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# Genetic Diagnostics Contribute to the Risk Stratification for Major Arrhythmic Events in Pediatric Patients with Long QT Syndrome Type 1–3

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**Abstract:** Long QT syndrome (LQTS) is an inherited arrhythmic disorder associated with sudden cardiac death (SCD). This study aimed to identify the clinical and molecular genetic risk factors that contribute to major arrhythmic events (MAEs) in patients with genetically confirmed childhood onset LQTS 1–3. This study was a retrospective double-center study. An MAE was defined as the occurrence of SCD, aborted SCD, appropriate implantable cardioverter defibrillator discharge, or sustained ventricular tachycardia. During a median follow-up of 4.6 years (range 0.1–24.3 years), MAEs occurred in 18 (17.8%) of 101 patients diagnosed with LQTS at a median of 7.7 years (range 0.0–18.0 years) despite the use of beta-blockers in 91.6% of patients at the last follow-up. A multivariate analysis identified a genetic diagnosis of LQTS2 and LQTS3 and variants within the *KCNH2* S5-loop-S6 pore region as independent risk factors for MAEs, independent of the QTc value or a history of syncope detected from a univariate analysis. MAEs occur frequently in childhood onset LQTS despite beta-blocker treatment. A detailed molecular genetic diagnosis can contribute to the arrhythmia risk stratification and optimize the use of preventive measures in this vulnerable patient population.

**Keywords:** Long QT; LQTS; risk factors; major arrhythmic event; pediatric



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## 1. Introduction

Long QT syndrome (LQTS) is an inherited arrhythmogenic disorder caused by variants in the genes encoding cardiac ion channels [1]. These ion channels generate the cardiac action potential by regulating the flux of ions across the membrane such as the influx of sodium and calcium or the outflow of potassium [2]. In LQTS, an increase in the sodium and calcium currents or a decrease in the potassium outflow can prolong the action potential duration, leading to the eponymous phenotype of a prolonged QT interval [3]. Seventeen distinct subtypes of LQTS were initially described with their associated diseases/genes; seven of those were recently confirmed in a re-evaluation study [4].

The most commonly affected genes are *KCNQ1* (LQTS1) and *KCNH2* (LQTS2), encoding for potassium currents ($I_{Ks}$ and $I_{Kr}$), and *SCN5A* (LQTS3), which regulates the sodium inflow ($I_{Na}$) [5]. A pathogenic variant in one of those three disease genes is identified in approximately 75% of all patients carrying a clinical diagnosis of LQTS, based on the

calculated Schwartz score [6,7]. The clinical consequences of LQTS include severe cardiac arrhythmia manifesting as ventricular tachycardia (VT) (e.g., Torsades de pointes), which can either be self-terminating or develop into ventricular fibrillation leading to sudden cardiac death (SCD) [8]. The rate of these life-threatening arrhythmic events is described in the literature as varying between 2.4% and 12.1% of cases [9–14].

The disease presentation and clinical course are variable amongst patients. Clinical symptoms such as syncope and the occurrence of sudden cardiac death can effectively be prevented by treatment with beta-blockers and by the implantation of implantable cardioverter defibrillators (ICDs) [15–17]. The identification of risk factors is crucial to identify patients at a high risk of life-threatening arrhythmias.

Previous studies, mostly carried out on adults, have described certain risk factors such as carriers of certain genotypes, age, sex, the length of the prolonged QTc value, and the presence of syncope [9,11,18–20].

More than 50% of patients with LQTS experienced their first cardiac event before the age of 15 years [20]; this subgroup of patients is of particular importance when it comes to individual risk stratification in LQTS.

Given the scarce data available for the risk stratification of pediatric patients, the aims of this study were to identify and confirm the clinical and genetic risk factors in this vulnerable patient population.

## 2. Materials and Methods

In this retrospective double-center study conducted at the German Heart Centers in Munich and Leipzig, the data were extracted from the medical records of 101 patients out of 82 families with genetically confirmed LQTS 1–3 (Munich: $n = 69$, Leipzig: $n = 32$). The patients were treated at the respective centers in the time between 1995 and 2019. All participants were 18 years or younger at the time of diagnosis. Those who were lost to follow-up were censored at the time of their last contact; part of this patient cohort was included in a recent publication [21].

The data extracted included the demographics, family history, use of medication, need for hospitalization and interventions, history of syncope, and the occurrence of major arrhythmic events (MAE, defined as sudden cardiac death (SCD), aborted cardiac arrest (ACA), appropriate cardioverter defibrillator discharge, or sustained ventricular tachycardia (VT)). Twelve-lead electrocardiogram (ECG) measurements of the heart rate and QT interval corrected for the heart rate by the Bazett formula (QTc) were obtained for all study subjects. The QTc measured on the baseline ECGs at enrollment was used for the statistical analysis. The Schwartz score [7] was calculated for each patient in order to summarize and objectify the clinical outcomes. Transthoracic echocardiography (TTE) was used to exclude patients with structural heart defects.

Details on the molecular genetic diagnosis were extracted from the reports of the respective accredited laboratories or from medical patient records. Only patients with variants in the three main causing genes *KCNQ1*, *KCNH2* and *SCN5A*—classified as pathogenic or likely pathogenic variants according to criteria of the American College of Medical Genetics and Genomics (ACMG) [22]—were selected for the statistical analysis. These variants were characterized by their location and type. For the *KCNQ1*-encoded Kv7.1 channel, amino acids before position 122 were defined as the N-term, residues from 122 to 261 as the S1–S4 region, from 262 to 348 as the S5-loop-S6 region, and from 349 as the C-term. Amino acids located before 404 (N-term), from 404 to 547 (S1–S4 region), from 548 to 659 (S5-loop-S6 region) and from 660 onwards (C-term) were defined for the *KCNH2*-encoded Kv11.1 channel. For the *SCN5A*-encoded Nav1.5 channel, the N-term, the transmembrane region of each domain (D1–D4) with their S5-loop-S6 region (pore region), and the C-term were defined as follows: up to 131 as the N-term; 132 to 410 as D1 (pore region: 253–410); 718 to 938 as D2 (pore region: 838–938); 1207 to 1466 as D3 (pore region: 1334–1466); 1530 to 1771 as D4 (pore region: 1657–1771); and 1772 to 2016 as the C-term. The location of the variants was reviewed by using the UniProt dataset (https://www.uniprot.org/, last accessed on

26 December 2021). The type of variant was divided into missense, frameshift, nonsense (stop codon), splice site, nearsplice, in-frame deletion/duplication, and intragenic deletion.

Univariate and multivariate analyses were performed to identify the clinical and molecular genetic risk factors for the occurrence of MAEs. The chi-squared test was used for the categorical variables; Mann–Whitney U and Kruskal–Wallis tests were used for the continuous variables given the small sample size. The cumulative probability of a first MAE was developed for the baseline covariates with the Kaplan–Meier estimator and compared with the log-rank test. To investigate the influence of the clinical and genetic factors as well as the time-dependent occurrence of syncope with the first occurrence of an MAE, the multivariable Cox proportional hazard regression model was used. Testing for multicollinearity was conducted to determine the degree of correlation between the variables. Multicollinearity was considered to be a Spearman Rho correlation coefficient of two variables greater than $r > 0.8$ [23]. The statistical software used for the analysis was SPSS version 28.0.0 (SPSS Inc.; IBM Company, Armonk, NY, USA) and a $p$-value of less than 0.05 (two-sided) was considered to be statistically significant.

## 3. Results

### *3.1. Study Population*

The data of 101 patients (54 females) diagnosed at a median (range) age of 7.7 years (0.0–18.0 years) were analyzed. The median (range) Schwartz score at the time of diagnosis was 4.0 (1.0–7.0). A total of 54 patients were affected by LQTS1 (53.5%), 40 by LQTS2 (39.6%), and 7 by LQTS3 (6.9%). During a median (range) follow-up time of 4.6 (0.1–24.3) years, MAEs occurred in 18 (17.8%) patients. Almost two-thirds of the patients (71.3%) received a beta-blocker therapy at the time of the study enrollment and almost all (91.6%) at the last follow-up. Metoprolol and propranolol were the most frequently used (47.4% and 39.5% of patients receiving beta-blockers, respectively). An ICD was implanted in 25 (24.8%) patients. The indication was a primary prevention in 16 (64.0%) patients and implantation occurred at a median (range) age of 12.8 years (1.8–30.0) in those subjects. Clinical risk factors prompting a primary prophylactic ICD implantation included syncope in 10 (62.5%) and VT in 6 (37.5%); all subjects with VT also suffered from syncope. The indication for a primary prophylactic ICD implantation was not clear in 6 out of 16 patients (37.5%). All patients received an appropriate beta-blocker therapy before the ICD implantation. Complications of primary prophylactic implanted devices occurred in 3 (18.8%) patients. A total of 9 patients received an ICD at a median (range) age of 14.3 years (4.9–23.7) for a secondary prevention with 1 of them (11.1%) experiencing an ICD complication. Complications included lead failure in 3 (12.0%) patients and an upper extremity deep vein thrombosis in 1 (4.0%) patient.

The detailed clinical and molecular genetic information can be found in Table 1.

There were no differences in sex, age at diagnosis, follow-up time, occurrence of syncope, and medication among the different LQTS types. Features varying upon the underlying affected genotype included the QTc value, rate of ICD implantation, and location of the pathogenic variant within the gene. The median (range) QTc was significantly longer in the LQTS2 and LQTS3 groups (LQTS2: 490 ms (400–630 ms); LQTS3: 480 ms (417–740 ms)) compared with the LQTS1 group (LQTS1: 460 ms (370–554 ms); $p = 0.047$, Kruskal–Wallis test for multiple independent non-parametric variables). There was a higher rate of ICD implantation in the LQTS2 group (45.0%) compared with the LQTS1 (9.3%) and LQTS3 (28.6%) groups ($p < 0.001$, Pearson chi-squared). In the LQTS1 group, the location of the pathogenic variant was most frequently found in the S1–S4 region and the C-term; it was in the S5-loop-S6 region in the LQTS2 group and in the C-term in the LQTS3 group (Table 1, Figure 1, and Supplementary Figure S1).

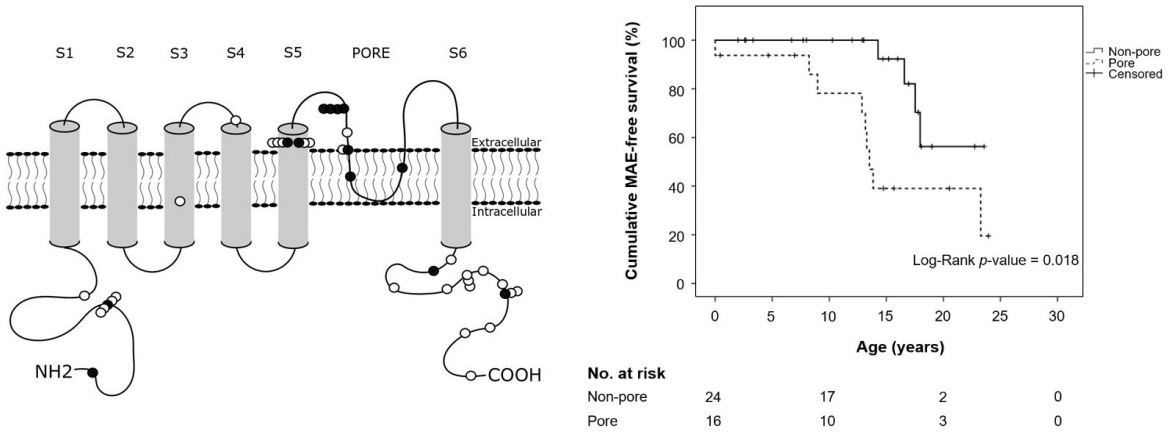
**Table 1.** Patient characteristics with clinical and genetic findings by genotype.

| Characteristics | Total ($n$ = 101) | LQT1 ($n$ = 54) | LQT2 ($n$ = 40) | LQT3 ($n$ = 7) | $p$-Value |
|---|---|---|---|---|---|
| Families, $n$ | 82 | 46 | 30 | 6 | 0.436 [a] |
| Female, $N/n$ (%) | 54/101 (53.5) | 32/54 (59.3) | 18/40 (45.0) | 4/7 (57.1) | 0.383 [a] |
| Age at diagnosis (years), median (min–max) | 7.7 (0.0–18.0) | 6.1 (0.0–17.8) | 8.4 (0.0–18.0) | 7.7 (0.0–13.2) | 0.265 [b] |
| Subjects with follow-up, $N/n$ (%) | 83/101 (82.2) | 44/54 (81.5) | 33/40 (82.5) | 6/7 (85.7) | 0.961 [a] |
| Follow-up time [c] (years), median (min–max) | 4.6 (0.1–24.3) | 4.5 (0.1–24.3) | 4.6 (0.2–17.7) | 7.9 (0.8–10.4) | 0.809 [b] |
| QTc time (ms), median (min–max) | 470 (370–740) | 460 (370–554) | 490 (400–630) | 480 (417–740) | 0.047 [b] |
| QTc categories (1–4), $N/n$ (%) | | | | | 0.163 [a] |
| ≤449 ms | 23/101 (22.8) | 14/54 (25.9) | 8/40 (20.0) | 1/7 (14.3) | 0.682 [a] |
| 450–499 ms | 50/101 (49.5) | 30/54 (55.6) | 17/40 (42.5) | 3/7 (42.9) | 0.427 [a] |
| 500–549 ms | 15/101 (14.9) | 8/54 (14.8) | 6/40 (15.0) | 1/7 (14.3) | 0.999 [a] |
| ≥550 ms | 13/101 (12.9) | 2/54 (3.7) | 9/40 (22.5) | 2/7 (28.6) | 0.012 [a] |
| Syncope, $N/n$ (%) | 29/101 (28.7) | 12/54 (22.2) | 16/40 (40.0) | 1/7 (14.3) | 0.116 [a] |
| Syncope at enrollment | 27/101 (26.7) | 10/54 (18.5) | 16/40 (40.0) | 1/7 (14.3) | 0.050 [a] |
| Syncope during follow-up | 16/83 (19.3) | 7/44 (15.9) | 9/33 (27.3) | 0/6 (0.0) | 0.211 [a] |
| Family history, $N/n$ (%) | 83/101 (82.1) | 45/54 (83.3) | 33/40 (82.5) | 5/7 (71.4) | 0.739 [a] |
| Definite LQTS of relative | 61/83 (73.5) | 33/45 (73.3) | 26/33 (78.8) | 2/5 (40.0) | 0.187 [a] |
| SCD/ACA of relative | 28/83 (33.7) | 13/45 (28.9) | 15/33 (45.5) | 0/5 (0.0) | 0.080 [a] |
| MAE, $N/n$ (%) | 18/101 (17.8) | 3/54 (5.6) | 13/40 (32.5) | 2/7 (28.6) | 0.002 [a] |
| Type of MAE, $N/n$ (%) | | | | | 0.334 [a] |
| SCD | 0/18 (0.0) | 0/3 (0.0) | 0/13 (0.0) | 0/2 (0.0) | n.a. |
| ACA | 8/18 (44.4) | 2/3 (66.7) | 4/13 (30.8) | 2/2 (100.0) | 0.130 [a] |
| Appropriate ICD discharge | 6/18 (33.3) | 1/3 (33.3) | 5/13 (38.5) | 0/2 (0.0) | 0.562 [a] |
| Sustained VT | 4/18 (22.2) | 0/3 (0.0) | 4/13 (30.8) | 0/2 (0.0) | 0.372 [a] |
| Age at first MAE (years), median (min–max) | 13.4 (0.0–23.3) | 13.6 (6.5–20.8) | 13.5 (0.0–23.3) | 0.0 (0.0–0.0) | 0.144 [b] |
| Schwartz score, median (min–max) | 4.0 (1.0–7.0) | 4.0 (1.0–6.0) | 4.0 (1.0–7.0) | 4.0 (3.0–5.0) | 0.005 [b] |
| Cardiac therapy [d], $N/n$ (%) | 87/101 (86.1) | 45/54 (83.3) | 36/40 (90.0) | 6/7 (85.7) | 0.652 [a] |
| ICD, $N/n$ (%) | 25/101 (24.8) | 5/54 (9.3) | 18/40 (45.0) | 2/7 (28.6) | <0.001 [a] |
| Primary prevention | 16/25 (64.0) | 3/5 (60.0) | 12/18 (66.7) | 1/2 (50.0) | 0.878 [a] |
| Secondary prevention | 9/25 (36.0) | 2/5 (40.0) | 6/18 (33.3) | 1/2 (50.0) | 0.878 [a] |
| Beta-blockers at enrollment, $N/n$ (%) | 72/101 (71.3) | 37/54 (68.5) | 31/40 (77.5) | 4/7 (57.1) | 0.440 [a] |
| Beta-blockers at follow-up, $N/n$ (%) | 76/83 (91.6) | 40/44 (90.9) | 30/33 (90.9) | 6/6 (100.0) | 0.742 [a] |
| Type of beta-blockers, $N/n$ (%), (mg/kg BW/day), median (min–max) | | | | | |
| Metoprolol | 36/76 (47.4), 1.4 (0.0–2.7) | 21/40 (52.5), 1.3 (0.0–2.1) | 13/30 (43.3), 1.6 (0.5–2.7) | 2/6 (47.4), 1.4 (1.2–1.7) | 0.579 [a] 0.112 [b] |

**Table 1.** *Cont.*

| Characteristics | Total ($n$ = 101) | LQT1 ($n$ = 54) | LQT2 ($n$ = 40) | LQT3 ($n$ = 7) | $p$-Value |
|---|---|---|---|---|---|
| Bisoprolol | 7/76 (9.2), 0.1 (0.0–0.1) | 5/40 (12.5), 0.1 (0.0–0.1) | 2/30 (6.7), 0.1 (0.0–0.1) | 0/6 (0.0), n.a. | 0.507 [a] 0.699 [b] |
| Atenolol | 3/76 (3.9), 1.5 (0.6–2.5) | 0/40 (0.0), n.a. | 2/30 (6.7), 0.6 (0.6–0.6) | 1/6 (16.7), 2.5 (2.5–2.5) | 0.091 [a] 0.317 [b] |
| Propranolol | 30/76 (39.5), 1.8 (1.1–4.8) | 14/40 (35.0), 1.7 (1.2–3.5) | 13/30 (43.3), 1.8 (1.1–3.7) | 3/6 (50.0), 3.2 (2.1–4.8) | 0.670 [a] 0.176 [b] |
| Location variant, $N/n$ (%) | | | | | 0.003 [a] |
| N-term | 10/101 (9.9) | 3/54 (5.6) | 7/40 (17.5) | 0/7 (0.0) | 0.105 [a] |
| S1–S4 region | 26/101 (25.7) | 22/54 (40.7) | 2/40 (5.0) | 2/7 (28.6) | <0.001 [a] |
| S5-loop-S6 region [e] | 28/101 (27.7) | 12/54 (22.2) | 16/40 (40.0) | 0/7 (0.0) | 0.039 [a] |
| C-term | 36/101 (35.6) | 17/54 (31.5) | 15/40 (37.5) | 4/7 (57.1) | 0.391 [a] |
| Interdomain | 1/101 (1.0) | n.a. | n.a. | 1/7 (14.2) | n.a. |
| Type of variant, $N/n$ (%) | | | | | 0.019 [a] |
| Missense | 66/101 (65.3) | 39/54 (72.2) | 20/40 (50.0) | 7/7 (100.0) | 0.011 [a] |
| Frameshift | 19/101 (18.8) | 6/54 (11.1) | 13/40 (32.5) | 0/7 (0.0) | 0.013 [a] |
| Small in-frame deletion/duplication | 6/101 (5.9) | 6/54 (11.1) | 0/40 (0.0) | 0/7 (0.0) | 0.062 [a] |
| Nonsense | 4/101 (4.0) | 2/54 (3.7) | 2/20 (5.0) | 0/7 (0.0) | 0.814 [a] |
| Intragenic deletion | 3/101 (3.0) | 0/54 (0.0) | 3/20 (7.5) | 0/7 (0.0) | 0.095 [a] |
| Splice | 2/101 (2.0) | 0/54 (0.0) | 2/20 (5.0) | 0/7 (0.0) | 0.211 [a] |
| Nearsplice | 1/101 (1.0) | 1/54 (1.9) | 0/20 (0.0) | 0/7 (0.0) | 0.644 [a] |

Abbreviations: LQTS: Long QT syndrome; MAE: major arrhythmic event; SCD: sudden cardiac death; ACA: aborted cardiac arrest; ICD: implantable cardioverter defibrillator; VT: ventricular tachycardia; BW: body weight; n.a.: not available. [a]: chi-squared test; [b]: Kruskal–Wallis test; [c]: from first diagnosis; [d]: ICD implantation or beta-blocker therapy; [e]: corresponds to the pore region.




(**a**) (**b**)

**Figure 1.** (**a**) Distribution of variants in the *KCNH2* potassium channel, depending on major arrhythmic event (MAE). Black dot: occurrence of MAE; white dot: without occurrence of MAE. (**b**) Kaplan–Meier estimates of survival without major arrhythmic event (MAE) among the 40 LQTS2 patients, depending on location of variant. Pore: S5-loop-S6 region. Non-pore: N-term, S1–S4 region, or C-term.

### *3.2. Risk Factors for Major Arrhythmic Events*

A total of 18 patients (17.8%) experienced an MAE during the follow-up (no SCD, 8 ACA in 8 patients, appropriate ICD discharge in 6 patients, and sustained VT in 4 patients (Table 1)). Comparing patients with and without MAEs in the univariate analysis, patients with MAEs had a longer follow-up time, higher Schwartz score, higher QTc value, higher rate of syncope, and were more often treated with beta-blockers at the time of enrollment or with an ICD (Table 2, Figure 2).

**Table 2.** Characteristics with clinical and genetic findings by MAE.

| Characteristics | Total ($n$ = 101) | MAE ($n$ = 18) | Non-MAE ($n$ = 83) | $p$-Value |
|---|---|---|---|---|
| Female, $N/n$ (%) | 54/104 (53.5) | 11/18 (61.1) | 43/83 (51.8) | 0.473 [a] |
| Age at diagnosis (years), median (min–max) | 7.7 (0.0–18.0) | 8.5 (0.0–18.0) | 7.5 (0.0–17.8) | 0.289 [b] |
| Subjects with follow-up, $N/n$ (%) | 83/101 (82.2) | 17/18 (94.4) | 66/83 (79.5) | 0.134 [a] |
| Follow-up time [c] (years), median (min–max) | 4.6 (0.1–24.3) | 8.4 (0.8–19.7) | 4.0 (0.1–24.3) | 0.023 [b] |
| Genetic findings, $N/n$ (%) | | | | 0.002 [a] |
| *KCNQ1*<br>*KCNH2*<br>*SCN5A* | 54/101 (53.5)<br>40/101 (39.6)<br>7/101 (6.9) | 3/18 (16.7)<br>13/18 (72.2)<br>2/18 (11.1) | 51/83 (61.4)<br>27/83 (32.5)<br>5/83 (6.0) | |
| QTc time (ms), median (min–max) | 470 (370–740) | 504 (417–740) | 470 (370–590) | 0.013 [b] |
| QTc categories (1–4), $N/n$ (%) | | | | 0.107 [a] |
| ≤449 ms | 23/101 (22.8) | 3/18 (16.7) | 20/83 (24.1) | 0.496 [a] |
| 450–499 ms | 50/101 (49.5) | 6/18 (33.3) | 44/83 (53.0) | 0.130 [a] |
| 500–549 ms | 15/101 (14.9) | 4/18 (22.2) | 11/83 (13.3) | 0.332 [a] |
| ≥550 ms | 13/101 (12.9) | 5/18 (27.8) | 8/83 (9.6) | 0.037 [a] |
| Syncope, $N/n$ (%) | 29/101 (28.7) | 12/18 (66.7) | 17/83 (20.5) | <0.001 [a] |
| Syncope at enrollment | 27/101 (26.7) | 11/18 (61.1) | 16/83 (19.3) | <0.001 [a] |
| Syncope during follow-up | 16/83 (19.3) | 9/17 (52.9) | 7/66 (10.6) | <0.001 [a] |
| Family history, $N/n$ (%) | 83/101 (82.1) | 13/18 (72.2) | 70/83 (82.2) | 0.223 [a] |
| Definite LQTS of relative | 61/83 (73.5) | 7/13 (53.8) | 54/70 (77.1) | 0.081 [a] |
| SCD/ACA of relative | 28/83 (33.7) | 4/13 (30.8) | 24/70 (34.3) | 0.805 [a] |
| Schwartz score, median (min–max) | 4.0 (1.0–7.0) | 6.0 (4.0–7.0) | 4.0 (1.0–5.0) | <0.001 [b] |
| Cardiac therapy [d], $N/n$ (%) | 87/101 (86.1) | 18/18 (100.0) | 69/83 (82.2) | 0.060 [a] |
| ICD, $N/n$ (%) | 25/101 (24.8) | 15/18 (83.3) | 10/83 (12.0) | <0.001 [a] |
| Primary prevention | 16/25 (64.0) | 6/15 (40.0) | 10/10 (100.0) | 0.002 [a] |
| Secondary prevention | 9/25 (36.0) | 9/9 (100.0) | 0/9 (0.0) | 0.002 [a] |
| Beta-blockers at enrollment, $N/n$ (%) | 72/101 (71.3) | 18/18 (100.0) | 54/83 (65.1) | 0.003 [a] |
| Beta-blockers at follow-up, $N/n$ (%) | 76/83 (91.6) | 16/17 (94.1) | 60/66 (90.9) | 0.671 [a] |
| Type of beta-blockers, $N/n$ (%), (mg/kg BW/day), median (min–max) | | | | |
| Metoprolol | 36/76 (47.4),<br>1.4 (0.0–2.7) | 7/16 (43.8),<br>1.5 (0.4–2.7) | 29/60 (48.3),<br>1.4 (0.0–2.5) | 0.744 [a]<br>0.845 [b] |

**Table 2.** *Cont.*

| Characteristics | Total ($n$ = 101) | MAE ($n$ = 18) | Non-MAE ($n$ = 83) | $p$-Value |
|---|---|---|---|---|
| Bisoprolol | 7/76 (9.2), 0.1 (0.0–0.1) | 4/16 (25.0), 0.1 (0.0–0.1) | 3/60 (78.9), 0.1 (0.1–0.1) | 0.014 [a] 0.629 [b] |
| Atenolol | 3/76 (3.9), 1.5 (0.6–2.5) | 0/16 (0.0), n.a. | 3/60 (5.0), 1.5 (0.6–2.5) | 0.361 [a] n.a. |
| Propranolol | 30/76 (39.5), 1.8 (1.1–4.8) | 5/16 (31.3), 3.1 (1.1–4.8) | 25/60 (41.7), 1.7 (1.2–3.5) | 0.449 [a] 0.186 [b] |
| Location variant, $N/n$ (%) | | | | 0.037 [a] |
| N-term | 10/101 (9.9) | 2/18 (11.1) | 8/83 (9.6) | 0.850 [a] |
| S1–S4 region | 26/101 (25.7) | 2/18 (11.1) | 24/83 (28.9) | 1.117 [a] |
| S5-loop-S6 region [e] | 28/101 (27.7) | 10/18 (55.6) | 18/83 (21.7) | 0.004 [a] |
| C-term | 36/101 (35.6) | 4/18 (22.2) | 32/83 (38.6) | 0.190 [a] |
| Interdomain | 1/101 (1.0) | n.a. | 1/83 (1.2) | n.a. |
| Type of variant, $N/n$ (%) | | | | 0.398 [a] |
| Missense | 66/101 (65.3) | 15/18 (83.3) | 51/83 (61.4) | 0.077 [a] |
| Frameshift | 19/101 (18.8) | 2/18 (11.1) | 17/83 (20.5) | 0.356 [a] |
| Small in-frame deletion/duplication | 6/101 (5.9) | 0/18 (0.0) | 6/83 (7.2) | 0.240 [a] |
| Nonsense | 4/101 (4.0) | 0/18 (0.0) | 4/83 (4.8) | 0.342 [a] |
| Intragenic deletion | 3/101 (3.0) | 0/18 (0.0) | 3/83 (3.6) | 0.413 [a] |
| Splice | 2/101 (2.0) | 1/18 (5.6) | 1/83 (1.2) | 0.230 [a] |
| Nearsplice | 1/101 (1.0) | 0/18 (0.0) | 1/83 (1.2) | 0.640 [a] |

Abbreviations: LQTS: Long QT syndrome; MAE: major arrhythmic event; SCD: sudden cardiac death; ACA: aborted cardiac arrest; ICD: implantable cardioverter defibrillator; BW: body weight; n.a.: not available. [a]: chi-squared test; [b]: Mann–Whitney U-test; [c]: from first diagnosis; [d]: ICD implantation or beta-blocker therapy; [e]: corresponds to the pore region.

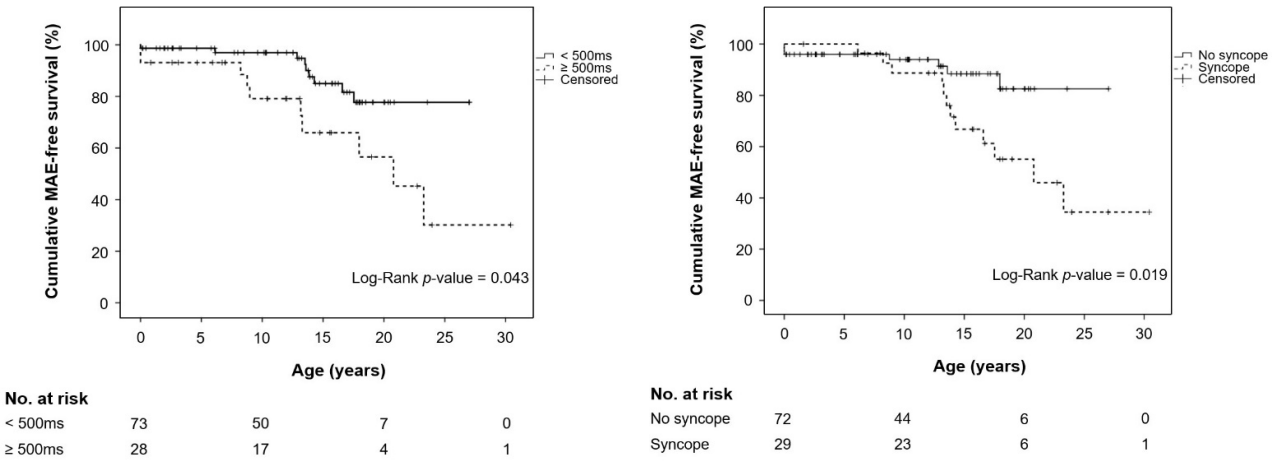



**Figure 2.** Kaplan–Meier estimates of survival without a major arrhythmic event (MAE) among the 101 patients with Long QT syndrome depending on (**a**) QTc value and (**b**) the occurrence of syncope.

Patients with MAEs were more likely to carry a pathogenic variant in *KCNH2* (13/40, 32.5%) or *SCN5A* (2/7 patients, 28.6%) than in *KCNQ1* (3/54, 5.6%; $p = 0.002$) (Tables 1 and 2, Figure 3a). The probability of a cumulative MAE-free survival was significantly lower if

the patient carried the variant within the pore region (S5-loop-S6 region) of the *KCNH2* gene (Figures 1 and 3b).

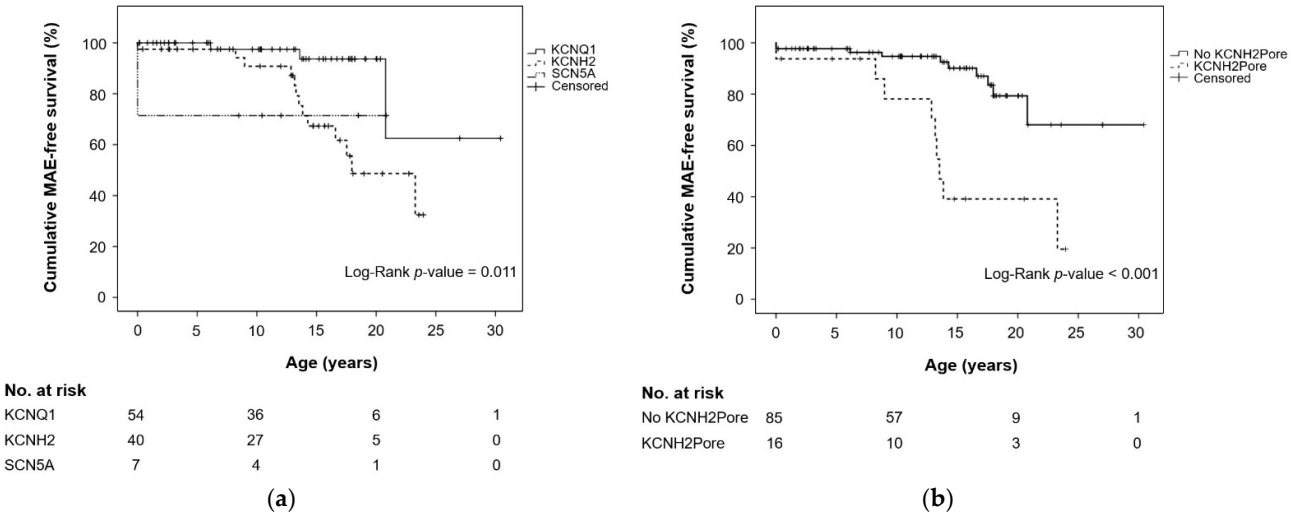



**Figure 3.** Kaplan–Meier estimates of survival without a major arrhythmic event (MAE) among the 101 patients with Long QT syndrome depending on (**a**) genetic locus of the variant and (**b**) location of the variant in the *KCNH2* gene. KCNH2Pore: variant in the *KCNH2* gene as well as in the S5-loop-S6 region (pore region). No KCNH2Pore: variant in the *KCNH2* gene and not in the S5-loop-S6 region or variant in other genes (*KCNQ1*, *SCN5A*).

A multivariate analysis revealed that patients with a variant in the *KCNH2* or *SCN5A* gene had a significantly higher risk of developing an MAE than the carriers of variants in the *KCNQ1* gene, independent of the QTc value and the occurrence of syncope (Table 3). This was also confirmed if only the index patients were analyzed (Supplementary Table S1). In addition, a multivariate analysis identified carriers of a pathogenic variant within the *KCNH2* pore region as an independent risk factor, increasing the risk of occurrence of an MAE four-fold (Table 4, Supplementary Table S2).

**Table 3.** Cox regression model: risk factors for MAE.

| | | **Univariable** | | | **Multivariable** | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | **95% CI** | ***p*-Value** | **HR** | **95% CI** | ***p*-Value** |
| Age at diagnosis (per additional year) | 0.948 | 0.865–1.040 | 0.262 | | | |
| Female | 1.322 | 0.511–3.420 | 0.565 | | | |
| QTc $\geq$ 500 ms | 2.588 | 1.002–6.681 | 0.049 | 0.870 | 0.262–2.891 | 0.820 |
| Time-dependent syncope [a] | 3.260 | 1.080–9.846 | 0.036 | 2.653 | 0.702–10.027 | 0.150 |
| SCD-FH | 0.764 | 0.234–2.492 | 0.656 | | | |
| LQT-FH | 0.451 | 0.151–1.349 | 0.154 | | | |
| Missense | 0.434 | 0.125–1.511 | 0.190 | | | |
| LQTS genotype | | | | | | |
| LQTS2 vs. LQTS1 | 5.361 | 1.523–18.868 | 0.009 | 5.403 | 1.191–16.281 | 0.026 |
| LQTS3 vs. LQTS1 | 6.033 | 0.998–36.472 | 0.050 | 8.853 | 1.402–55.919 | 0.020 |
| LQTS2 vs. LQTS3 | 0.889 | 0.197–3.999 | 0.878 | | | |

**Table 3.** *Cont.*

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | **95% CI** | ***p*-Value** | **HR** | **95% CI** | ***p*-Value** |
| Pore region [b] | 3.214 | 1.254–8.236 | 0.015 | 2.257 | 0.724–7.034 | 0.160 |
| Time-dependent beta-blocker use [c] | 1.294 | 0.433–3.867 | 0.644 | | | |

Abbreviations: LQTS: Long QT syndrome; MAE: major arrhythmic event; SCD: sudden cardiac death; FH: family history. [a]: patients with syncope before the occurrence of MAE vs. patients without syncope or patients with syncope after the occurrence of MAE; [b]: corresponds to the S5-loop-S6 region; [c]: patients with beta-blocker use before the occurrence of MAE vs. patients without beta-blocker use or with beta-blocker use after the occurrence of MAE.

**Table 4.** Cox regression model: risk factors for MAE with KCNH2Pore.

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | **95% CI** | ***p*-Value** | **HR** | **95% CI** | ***p*-Value** |
| QTc $\geq$ 500 ms | 2.588 | 1.002–6.681 | 0.049 | 0.870 | 0.262–2.891 | 0.820 |
| Time-dependent syncope [a] | 3.260 | 1.080–9.846 | 0.036 | 2.653 | 0.702–10.027 | 0.150 |
| KCNH2Pore [b] | 5.299 | 2.071–13.556 | 0.001 | 4.241 | 1.408–12.774 | 0.010 |

Abbreviations: MAE: major arrhythmic event. [a]: patients with syncope before the occurrence of MAE vs. patients without syncope or patients with syncope after occurrence of MAE; [b]: patients with a variant in the *KCNH2* gene as well as in the S5-loop-S6 region (pore region) vs. patients with a variant in the *KCNH2* gene and not in the S5-loop-S6 region or with a variant in other genes (*KCNQ1*, *SCN5A*).

## 4. Discussion

This study with LQTS patients diagnosed during childhood shows the importance of molecular genetic findings for risk stratification. A molecular genetic diagnosis of LQTS2 and LQTS3 as well as variants in the *KCNH2* S5-loop-S6 region were identified as independent risk factors for an MAE, irrespective of the QTc value and the occurrence of syncope.

Overall, life-threatening arrhythmic events occurred in almost 18% of a population with childhood onset LQTS despite the use of beta-blockers. When only taking ACA and SCD into account, the observed frequency of 8% in this study was in accordance with previous studies that reported events in 2.4–12.1% of cases. These studies did not include appropriate ICD discharges and a sustained VT [9–11].

The clinical risk factors associated with a higher risk of MAEs included a longer QTc duration and a history of syncope in the pediatric population of this study. The median QTc was 470 ms, which was about 10 ms higher than in a comparable study including only genotyped patients aged 0–18 [24]. Compared with the other studies, which also included non-genotyped patients, the QTc was lower (490–494 ms) [9,10]. In most studies, a high QTc was shown to be an independent risk factor of life-threatening events [9,19,20,24]. In line with the findings of other studies [10,24], an event-free survival was significantly lower in the pediatric patients of our study with QTc values greater than 500 ms. The finding of a history of syncope as a risk factor for the occurrence of MAEs was also reported by others [9,10,20].

Patients diagnosed with LQTS2 and LQTS3 were more likely to experience MAEs compared with LQTS1 patients. The findings of the present study were in line with studies of young adult LQTS patients who showed a higher rate of cardiac events in the carriers of variants in the *KCNH2* and the *SCN5A* genes [18]. Those findings were later confirmed in patients who had already been treated with beta-blockers [15], which was also the case in the present study. Previous studies focusing on children and adolescents with LQTS failed to identify the genotype as a risk factor for MAEs [9,10]. When adults were included, LQTS1 and LQTS2 were shown to be independent risk factors. However, there were differences in

the study design in that a syncope was not counted as a separate risk factor but as a cardiac event [25].

Consistent with reports from others [26], about two-thirds of the patient population in our study carried a missense variant. The location of the variants was within a pore region in about a third of the patients, similar to the findings from previous studies (17–30%) [27–29]. Although the type of variant did not influence the risk of an MAE, the location of variants in the S5-loop-S6 pore region of *KCNH2* was identified as an independent risk factor for life-threatening arrhythmic events in the present study. This was in line with findings from others that showed an association between the variant location and the risk of life-threatening events in young adults [29]. The pore region often contains variants with dominant negative effects on $I_{Kr}$ because the potassium conductance pathway is generated in this region and is, therefore, a critical zone [30].

Due to the limited number of patients, a subgroup analysis on the genotype-related risks dependent on age and sex [9,12,31] was not performed. Given the retrospective character of the present study, there was a lack of information on the circumstances under which MAEs occurred. Therefore, a subanalysis on the triggering factors dependent on the underlying genotype could not be performed. Exact information about the methods used for the respective molecular genetic diagnosis was not available for all patients, specifically if information about the molecular genetic diagnosis was extracted from the medical records of the patients. Finally, given that this study included only genotyped patients with variants in the *KCNQ1*, *KCNH2*, and *SCN5A* genes, this risk stratification could not be extrapolated for all LQTS patients.

Despite these limitations, the current study has contributed toward a better understanding of variant-specific risk stratification in LQTS in pediatric patients. The clinical phenotype of patients with LQTS in childhood and adolescence is heterogeneous and influenced by numerous factors. As variant-specific risk stratification has still not been explicitly studied in this age group, further studies are needed to identify and prove the predictors of severe arrhythmias leading to SCD in pediatric patients with LQTS.

## 5. Conclusions

MAEs frequently occur in childhood onset LQTS despite the use of beta-blockers. The clinical factors associated with a higher risk of life-threatening events from a univariate analysis included a longer follow-up time, longer QTc intervals, and a history of syncope. From a multivariate analysis, a molecular genetic diagnosis of LQTS2 and LQTS3 as well as variants in the *KCNH2* S5-loop-S6 pore region were identified as independent risk factors irrespective of the QTc and clinical symptoms. These findings underline the importance of genetic diagnostics in the risk stratification of pediatric LQTS patients.

**Supplementary Materials:** The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cardiogenetics12010009/s1. Figure S1: Distribution of variants in *KCNQ1* and *SCN5A* gene; Table S1: Cox regression model: risk factors for MAE in index patients; Table S2: Cox regression model: risk factors for MAE with KCNH2Pore in index patients; Table S3: Genetic characteristics in the *KCNQ1* gene; Table S4: Genetic characteristics in the *KCNH2* gene; Table S5: Genetic characteristics in the *SCN5A* gene.

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki. The study was approved by the institution's ethical committee (approval number 243/17S from 16 October 2017).

**Informed Consent Statement:** All parents or legally authorized representatives of the pediatric patients gave written consent for the anonymous publication of their data.

**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Conflicts of Interest:** The authors declare that there is no conflict of interest related to the content of this study.

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