation: 1.12
[1.0-1.2]; $p = 0.005$

SCEs predictors
(HR [95%CI]):
-Proband status: 8.13
[1.7-38.8]; $p = 0.009$

Cox model predicted age at first SCE



Median [IQR] follow-up: 11 [6.0-16.0] years

1 **Structured Abstract**

2 **Background:** Efficacy of beta blocker treatment in type 3 long QT syndrome (LQT3) remains
3 debated.

4 **Objectives:** To test the hypothesis that beta-blocker use is associated with cardiac events in a
5 French cohort of LQT3 patients.

6 **Methods:** All the patients with a likely pathogenic/pathogenic variant in the *SCN5A* gene
7 (linked to LQT3) were included and followed up. Documented ventricular
8 tachycardia/ventricular fibrillation, torsade de pointes, aborted cardiac arrest, sudden death,
9 and appropriate shocks were considered as severe cardiac events (SCEs). Cardiac events
10 (CEs) also included syncope.

11 **Results:** We included 147 patients from 54 families carrying 23 variants. Six of the patients
12 developed symptoms before the age of 1 year and were analyzed separately. The 141
13 remaining patients (52.5% male, median age at diagnosis 24.0 years) were followed-up for a
14 median of 11 years. The probabilities of a CE and an SCE from birth to the age of 40 were
15 respectively 20.5% and 9.9%. QTc prolongation (HR = 1.12 [1.0-1.2]; p=0.005) and proband
16 status (HR = 4.07 [1.9-8.9]; p<0.001) were independently associated with the occurrence of
17 CEs. Proband status (HR = 8.13 [1.7-38.8]; p=0.009) was found to be independently
18 associated with SCEs, while QTc prolongation (HR = 1.11 [1.0-1.3]; p=0.108) did not reach
19 statistical significance. The cumulative probability of the age at first CE/SCE was not lower in
20 patients treated with a beta-blocker.

21 **Conclusion:** In agreement with the literature, proband status and lengthened QTc were
22 associated with a higher risk of CEs. Our data do not show a protective effect of beta-blocker
23 treatment.

24

1 **Keywords:** type 3 long QT syndrome – SCN5A – beta-blocker treatment – prognosis –

2 personalized medicine

3

4 **Abbreviation list**

5 ACA: aborted cardiac arrest

6 CE: cardiac event

7 ICD: implantable cardioverter defibrillator

8 LQTS: long QT syndrome

9 LQT3: type 3 LQTS

10 SCD: sudden cardiac death

11 SCE: severe cardiac event

12 TdP: torsade de pointes

13 VT/VF: ventricular tachycardia / ventricular fibrillation

14

1 **1. Introduction**

2 Congenital long QT syndrome (LQTS), the most frequent inherited arrhythmic syndrome, is a
3 significant cause of SCD in young patients with structurally normal heart.

4 Type 3 LQTS (LQT3) is found in 5 to 10% of genotype-positive patients. Despite its
5 rarity, LQT3 differs from types 1 and 2 LQTS (LQT1 and LQT2) with regard to the disease
6 mechanisms¹, the circumstances of symptom onset²⁻⁴, prognosis⁵, and responsiveness to
7 treatment.

8 Although experimental data^{6,7}, as well as results from previous clinical studies^{8,4,9},
9 suggested that beta-blocker treatment could be less effective or even harmful in LQT3, more
10 recent studies have challenged this finding. A meta-analysis published in 2017¹⁰, could not
11 provide a conclusive statement on the role of beta-blockers in LQT3. However, Wilde et al.¹¹
12 study of the largest yet international cohort of LQT3 patients (n=391) found a strong
13 protective effect of beta-blockers in women. In contrast, the latest work on the subject was
14 unable to show a beneficial effect of beta blockers.¹²

15 In order to confirm the effectiveness of beta-blocker treatment in an independent
16 cohort of LQT3 patients, we sought to identify predictors of cardiac events (CEs) and severe
17 cardiac events (SCEs) in a large French multicenter cohort of LQT3 patients.

18

1 **2. Methods**

2 2.1. Study population

3 Probands were initially diagnosed with LQTS based on ECG and clinical data in three French
4 reference centers for inherited arrhythmias. LQT3 was subsequently diagnosed in presence of
5 a likely pathogenic/pathogenic variant in *SCN5A*. Cascade screening was offered to family
6 members.

7 All probands and family members carrying *SCN5A* LQT3 likely
8 pathogenic/pathogenic variants were included in the study. Patients with Cardiac Event
9 (aborted cardiac arrest (ACA), SCD or syncope) before 1 year of age were excluded from the
10 study population.

11 All patients or the authorized family members gave their written, informed consent for
12 the genetic testing and the use of their personal medical data for research purposes. The study
13 protocol complied with the ethical guidelines of the Declaration of Helsinki as revised in 2013
14 and its subsequent amendments. In line with the French legislation on studies of routine
15 clinical practice, the study protocol was approved by a hospital committee with competency
16 for studies not requiring approval by an institutional review board. Furthermore, the study
17 database was anonymized and registered with the French National Data Protection
18 Commission (*Commission nationale de l'informatique et des libertés* (Paris, France);
19 reference: PI2022_843_0059).

20 Mutations were analyzed according to standard protocols for genetic testing. Details
21 are provided in supplementary data.

22

23

1 2.2. Data on the natural history of the disease

2 The time of diagnosis was defined as the date on which LQTS was diagnosed from clinical
3 and ECG data or on which a LQT3-associated gene mutation was found, whichever first.

4 Personal and family medical histories prior to diagnosis were collected retrospectively.

5 Cardiac events were defined as syncope (after excluding orthostatic, reflex and vaso-
6 vagal mechanisms), documented polymorphic VT, VF or torsade de pointes (TdP), ACA,
7 SCD, and appropriate shocks. Serious cardiac events were defined as polymorphic VT/VF,
8 TdP, ACA, SCD, and appropriate shocks.

9 ECG measurements and LQTS score are described in supplemental data.

10

11 2.3. Follow-up data and outcomes

12 Patients were followed up prospectively from the LQTS diagnosis to the last follow-up visit
13 or death. Treatment decisions were left to the attending physician. We recorded the drug
14 name, the treatment periods, and the time of event occurrence.

15 The study's primary and secondary outcomes were the time from birth to the
16 occurrence of the first CE and the first SCE (as defined above), respectively.

17

18 2.4. Statistical analysis

19 Continuous variables were expressed as the mean \pm standard deviation or the median
20 [interquartile range (IQR)] for normally and non-normally distributed data, respectively, and
21 group values were compared using Student's *t*-test or the Mann–Whitney–Wilcoxon test, as
22 appropriate. Categorical variables were expressed as the number (percentage), and group
23 values were compared using a chi-squared test.

24 The time to the first CE or first SCE was represented graphically as a Kaplan-Meier
25 curve, and groups were compared in a log-rank test. For patients with no CEs during the

1 follow-up period, the data were censored either at death, loss to follow-up, the end of the
2 follow-up period, or the initiation of treatment with an antiarrhythmic drug other than a
3 betablocker.

4 Furthermore, the time-to-event outcomes were modeled using Cox proportional-
5 hazards regressions. Single-variable analyses (for individual variable effects) and
6 multivariable analyses were conducted sequentially. The models included the following
7 covariates: beta-blocker status, p.(Glu1784Lys) variant, QTc level (per 10 ms increment), sex,
8 and proband status.

9 Since the betablocker status can change over time the treatment variable was
10 introduced as a time-varying covariate in the Cox models. We also introduced syncope into
11 the model as a time-varying covariate predictor of the CE or SCE.

12 Relative risks for each covariate were expressed as the hazard ratio (HR) [95%
13 confidence interval (CI)]. All tests were two-sided. The threshold for statistical significance
14 was set to $p < 0.05$.

15

16

1 3. Results

2 3.1. The study population

3 181 patients from 72 families carrying 40 different *SCN5A* variants were identified in the
4 databases. After review, 17 variants were considered variants of uncertain significance (33
5 carriers and 17 families). Hence, 148 patients from 55 families carrying 23 different *SCN5A*
6 variants were eligible. One proband also carried a pathogenic *KCNQ1* variant and was
7 excluded.

8 Our final study population therefore included 147 patients from 54 families carrying
9 23 variants (22 missense variants and 1 deletion) (Supplemental Table S1).

10 Six (4.1%) patients showed LQTS-related events before 1 year of age (Supplemental
11 Table S2 and S3). These 6 patients were excluded from further analyses.

12

13 3.2. Clinical characteristics at diagnosis

14 Table 1 displays the clinical characteristics of the 141 patients (52.5% males, median age 24.0
15 years [12.0-43.0]).

16 Half of patients carried the p.(Gly1784Lys) variant. Comparison with patients carrying
17 other mutations are shown in Supplemental Table S4.

18 At diagnosis, 26 patients (17.7%) had a history of CEs (including SCEs in 6 cases).
19 These patients were more likely to be probands and had a longer QTc interval and a higher
20 LQTS risk score (Supplemental Table S5).

21

22 3.3. Follow-up data

23 Two patients (both asymptomatic at diagnosis) were lost to follow-up. The remaining 139
24 patients were followed up for a mean of 11.2 ± 6.9 years (median: 11; IQR: 6.0-16.0).

1 Beta-blocker treatment was initiated in 61 (43.3%) patients. Characteristics of patients
2 according to initiation of beta-blocker treatment are shown Table 2. Nadolol was the most
3 frequently prescribed (50.8%), followed by bisoprolol (29.5%), acebutolol (6.6%),
4 propranolol (4.9%), atenolol, celiprolol (3.3% each), and betaxolol (1.6%).

5 Three patients were treated with flecainide immediately after diagnosis, and 3 others
6 after experiencing a SCE during follow-up. In the latter 3 cases, an SCE recurred during the
7 flecainide treatment period.

8 Twenty-four patients (17.0%) received an ICD.

9 None had left cardiac sympathetic denervation.

10 Twenty patients (14.2%) experienced at least one CE during follow-up, and 12 (8.5%)
11 experienced at least one SCE (1 SCD, 3 ACA, and 8 appropriate shocks) (Supplemental Table
12 S6). Treatment at the time of Severe cardiac events occurring before and after diagnosis are
13 described in Table 3. None of the SCE observed in p.(Glu1784Lys) carriers occurred while on
14 beta blocker. None of the appropriate ICD shocks occurred while on beta blocker (Table 3).

15 Patients who died from LQTS are described in Supplemental Table S7.

16

17 3.4. Predictors of CEs

18 The cumulative [95%CI] probabilities of a first CE and SCE at the age of 40 were
19 respectively 20.5% [14.2-29.0] and 9.9% [5.5-17.5] (Figure 1). The risk of a CE and an SCE
20 was associated with the degree of QTc prolongation (Supplemental Figure 1).

21 QTc prolongation (HR = 1.12 [1.0-1.2]; p=0.005) and proband status (HR = 4.07
22 [1.9-8.9]; p<0.001) were independently associated with the occurrence of CEs (Table 4).

23 When syncope was included in a time-dependent model, proband status (HR = 8.13 [1.7-
24 38.8], p=0.009) was the only independent factor associated with SCEs (Table 5). When

25 syncope was excluded, QTc prolongation (HR = 1.14 [1.0-1.3]; p=0.027), proband status (HR

1 = 8.59 [1.8-40.2]; p=0.006), and time-dependent beta-blocker treatment (HR = 3.43 [1.1-
2 10.8]; p=0.036) were independently associated with SCEs (Supplemental Figure 2).

3 Figures 2 and 3 show the Cox-predicted age at first SCE by beta-blocker treatment
4 status and sex. In asymptomatic patients (i.e. no prior syncope) beta-blocker treatment was
5 not associated with lower probability of SCE in both sexes; in both patients with QTc above
6 or below 500 ms (Figure 2). Likewise, in patients with prior syncope, beta-blocker treatment
7 was not associated with a lower probability of an SCE in both sexes, regardless of whether the
8 QTc was below or above 500 ms (Figure 3). Exclusion of patients carrying the
9 p.(Glu1784Lys) mutation did not change the pattern (Supplemental Figure 3 and 4).

10

1 **4. Discussion**

2 We analyzed the predictors of LQTS-related events in a large, independent cohort of
3 genotyped patients with LQT3 in France. We found the usual risk factors for events (such as
4 proband status and QTc prolongation) in LQT3 patients but we did not observe the protective
5 effect of beta-blocker treatment described in recent studies.

6

7 4.1. Representativeness of the cohort

8 The distribution of QTc durations observed in our study was in line with recent
9 reports^{11,13}, although the values were mostly shorter than in some older studies^{2,4,8,9}. As
10 previously described¹⁴, including genotype-positive but phenotype-negative patients affects
11 the clinical characteristics and the prognosis of LQTS patients with LQTS (see Supplemental
12 Table 8 for review).

13 We found that QTc prolongation was a strong predictor of CEs and SCEs, as
14 consistently reported in the literature.^{2,5,11,14} In our study (as in others), the *SCN5A*
15 p.(Glu1784Lys) variant was the most frequent. The latter is reportedly associated with high
16 event rates¹⁵ and/or a benign clinical course¹¹. In our study, the event rate was lower in
17 p.(Glu1784Lys) carriers but this difference vs. other variants was not statistically significant.

18

19 4.2. The effectiveness of beta-blockers

20 In contrast to LQT1 (and in a lesser degree in LQT2), most events occur at night or
21 when resting in patients with LQT3.⁴ Although the autonomic state changes during different
22 sleep phases, this suggests that adrenergic stimulation is not a major trigger in LQT3, and
23 intuitively, that beta-blocker treatment would not protect against these events occurring at rest
24 or during sleep.

1 Accordingly, the earliest cohort studies found that beta-blocker treatment was less
2 effective in LQT3 than in LQT1 or LQT2.^{4,8,9} However, more recent data have challenged
3 these studies. A meta-analysis¹⁰ published in 2017 was not able to make a conclusive
4 statement. While, the study published in 2016 by Wilde et al.¹¹ showed a strong protective
5 effect of beta-blocker treatment in females, but not in males.

6 Mazzanti et al.¹⁴ showed that nadolol was associated with a significant risk reduction
7 in LQTS patients without significant statistical interaction with genotype. However, the lack
8 of a statistically significant result does not rule out the presence of an interaction; the authors
9 did not report event rates on and off beta-blockers by genotype, and so firm conclusions about
10 the effectiveness of beta-blockers in LQT3 cannot be drawn from their study.

11 Noteworthy, the same group had previously reported¹⁶ that beta-blockers failed to
12 significantly reduce the mean number of patients with ACA/SCD (from 6 to 4, $p=0.688$), the
13 mean number of ACAs/SCDs per patient (from 0.13 to 0.10, $p= 0.763$).

14 The European Society of Cardiology's latest guidelines on the management of patients
15 with ventricular arrhythmia¹⁷ highlighted "the uncertain role of beta-blockers in LQT3".

16 A recent work by Younis et al.¹² showed that the positive effect of beta-blockers was
17 highest in patients with exercise or stress related events. However, despite including 501
18 LQT3 patients, the study could not demonstrate a positive effect of beta-blockers in LQT3
19 patients.

20 In the present study, a multivariate analysis and Cox prediction models did not show a
21 protective effect of beta-blocker treatment.

22 There are several possible explanations for the differences in the effectiveness of beta-
23 blocker treatment between Wilde et al.'s study and our study.

24 Firstly, the two study populations were genetically dissimilar, with a higher prevalence
25 of the p.(Gly1784Lys) mutations in our study. In a recent study, 75% of the patients carrying

1 the *SCN5A* Glu1784Lys mutation had a Brugada ECG pattern after an ajmaline challenge¹⁸.
2 The additional presence of Brugada syndrome would contra-indicate the use of sodium
3 channel blockers and would raise questions about the safety of beta-blocker treatment.
4 Noteworthy, all the 6 SCEs recorded in our p.(Glu1784Lys) carrier patients occurred while
5 off beta blockers. Hence, these events are not related to a proarrhythmic effect of treatment in
6 LQT3-Brugada patients, and the absence of efficacy of beta-blocker treatment in our study
7 cannot be explained by a specific treatment effect in p.(Glu1784Lys) carriers. Moreover, the
8 multivariate analysis was adjusted on the p.(Glu1784Lys) presence to take into account its
9 possible specific response to beta-blocker treatment. The prediction model performed on the
10 population without the p.(Glu1784Lys) was consistent with the trend shown by the same
11 model for the whole population. These various arguments suggest that our results are not
12 driven by the significant proportion of the p(Glu1784Lys) carriers. Mutation types are not
13 necessarily similar in different cohorts and may affect treatment effect. For instance, it has
14 been shown that some LQT3 mutations do not respond to mexiletine.^{19,20}

15 Secondly, appropriate shocks, which are not good surrogates of ACA/SCD, were
16 included in our definition of SCEs but were not taken into account by Wilde et al.. However,
17 none of the appropriate ICD shocks observed in our study occurred while on beta-blocker.
18 Hence, including appropriate shocks in the SCE category should have driven the results
19 toward a detrimental effect of not prescribing beta-blockers.

20 Thirdly, we note that only around half (56%) of our beta-blocker-treated patients were
21 on propranolol or nadolol. More frequent prescription of beta-blockers with a late sodium
22 current blocking effect might have tilted the results toward a beneficial effect of treatment.
23 The proportion of patients on different beta-blockers type are not clearly described in all
24 previous studies.¹¹

1 Last, the absence of protective effect found in our study could be related to the
2 selection bias induced by treatment decision. Indeed, patients in whom beta-blocker treatment
3 was prescribed had a higher risk profile (Table 2). We did our best to try to account for such a
4 bias by using multivariate analyzes and complex modelling with the treatment variable
5 introduced as a time-varying covariate in the Cox models.

6 7 4.3. Other treatment options for patients with LQT3

8 Our results raise questions about the effectiveness of beta-blocker treatment in LQT3 patients.
9 However, this does not mean that we recommend broadening the indication for ICD
10 implantation for primary prevention, because ICDs are associated with high complication
11 rates - especially in younger patients.

12 Other therapeutic options exist, and recent studies have underlined the potential
13 efficacy of various drug-based approaches. Small series have described good levels of
14 effectiveness for flecainide in LQT3 patients.²¹⁻²³ In our study, flecainide did not prevent
15 recurrences in the 3 patients treated with flecainide after a severe event.

16 The late sodium current channel blockers are promising avenues. In a study of a cohort
17 of 34 LQTS patients, mexiletine shortened QTc and was associated with a major reduction in
18 the frequency of life-threatening arrhythmic events.²⁴ In two small clinical series of LQT3
19 patients, treatment with ranolazine resulted in a shorter QT interval – despite the associated
20 IKr blockade effect.^{25,26} Mexiletine is now recommended for patients with LQT3 and
21 prolonged QTc.¹⁷

22 Left cardiac sympathetic denervation is recommended in the last guidelines, regardless
23 of the LQTS¹⁷ but specific data in LQT3 are scarce.

1 4.4. Limitations

2 Although our cohort was relatively large for a single country, it accounted for only a small
3 proportion of the patients with LQT3 in France; hence, selection bias cannot be ruled out.

4 Furthermore, given the small number of events, a lack of statistical power cannot be ruled out.

5 Our work also presents the limitations of a non-randomized study, with possible selection bias
6 – particularly regarding the prescription of beta-blocker treatment. This selection bias,

7 inherent to non-randomized studies, was most likely also present in previous published studies
8 on the topic.¹¹ Finally, low beta-blocker treatment observance has been related to increase risk

9 of event occurrence.²⁷ Since we could not ascertain, beyond history taking, the patients

10 treatment observance at the time of event occurrence, we cannot exclude that some events

11 classified as occurring on beta blocker treatment actually took place off treatment. It should

12 be noted that our population has a high prevalence of the p.(Glu1784Lys) variant, potentially

13 responsible of overlap syndrome, and consequently with a potentially worse response to beta-

14 blocker treatment. We took this parameter into account by adjusting the multivariate analyses

15 on the presence of this particular variant.

16

17

1 **5. Conclusion**

2 In accordance with previous studies of LQT3 patients, proband status and QTc duration were
3 independently associated with the occurrence of cardiac events in our LQT3 cohort. Our data
4 do not find a protective effect of beta-blocker treatment in LQT3 patients. This result suggests
5 that the response to beta-blocker treatment may depend on clinical and/or genetic
6 characteristics of patients.

7 The best therapeutic approach for LQT3 patients needs to be refined, in order to better
8 define the indications for beta-blockers or late sodium current inhibitors and to avoid overly
9 frequent implantation of ICDs. Further analyses of historical cohorts would probably be
10 subject to the same methodological limitations as our present work. Given the rarity of LQT3,
11 we consider that collaborative, randomized controlled studies are now warranted.

12

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15

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20

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1 9. Figure titles and captions

2 Figure 1. The cumulative probability of the first LQT3-triggered CE or SCE.

3 The probabilities [95%CI] of CE and SCE at the age of 40 were respectively 20.5% [14.2-29.0]
4 and 9.9% [5.5-17.5].

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7 Figure 2. Predicted age at first SCE (based on a Cox model) by beta-blocker treatment status
8 and sex for asymptomatic patients (no prior syncope) and A. a QTc <500 ms. B. a QTc ≥500
9 ms

10 In asymptomatic patients (no prior syncope) without a low-risk mutation p.(Glu1784Lys), beta-
11 blocker treatment was associated with higher probability of SCE in both sexes, regardless of
12 whether the QTc was below or above 500 ms (left and right panels, respectively).

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14

15 Figure 3. Predicted age at first SCE (based on a Cox model) by beta-blocker treatment status
16 and sex, for symptomatic patients (with prior syncope) and A. a QTc <500 ms B. a QTc ≥500
17 ms

18 Beta-blocker treatment was associated with higher probability of SCE in patients with prior
19 syncope (of both sexes, and regardless of whether the QTc was below or above 500 ms).

Table 1. Clinical characteristics and phenotypes of the population at diagnosis

	Total population n=141	Probands n=50	Family members n=91	p
Male	74 (52.5%)	29 (58.0%)	45 (49.4%)	0.33
Age at diagnosis				
Median [IQR]	24.0 [12.0-43.0]	20.0 [11.0-38.0]	25.0 [12.0-46.0]	0.20
Diagnosis mode				
Severe event	6 (4.3%)	5 (10.0%)	1 (1.1%)	
Syncope	16 (11.3%)	14 (28.0%)	2 (2.2%)	<0.001
Fortuitous	30 (21.3%)	30 (60.0%)	0	
Family screening	89 (63.1%)	1 (2.0%)*	88 (96.7%)	
RR (ms) Mean ± SD	922 ± 247	967 ± 261	898 ± 237	0.12
QT (ms) Mean ± SD	451 ± 76	480 ± 72	435 ± 74	<0.001
QTc Bazett (ms)				
Mean ± SD	473 ± 44	494 ± 41	462 ± 42	<0.001
QTc Fridericia (ms)				
Mean ± SD	465 ± 49	488 ± 44	452 ± 47	<0.001
QTc				
<480 ms	83 (59.7%)	23 (46.9%)	60 (66.7%)	
480–500 ms	23 (16.5%)	9 (18.4%)	14 (15.6%)	0.05
>500 ms	33 (23.7%)	17 (34.7%)	16 (17.8%)	
LQTS risk score				
Mean ± SD	2.7 ± 1.6	3.3 ± 1.3	2.4 ± 1.6	<0.001

* One proband was diagnosed after sudden death of his (*SCN5A*-negative) father.

Table 2. Characteristics of the patients, according to initiation of beta-blocker treatment.

	No beta blocker treatment n=80	Beta-blocker treatment n=61	p
Male	39 (48.7%)	35 (57.4%)	0.31
Probands	12 (15.0%)	38 (62.3%)	<0.001
Age at diagnosis			
Mean \pm SD	29.3 \pm 20.0	27.7 \pm 22.3	0.64
Median [IQR]	26.0 [12.5-44.0]	20.0 [11.0-43.0]	
Symptomatic at diagnosis	3 (3.7%)	23 (37.7%)	<0.001
QTc Bazett (ms)			
Mean \pm SD	466 \pm 45	483 \pm 42	0.07
Median [IQR]	465 [424-496]	472 [447-497]	
QTc Fridericia (ms)			
Mean \pm SD	459 \pm 53	473 \pm 42	0.07
Median [IQR]	458 [424-496]	472 [447-497]	
LQTS risk score			
Mean \pm SD	2.5 \pm 1.6	2.9 \pm 1.5	0.22
Median [IQR]	3.0 [1.0-4.0]	3.0 [2.0-4.0]	

Table 3. Characteristics of patients with severe cardiac events (before and/or after diagnosis).

Mutation	Proband	Sex	Description	Age at event	QTcB (ms)	Treatment
p.(Asp1790Gly)	Yes	F	Appropriate shocks	21 years	546	0
p.(Asp1790Gly)	Yes	F	TdP (before diagnosis)	38 years	455	0
p.(Glu1784Lys)	No	M	Appropriate shocks	76 years	493	0
p.(Pro336Leu)	Yes	M	Syncope	4 years	521	0
p.(Val1763Met)	Yes	F	ACA SCD	9 years 1.5 years	515	Beta-blocker (nadolol) Beta-blocker (propranolol)
p.(Phe1460Leu) homozygous	Yes	M	Syncope	2 years	512	0
p.(Val411Met)	Yes	F	ACA Syncope	12 years 14 years	480	Beta-blocker (nadolol) 0
p.(Glu1784Lys)	Yes	F	ACA Syncope	15 years 32 years	480	Beta-blocker (nadolol) 0
p.(Glu1784Lys)	No	M	Appropriate shocks	58 years	518	0
p.(Glu1784Lys)	Yes	F	Syncope Appropriate shocks	32 years 36 years	461	0 0
p.(Glu1784Lys)	No	M	ACA (before diagnosis) Appropriate shock	59 years 66 years	477	0 0
p.(Glu1784Lys)	No	M	Syncope Appropriate shock	20 years 49 years	576	0 0
p.(Val411Met)	Yes	M	VF (before diagnosis)	21 years	603	0
p.(Val1777Met)	Yes	M	TdP (before diagnosis)	15 years	441	0
p.(Val411Met)	Yes	M	ACA (before diagnosis) Aborted VF	5 years 7 years	568	0 Beta-blocker (nadolol)
p.(Glu1784Lys)	Yes	M	Appropriate shock	61 years	520	0
p.(Val 411Met)	Yes	F	ACA (before diagnosis)	20 years	533	0

Patients with symptom onset before 1 year of age were excluded from the analysis.

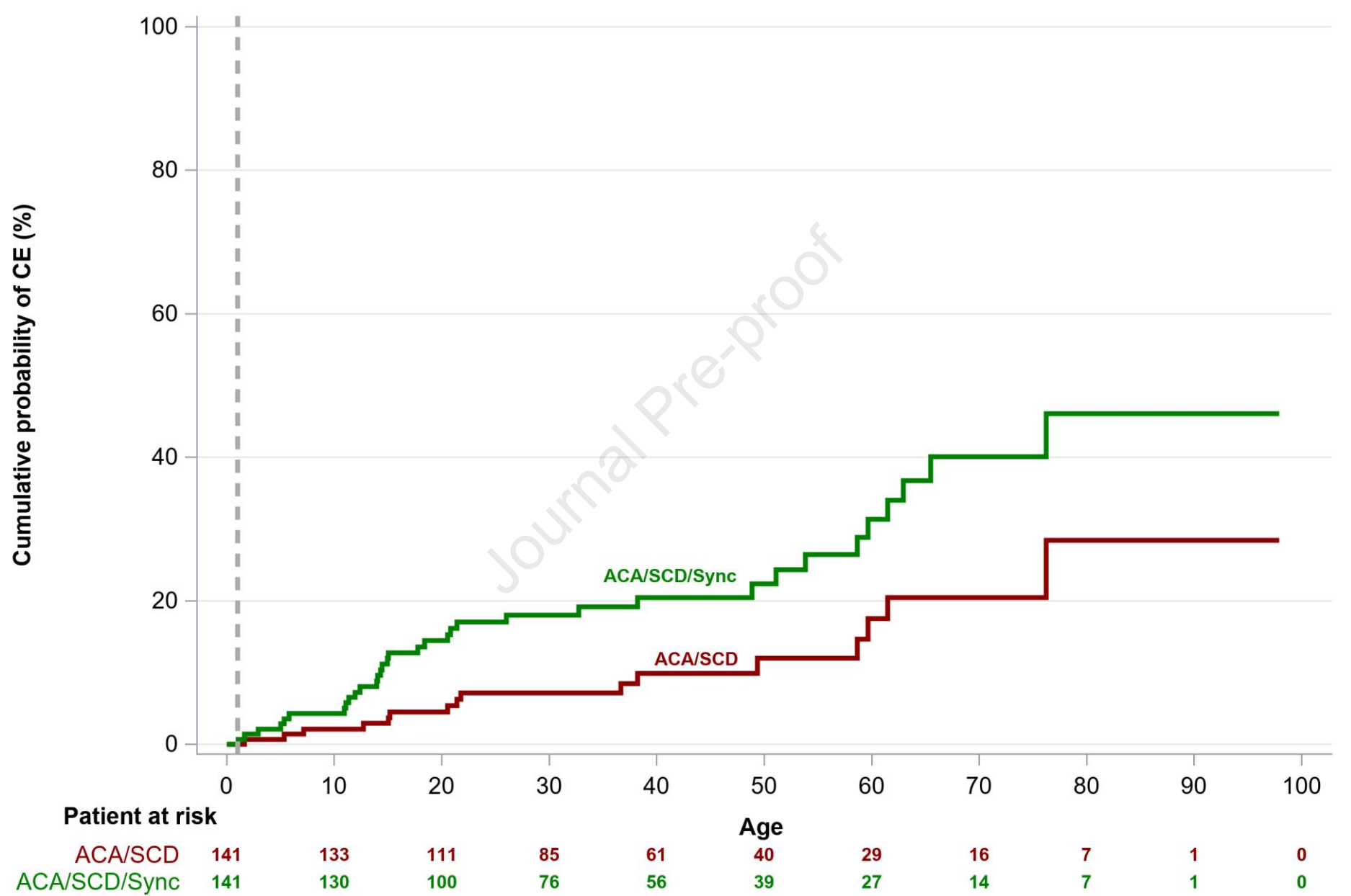
ACA: aborted cardiac arrest, AV: atrioventricular, VF: ventricular fibrillation, TdP: torsade de pointes, SCD: sudden cardiac death

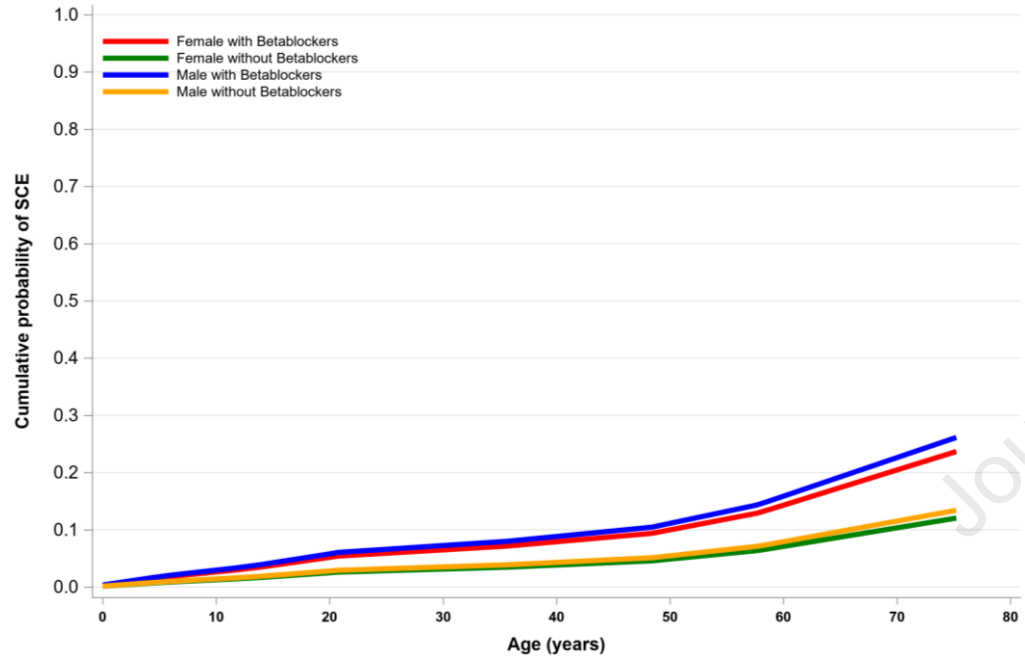
Table 4. Univariate and multivariate analysis of predictors of the first LQT3-triggered CE for combinations of syncope, ACA, and SCD

	Univariate analysis		Multivariate analysis	
	Hazard ratio [95% CI]	P value	Hazard ratio [95% CI]	P value
Beta-blockers	1.22 [0.4-4.2]	0.747	1.15 [0.3-4.0]	0.829
p.(Glu1784Lys)	0.55 [0.3-1.1]	0.096	0.76 [0.4-1.6]	0.464
QTc duration (per 10 ms increment)	1.14 [1.1-1.2]	<.001	1.12 [1.0-1.2]	0.005
Sex (ref: Female)	1.06 [0.5-2.1]	0.869	0.88 [0.4-1.8]	0.733
Proband status	5.37 [2.5-11.3]	<.001	4.07 [1.9-8.9]	<0.001

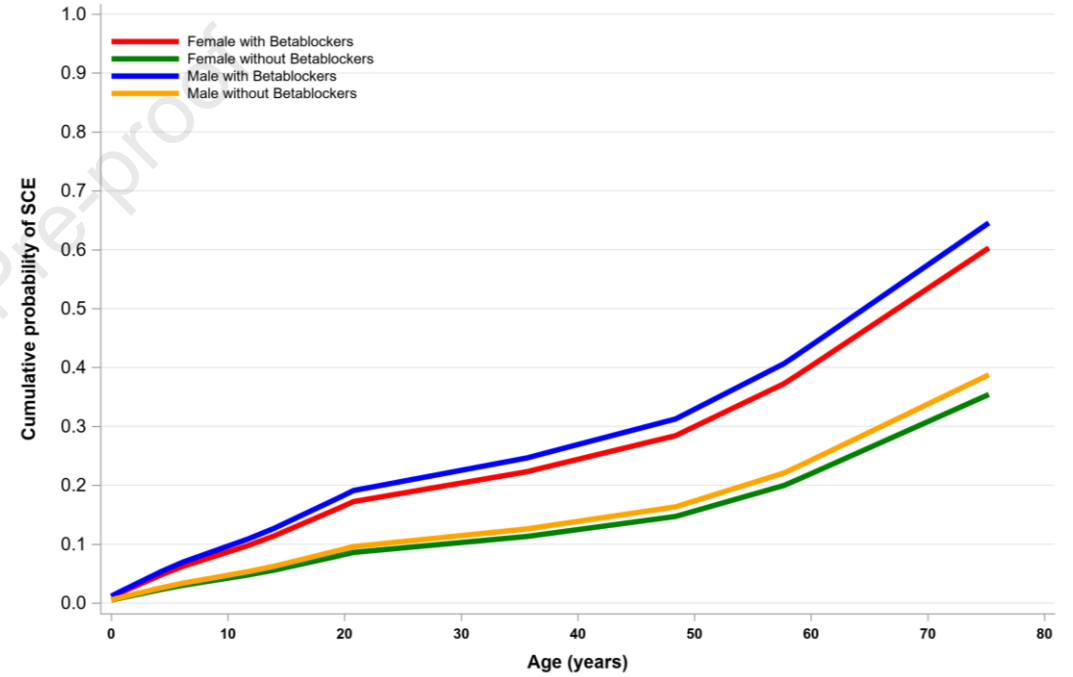
Table 5. Univariate and multivariate analysis of predictors of the first LQT3-triggered event for combinations of ACA and SCD

	Univariate analysis		Multivariate analysis	
	Hazard ratio [95% CI]	P value	Hazard ratio [95% CI]	P value
Beta-blockers	5.59 [1.9-16.0]	0.001	1.96 [0.5-8.5]	0.364
p.(Glu1784Lys)	0.54 [0.2-1.2]	0.120	1.03 [0.3-3.3]	0.959
QTc duration (per 10 ms increment)	1.20 [1.1-1.3]	<.001	1.11 [1.0-1.3]	0.106
Sex (ref.: female)	1.09 [0.5-2.3]	0.810	0.97 [0.3-3.1]	0.954
Proband status	12.01 [3.6-39.7]	<.001	8.13 [1.7-38.8]	0.009
Syncope	9.74 [3.3-28.5]	<.001	2.62 [0.5-11.3]	0.197

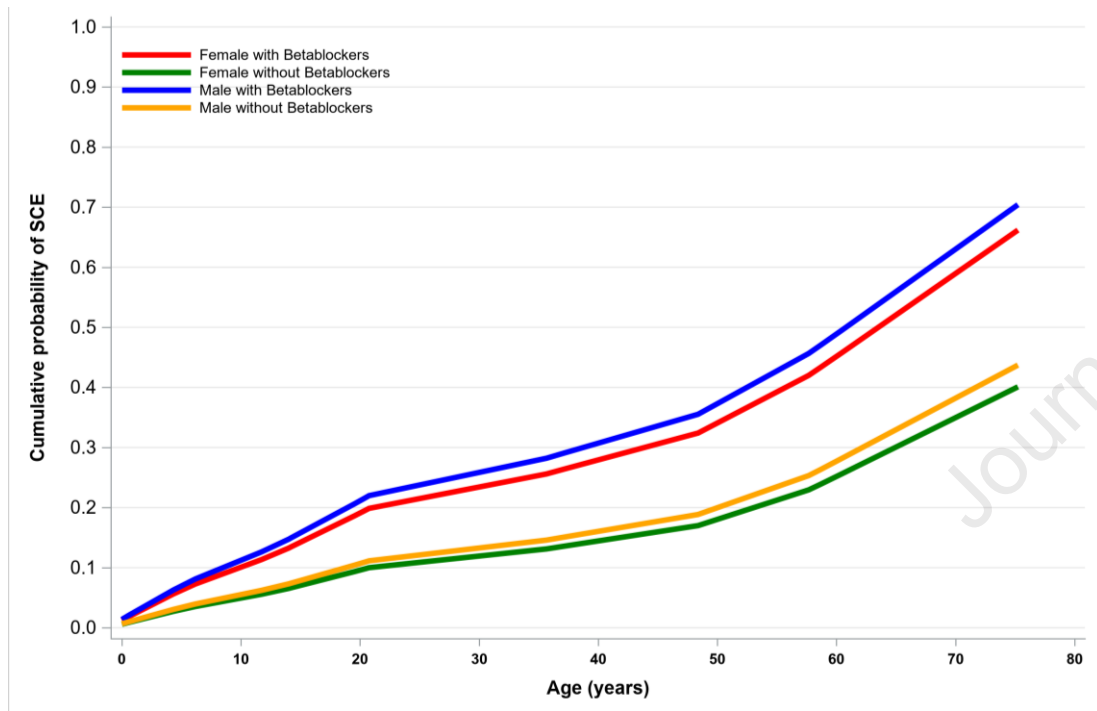




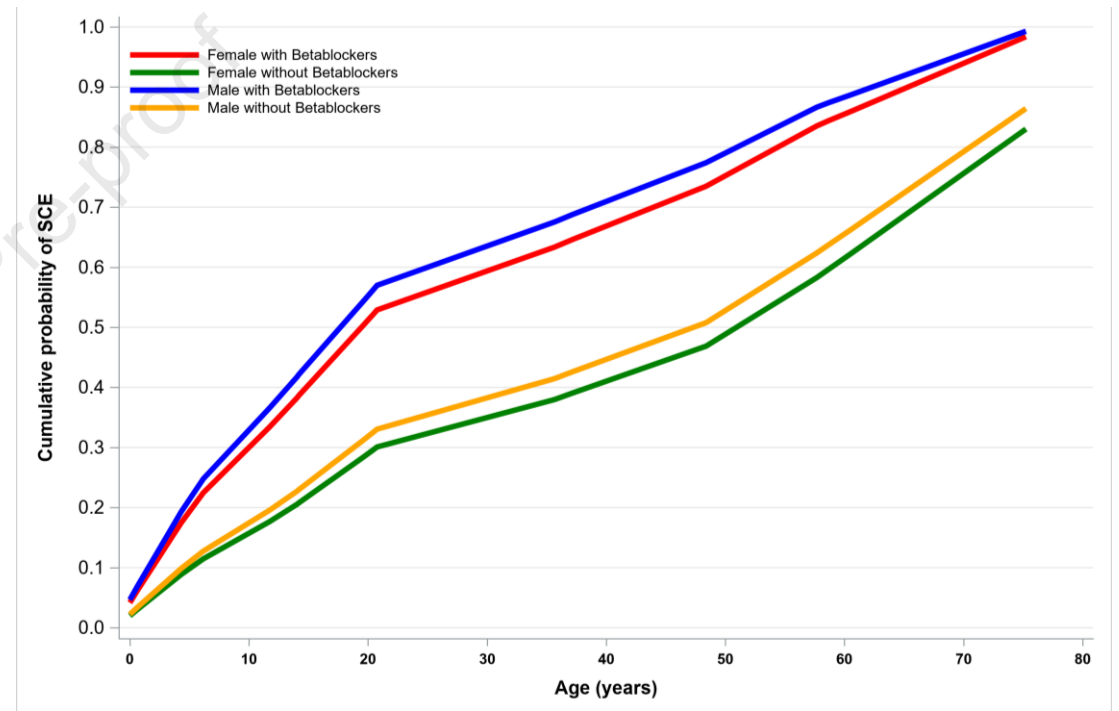
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SUPPLEMENTAL METHOD

Genetic testing

Common variants were filtered out by checking their minor allele frequency in the GnomAD database (<https://gnomad.broadinstitute.org/>); variants with minor allele frequency >0.1% were classified as polymorphisms. Variants (missense, non-sense, truncating, and in-frame indel variants) were then classified as pathogenic, likely pathogenic variants or of uncertain significance. Variants were classified by two of the investigators (VF and FK) according to the American College of Medical Genetics and Genomics criteria, using disease-causative mutation databases, the CLINVAR database (www.ncbi.nlm.nih.gov/clinvar), localization to highly conserved amino acid residues/key functional domains, co-segregation of the variant with the disease phenotype, evidence of perturbed ion channel function from *in vitro* functional studies, and bioinformatics algorithms indicating the variants' likelihood of pathogenicity: Sorting Intolerant From Tolerant, MutationTaster, Polyphen-2, Combined Annotation Dependent Depletion, and Align.

Pre-treatment ECG measurements

Pre-treatment ECG measurements were performed on three consecutive QRS-T complexes, using on-screen calipers (Rigel software, AMPS LLC, New York, NY). The end of the T-wave was determined using the tangent method or (if a U wave was present) at the trough between the T and U waves. The mean RR and mean QT intervals were used to calculate the QTcB and QTcF interval, using Bazett's and Fridericia's formulae, respectively¹. The QTc was expressed as a continuous value and in three risk categories. We calculated the LQTS diagnostic score developed by Schwartz et al.²⁻⁴

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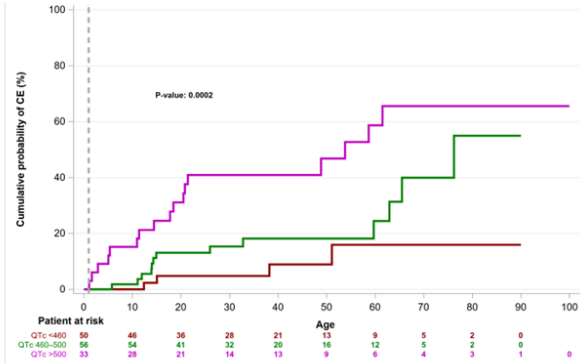
Supp Table S8. Published cohorts including patients with LQT3

	Population	Age at diagnosis (years)	QTc	Variants	Beta-blockers n (%)	ICD n (%)	Follow-up
Zareba 1998	62 patients Males: n=35 (66%)	18 (median)	510±48 ms	-	24 (39)	1 (2)	Cardiac events until the age of 40: - ≥ 1 cardiac event: 11 (18) - ≥ 2 cardiac event: 3 (5) ACA: 2 (3) SCD: 2 (3)
Moss 2000	28 patients	-	530±50 ms	-	-	-	Before beta-blockers: -Cardiac event (syncope, ACA, or SCD) rate: 0.03±0.07 per patient per year -ACA or death: 0 After beta-blockers: -Cardiac event rate: 0.03±0.08 per patient per year -ACA or death: 3 (10%)
Schwartz 2001	65 patients Probands: n=21 (32%) Males: 42%	-	506 ms	-	18	-	Recurrence of a cardiac event (syncope, ACA, or SCD) on beta blockers: 9/18 (50%)
Priori 2004	28 patients	22±17	511±45 ms	-	All (the study's inclusion criteria)	-	Follow-up pre-therapy: 18±16 years Follow up on therapy: 4.2±3.9 years Pre-therapy: -events (syncope, ACA, SCD, VT, TdP):16/28 (57%) -cardiac arrest: 5/28 (18%) On therapy: -events: 9/28 (32%) -cardiac arrest: 4/28 (14%)

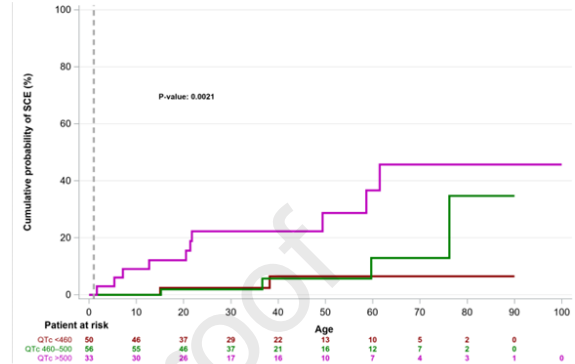
Priori 2003	55 patients Male: n=25 (45%)	-	-	-	-	-	Observation period: 25+18 years. Events (syncope/ACA/SCD) before 40 years of age and before therapy: 23 (42%)
Tester 2005	26 patients Male: n=8 (30.8%)	24±17	494±61 ms Schwartz score ≥ 4: 24%	32 variants (31 missense)	-	-	-
Hobbs 2006	80 patients	-	-	-	-	-	-
Schwartz 2010	31 patients Males: n=11 (36%)	-	484±66 ms >500 ms: n=12 (40%) ≤440 ms: n=10 (33%)	-	9 (75)	All (the study's inclusion criterion)	Events (syncope/ACA) on therapy: 5 (42%)
Wilde 2016	391 patients Probands: n=82 (21%) Males: n=174 (45%)	28±20	476±57 ms	Missense: n=322 (82) p.(Gly1784Lys): n=69 (18)	111 (29)	69 (18)	Syncope/ACA/SCD: 38% at 40 years of age ACA/SCD: 20% at 40 years of age Beta-blockers in females with syncope, ACA or SCD: HR=0.17 [0.04;0.70] p=0.014. Beta-blockers in males with syncope, ACA or SCD: HR=0.895 [0.40;2.21] p=0.895. Beta-blockers in females with ACA or SCD: HR=0.20 [0.05;0.87] p=0.032. Beta-blockers in males with ACA or SCD: HR=0.51 [0.14;1.88] p=0.308.
Mazzanti 2018	196 patients	-	≤ 460 ms: n=69 (35%)	VUS included (11%)	All (the study's inclusion criterion)	-	Life-threatening arrhythmic events: 19/1739 person-years

Wang 2021	211 patients	-	-	-	-	78 (18.8)	-
Our cohort	141 patients Probands: n=50 (35%) Males: n=74 (52%)	25 (median)	473±44 ms Probands: 494±41 ms	Only LP/P variants Missense: n=139 (99%) p.(Gly1784Lys): n=71 (50)	61 (43)	24 (17)	CE = 20.5% at 40 years of age SCE = 9.9% at 40 years of age Beta-blockers, CE: HR=1.15 [0.3-4.0], p=0.829 Beta-blockers, SCE: HR=3.43 [1.1-10.8], p=0.036

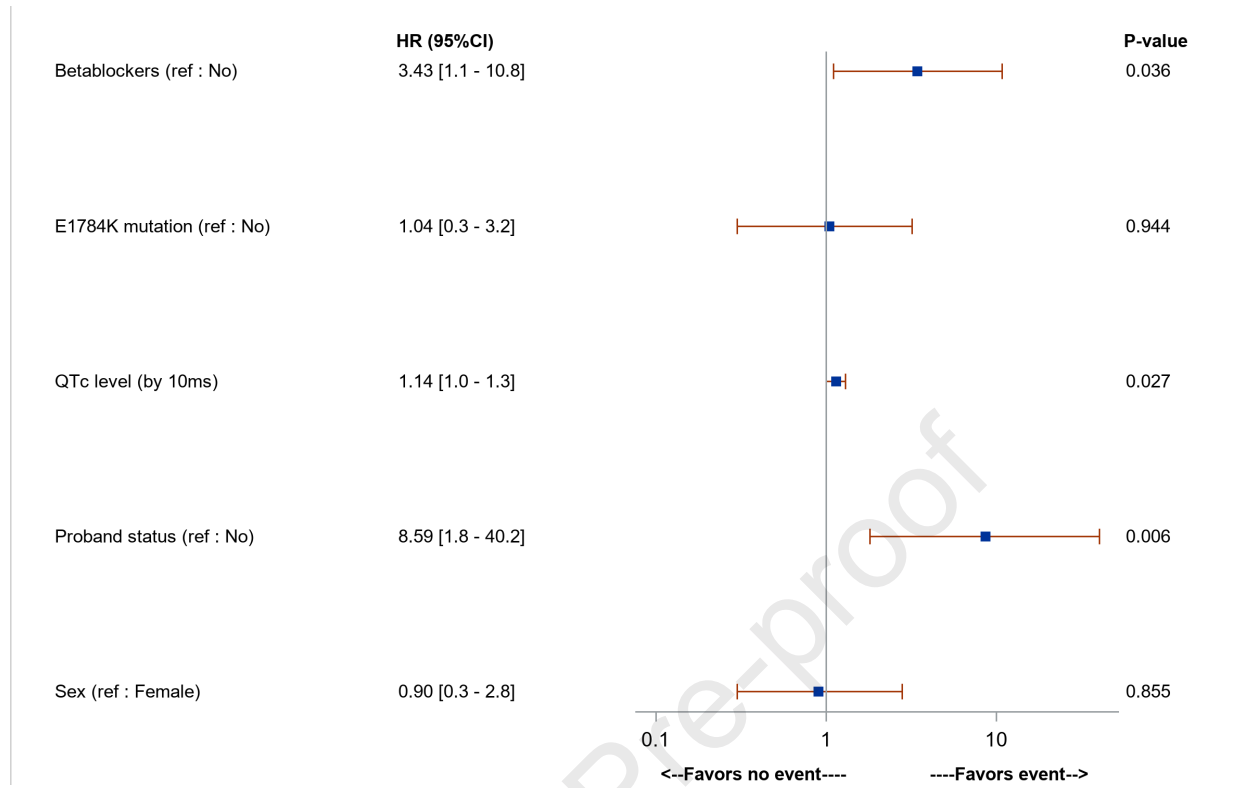
ACA: aborted cardiac arrest, CE: cardiac event, LP: likely pathogenic, P: pathogenic, SCE: severe cardiac event, SCD: sudden cardiac death, TdP: torsade de pointe, VT: ventricular tachycardia

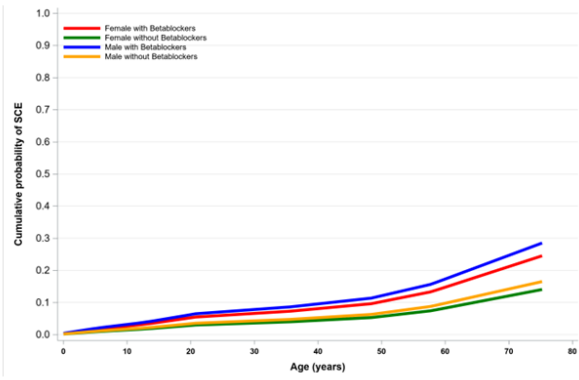


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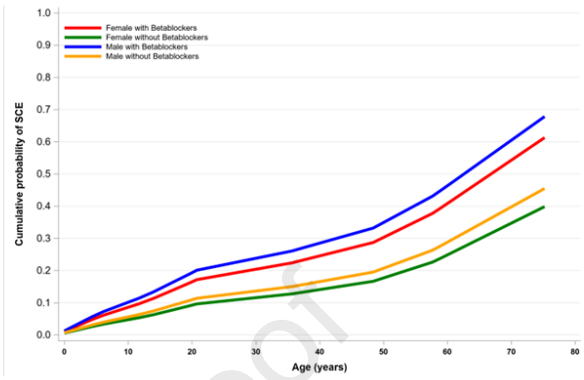


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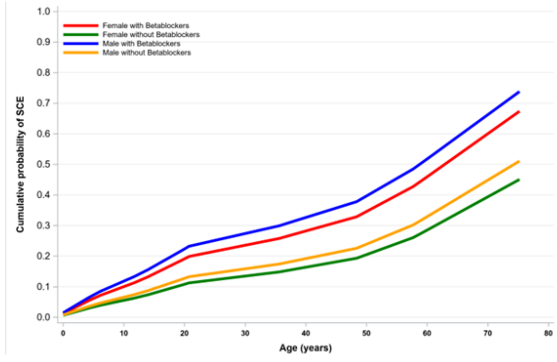




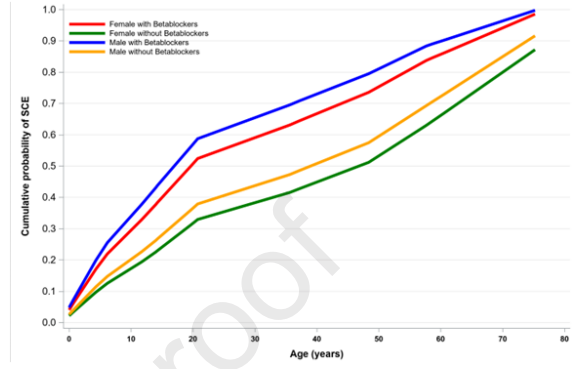
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Supplemental Table S1. Variants included in the study.

cNomen	pNomen	coding effect	exon	domain	gnomad Allele Count	gnomad V2.1.2 AllFreq	ACMG	ACMG classification	Labs Classification	CADD	Probands (n)	Family members (n)
c.820G>A	p.(Gly274Ser)	missense	7	DI- S5-Pore	0	-	PM2 PP2 PP3	VUS	LP	29,7	1	0
c.1007C>T	p.(Pro336Leu)	missense	9	DI- S5-Pore	0	-	PM2 PP2 PP3 PP5	LP	P	25,6	1	0
c.1109C>T	p.(Thr370Met)	missense	9	DI-Pore	0	-	PM1 PM2 PP2 PP3	LP	LP	27,1	1	3
c.1231G>A	p.(Val411Met)	missense	10	DI-S6	0	-	PM2 PP2 PP3 PP5	P	P	28,6	6	0
c.2554A>G	p.(Ile852Val)	missense	16	DII-S5	0	-	PM1 PM2 PP2 PP3	LP	P	21,7	1	0
c.2822C>T	p.(Ser941Phe)	missense	17	Linker DII-III	0	-	PM2 PM5 PP2 PP3	LP	P	28,4	1	0
c.3974A>G	p.(Asn1325Ser)	missense	23	DIII-S4-S5	0	-	PM1 PM2 PP5 PP2 PP3	LP	P	23,5	1	1
c.3988G>A	p.(Ala1330Thr)	missense	23	DIII-S4-S5	0	-	PM2 PM5 PP2 PP3; PP5	P	P	27,1	1	0
c.3995C>A	p.(Pro1332Gln)	missense	23	DIII-S4-S5	0	-	PM1 PM2 PM5 PP2 PP3	LP	P	27,3	1	0
c.4380C>A	p.(Phe1460Leu)	missense	25	DIII-S6	0	-	PM1 PM2 PP2 PP3	LP	P	24,5	1	2
c.4442G>T	p.(Gly1481Val)	missense	26	Linker DIII-IV	0	-	PM2 PM5 PP2 PP3	LP	P	24,2	1	0
c.4473G>T	p.(Gln1491His)	missense	26	Linker DIII-IV	0	-	PS3 PM2 PP2 PP3	LP	P	24,2	1	0
c.4501C>G	p.(Leu1501Val)	missense	26	Linker DIII-IV	5	0,00002	PM1 PM2 PP2 PP3 PP5	LP	LP	23,9	1	0
c.4931G>A	p.(Arg1644His)	missense	28	DIV-S4-S5	0	-	PP5 PM1 PM2 PM5 PP2 PP3	P	P	25,1	2	0
c.5272_5274del	p.(Ile1758del)	in-frame	28	DIV-S6	0	-	PM1 PM2 PP3 PP5	LP	LP	-	1	3
c.5287G>A	p.(Val1763Met)	missense	28	DIV-S6	0	-	PM1 PM2 PP5 PP2 PP3	LP	P	27,2	1	1
c.5329G>A	p.(Val1777Met)	missense	28	Cterm	5	0,000018	PM2 PP2 PP3 PP5	LP	LP	26,9	2	7
c.5350G>A	p.(Glu1784Lys)	missense	28	Cterm	0	-	PP5 PM1 PM2 PP2 PP3	P	P	24,9	18	53

c.5357T>C	p.(Leu1786Pro)	missense	28	Cterm	0	-	PM2 PP2 PP3 PP5	LP	P	27,9	1	0
c.5368G>A	p.(Asp1790Asn)	missense	28	Cterm	3	0,000012	PM1 PM2 PM5 PP2 PP3	LP	LP	29,1	6	7
c.5369A>G	p.(Asp1790Gly)	missense	28	Cterm	0	-	PM1 PM2 PP2 PP3 PP5	LP	P	28,1	3	15
c.5384A>G	p.(Tyr1795Cys)	missense	28	Cterm	0	-	PM1 PM2 PM5 PP5 PP2 PP3	LP	P	28,3	1	1
c.5546A>G	p.(His1849Arg)	missense	28	Cterm	0	-	PM1 PM2 PP2 PP3 PP5	LP	P	25,6	1	0

ACMG: American College of Medical Genetics, AGVGD: Align Grantham Variation Grantham Deviation, CADD: Combined Annotation Dependent Depletion, MPA: MoBiDiC prioritization algorithm, SiFT: Sorting Intolerant From Intolerant

SUPPLEMENTAL MATERIALSupplemental figure legends

Supplemental Figure 1. Cumulative probability of A. cardiac events and B. severe cardiac events, according to the QTc prolongation.

Red curve: patients with $QTc < 460$ ms. Green curve: patients with $450 \text{ ms} \leq QTc \leq 500$ ms.

Pink curve: patients with $QTc > 500$ ms.

SCE: severe cardiac event. CE: cardiac event.

Supplemental Figure 2. Multivariate analysis of predictors of the first LQT3-triggered severe cardiac event (syncope excluded).

Supplemental Figure 3. Predicted age at first SCE (based on a Cox model) by beta-blocker treatment status and sex for asymptomatic patients (no prior syncope) and A. a $QTc < 500$ ms.
B. a $QTc \geq 500$ ms

In asymptomatic patients (no prior syncope) without a low-risk mutation p.(Glu1784Lys), beta-blocker treatment was associated with higher probability of SCE in both sexes, regardless of whether the QTc was below or above 500 ms (left and right panels, respectively).

Supplemental Figure 4. Predicted age at first SCE (based on a Cox model) by beta-blocker treatment status and sex, for symptomatic patients (with prior syncope) and A. a $QTc < 500$ ms
B. a $QTc \geq 500$ ms

Beta-blocker treatment was associated with higher probability of SCE in patients with prior syncope (of both sexes, and regardless of whether the QTc was below or above 500 ms).

Supplemental Table S2. Clinical characteristics and outcome by age at diagnosis (<1 or >1 year of age)

	No symptoms before 1 year of age n=141	Symptoms before 1 year of age n=6	p
Age at diagnosis			
Median (IQR)	24.0 (12.0-43.0)	0 (0.0-0.0)	0.001
Males	74 (52.5%)	3 (50.0%)	0.90
Probands	50 (35.5%)	4 (66.7%)	0.12
Diagnosis mode			
Severe cardiac event	6 (4.3%)	4 (66.7%)	<0.001
Syncope	16 (11.3%)	1 (16.7%)	
Fortuitous	30 (21.3%)	0 (0%)	
Family screening	89 (63.1%)	1 (16.7%)	
QTc Bazett (ms)			
Mean \pm SD	473 \pm 44	544 \pm 176	0.004
Median [IQR]	468 [444-497]	447 [425-592]	
QTc Fridericia (ms)			
Mean \pm SD	465 \pm 49	522 \pm 187	0.03
Median [IQR]	464 [430-497]	448 [418-548]	
LQTS risk score			
Mean \pm SD	2.7 \pm 1.6	2.8 \pm 1.7	0.86
Median [IQR]	3.0 [1.0-4.0]	2.5 [2.0-3.0]	
Symptomatic at diagnosis	26 (18.4%)	5 (83.3%)	<0.001
Symptomatic during follow-up	20 (14.2%)	4 (66.7%)	<0.001

Supplemental Table S3. Characteristics of the six patients with symptom onset before the age of 1 year

	#1	#2	#3	#4	#5	#6
Status	Proband	Proband	Proband	Proband	Relative	Relative
Sex	Male	Male	Male	Female	Female	Female
Mutation	p.(Gly1481 Val)	p.(Gln1491 His)	p.(Val411 Met)	p.(Ile1758 del)	p.(Ile1758 del)	p.(Asp1790 Gly)
Age at diagnosis	0 (birth)	0 (birth)	0 (birth)	2 months	1 months	3 months
QTcB (ms)	-	833	592	447	425	422
LQTS risk score	-	5.5	3	2.5	2	1
Diagnostic mode	2/1 AV block. Electrical storm	2/1 AV block. Electrical storm	2/1 AV block	Sustained VA at two months (cardioversion)	Sustained VA at one month (cardioversion)	Family screening
Outcome	1. Pacemaker 2. Beta-blocker 3. Refractory electrical storm despite mexiletine treatment	1. Pacemaker 2. Beta-blockers (propranolol) 3. Refractory electrical storm	1. Pacemaker 2. Beta-blocker (propranolol) 3. SCD (39 months)	1. No events during 44 years of follow-up (off beta-blockers)	1. No events during 51 years of follow-up (off beta-blockers)	1. Brief, resolved, unexplained event at 2 months 2. Beta-blockers (propranolol) 3. No recurrence of cardiac

	4. Death (2.5 months)	despite mexiletine treatment 4. Death (4 months)				event after 7 years follow-up
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AV: atrio ventricular, VA: ventricular arrhythmia, SCD: sudden cardiac death

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Supplemental Table S4. Comparisons of patients carrying the p.(Glu1784Lys) mutation vs. other mutations.

	Other mutations n=70	p.(Glu1784Lys) mutation n=71	p
Probands	32 (45.7%)	18 (25.4%)	0.012
Male	34 (48.6%)	40 (56.3%)	0.36
Age at diagnosis			
Mean \pm SD	26.9 \pm 22.3	30.3 \pm 19.6	0.34
Median [IQR]	19.5 [10.0-43.0]	27.0 [13.0-45.9]	
Diagnosis mode			
Severe event	5 (7.1%)	1 (1.4%)	0.047
Syncope	11 (15.7%)	5 (7.0%)	
Fortuitous	17 (24.3%)	13 (18.3%)	
Familial screening	37 (52.9%)	52 (73.2%)	
QTc Bazett (ms)			
Mean \pm SD	472 \pm 50	475 \pm 38	0.75
Median [IQR]	466 [438-498]	474 [450-493]	
QTc Fridericia (ms)			
Mean \pm SD	458 \pm 54	472 \pm 42	0.11
Median [IQR]	458 [428-493]	470 [436-500]	
LQTS risk score			
Mean \pm SD	2.4 \pm 1.6	2.9 \pm 1.5	0.06
Median [IQR]	2.5 [1.0-4.0]	3.0 [2.0-4.0]	
Symptomatic at diagnosis	18 (25.7%)	8 (11.3%)	0.027
Symptomatic during follow-up	11 (15.7%)	9 (12.7%)	0.61

Supplemental Table S5. Comparisons of patients who were asymptomatic vs. symptomatic at diagnosis.

	Symptomatic patients n=26	Asymptomatic patients n=115	p
Male	16 (61.5%)	58 (50.4%)	0.31
Probands	20 (76.9%)	30 (26.1%)	<0.001
Age at diagnosis			
Mean \pm SD	24.4 \pm 19.4	29.6 \pm 21.3	0.25
Median [IQR]	19.0 [11.0-36.0]	25.0 [12.0-45.0]	
Age at symptom onset (years)			
Mean \pm SD	22.4 \pm 19.1	-	-
Median [IQR]	14.0 [10.7-33.5]		
Time interval between symptom onset and diagnosis (months)			
Mean \pm SD	23.4 \pm 61.4	-	-
Median [IQR]	0 [0.0-5.0]		
QTc Bazett (ms)			
Mean \pm SD	504 \pm 47	466 \pm 41	<0.001
Median [IQR]	495 [476-526]	463 [440-490]	
QTc Fridericia (ms)			
Mean \pm SD	503 \pm 46	456 \pm 46	<0.001
Median [IQR]	491 [472-532]	457 [427-488]	
LQTS risk score			
Mean \pm SD	4.1 \pm 1.3	2.3 \pm 1.4	<0.001
Median [IQR]	4.2 [3.5-5.0]	2.5 [1.0-3.5]	

Supplemental Table S6. Clinical characteristics of the patients, according to the occurrence of CEs during follow-up

	No symptoms during follow-up n=121	Severe cardiac event during follow-up n=12	Syncope during follow-up n=8	P
Male	63 (52.1%)	8 (66.7%)	3 (37.5%)	0.43
Probands	39 (32.2%)	9 (75.0%)	2 (25.0%)	0.01
Age at diagnosis				
Mean \pm SD	28.8 \pm 20.9	27.5 \pm 25.4	27.2 \pm 16.1	0.96
Median [IQR]	24.0 [12.0-43.0]	20.5 [3.5-56.0]	23.5 [13.5-40.5]	
Diagnosis mode				
Severe event	4 (3.3%)	2 (16.7%)	0 (0%)	<0.001
Syncope	9 (7.4%)	4 (33.3%)	3 (37.5%)	
Fortuitous	26 (21.5%)	4 (33.3%)	0 (0%)	
Family screening	82 (67.8%)	2 (16.7%)	5 (62.5%)	
QTc Bazett (ms)				
Mean \pm SD	468 \pm 43	516 \pm 35	494 \pm 48	<0.001
LQTS risk score				
Mean \pm SD	2.5 \pm 1.5	4.0 \pm 1.3	3.9 \pm 1.5	<0.001

Supplemental Table S7. Characteristics of the five patients who died from LQTS

	#1	#2	#3	#4	#5
Status	Proband	Proband	Proband	Proband	Proband
Sex	Male	Male	Male	Female	Male
Mutation	p.(Gly1481Val)	p.(Pro336Leu)	p.(Gln1491His)	p.(Val1763Met)	p.(Val411Met)
Age at diagnosis	0 (birth)	60 months	0 (birth)	0 (birth)	0 (birth)
QTcB (ms)	-	521	833	515	592
LQTS risk score	-	5	5.5	3	3
Diagnostic mode	2/1 AV block Electrical storm	Polymorphic VT/VF during anesthesia	2/1 AV block Electrical storm	Atrial premature beats	2/1 AV block
Evolution	1. Pace-maker 2. Beta-blocker 3. Refractory electrical storm despite mexiletine treatment 4. Death	1. Pace-maker 2. Beta- blocker 3. ACA (110 months) 4. SCD	1. Pace-maker 2. Beta-blockers 3. Refractory electrical storm despite mexiletine treatment 4. Death	1. Beta-blocker 2. SCD	1. Pace-maker 2. Beta-blocker 3. SCD
Age at death (months)	2.5	124	4	20	39

ACA: aborted cardiac arrest, AV: atrioventricular, VF: ventricular fibrillation, VT : ventricular tachycardia, SCD : sudden cardiac death