



Clinical Impact of Genetic Testing for Long QT Syndrome

— Evidence From a Nationwide LQTS Registry in Japan —

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Background: Genetic testing for long QT syndrome (LQTS) is useful for diagnosis, risk stratification, and therapeutic strategies. This study investigated the clinical impact of genetic testing for LQTS patients.

Methods and Results: Total 3,851 patients (proband: 2,316 [60%]; female: 2,283 [59%]; median age: 14 years [interquartile range 9–36 years]) diagnosed with LQTS (LQTS score ≥ 3.5 , QTc ≥ 500 ms, pathogenic variants in LQTS-associated genes, or unexplored syncope with QTc 480–499 ms) were enrolled in this study. Of these patients, 1,146 (29.8%) experienced syncope and 322 (8.5%) experienced ventricular fibrillation (VF) or cardiopulmonary arrest (CPA) at ≤ 70 years of age. Genetic testing using a next-generation sequencing panel and/or Sanger sequencing was performed for 3,770 (98%) patients, genotype was then identified in the following LQTS-associated genes: *KCNQ1* (45%), *KCNH2* (34%), *SCN5A* (8%), *KCNE1* (0.1%), *KCNE2* (0.03%), *KCNJ2* (2.7%), *CACNA1C* (1.2%), and *CALM1,2* (0.3%). Forty-seven (1.2%) patients had double or compound heterozygous variants in LQTS-associated genes, whereas the genotype remained unknown in 220 (5.8%) patients. When comparing phenotype with genotype, QTc was significantly longer in *CALM1,2* patients than in others except for *CACNA1C*, whereas QTc was almost normal in *KCNJ2* patients. The incidence of the first cardiac event (syncope, VF/CPA) differed among the genotypes, and prognosis was significantly worse for *CALM1,2* patients.

Conclusions: Comprehensive genetic testing, including non-major LQTS genes, is important for diagnosis and risk stratification of LQTS.

Key Words: Arrhythmia; Diagnosis; Genetic testing; Long QT syndrome; Sudden cardiac death

Long QT syndrome (LQTS) is characterized by a prolonged QT interval on electrocardiogram (ECG) and a polymorphic ventricular tachycardia, known as torsade de pointes (TdP), triggered primarily by exercise or stress, resulting in syncope or sudden cardiac death (SCD).^{1,2} The first symptoms usually occur in children

or adolescents, but in some cases may occur in the adult or older population. Continuous medical care from childhood/adolescence to adulthood is important for those with LQTS.

Most cases of congenital LQTS are autosomal dominant inherited (Romano-Ward syndrome). Pathogenic variants in the genes encoding cardiac ion channels or their associated

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proteins have been identified in approximately 70% of patients with LQTS.³ Previous studies have demonstrated genotype-⁴⁻⁶ or variant-specific⁷⁻¹¹ differences in prognosis and therapeutic strategies in LQTS, suggesting that genetic testing is extremely important for patients with LQTS and their families. More than 17 genes have been reported as causative or associated genes for LQTS. The Clinical Genome Resource (ClinGen) Working Group for LQTS has classified the LQTS-associated genes as definitive, strong, and moderate,¹² with these classifications being cited in the 2022 European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement.¹³ However, the clinical impact of genetic testing for LQTS based on the recent statement is still unexplored.

In this study, we enrolled nearly 4,000 patients with LQTS using a nationwide Japanese LQTS registry and then investigated the clinical impact of genetic testing, as well as the association between the genotype and phenotype, for patients with LQTS.

Methods

Patients

This multicenter registry retrospectively enrolled patients with LQTS and their families who had been diagnosed with LQTS at 19 Japanese institutions (National Cerebral and Cardiovascular Center, Saitama Medical University International Medical Center, Tsukuba University, Kagoshima Medical Center, Shiga University of Medical Science, Kanazawa University, Okayama University, Gunma University, Niigata University, Shinshu University, Osaka City General Hospital, Hokkaido Children's Hospital, Teine-Keijinkai Hospital, Yamagata University, Nagoya University, Tokushima University, Fukuoka Children Hospital, and Yokohama City University). The number of enrollments from each institution are presented in **Supplementary Table 1**.

LQTS was diagnosed if any of the following criteria were met:

- LQTS risk score ("Schwartz score") ≥ 3 .¹⁴
- QTc ≥ 500 ms on repeated ECG recordings after excluding secondary LQTS
- the presence of pathogenic or likely pathogenic (P/LP) variants in LQTS-associated genes (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNJ2*, *CACNA1c*, *CALM1-3* and

TRDN) regardless of QT interval.

A diagnosis of LQTS was also made for those who had unexplained syncope and a QTc of 480–499 ms on repeated ECGs after excluding secondary LQTS.

Written informed consent was obtained from all patients, or from the parents or legal guardians of minors, for both clinical and molecular screening, as well as study participation. This study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the National Cerebral and Cardiovascular Center (R22006-5).

Clinical Characteristics and ECG Parameters

All clinical characteristics, including age at diagnosis, sex, previous cardiac events, such as syncope, ventricular fibrillation (VF), cardiopulmonary arrest (CPA) or SCD, a family history of LQTS and SCD, and ECG parameters were obtained from the electronic data capture system. For the ECG parameters, the QT and RR intervals were measured in lead II or V5, and the QT interval was corrected for heart rate (QTc) according to Bazett's formula. In addition, data was collected in the registry for the QTc 4 min after recovery from an exercise stress test (if applicable), the presence or absence of TdP, T wave alternans (TWA), notched T wave in 3 leads, and bradycardia for age.¹⁴

Genetic Testing

Genetic testing for at least the major LQTS genes, such as *KCNQ1*, *KCNH2* and *SCN5A*, was performed locally at each institution using standard technologies. However, some probands had undergone more recent comprehensive genetic testing using next-generation sequencing (NGS) targeting not only the major LQTS genes but also relatively rare LQTS genes, such as *CALM1-3*, *KCNE1*, *KCNE2*, *TRDN*, *CACNA1c*, and *KCNJ2*. Family members underwent genetic screening focused on the disease-causing variant identified in the probands. Variant pathogenicity was evaluated using ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) and Franklin ACMG classification (<https://franklin.genoox.com/>). The variant position was based on the transcript ID NM_000218 (*KCNQ1*), NM_000238 (*KCNH2*), and NM_001099404 or NM_198056 (*SCN5A*).

Statistical Analysis

Continuous variables are presented as the mean $\pm$ SD or median with interquartile range (IQR), as appropriate, and categorical variables are presented as numbers and percentages. The significance of differences in baseline char-

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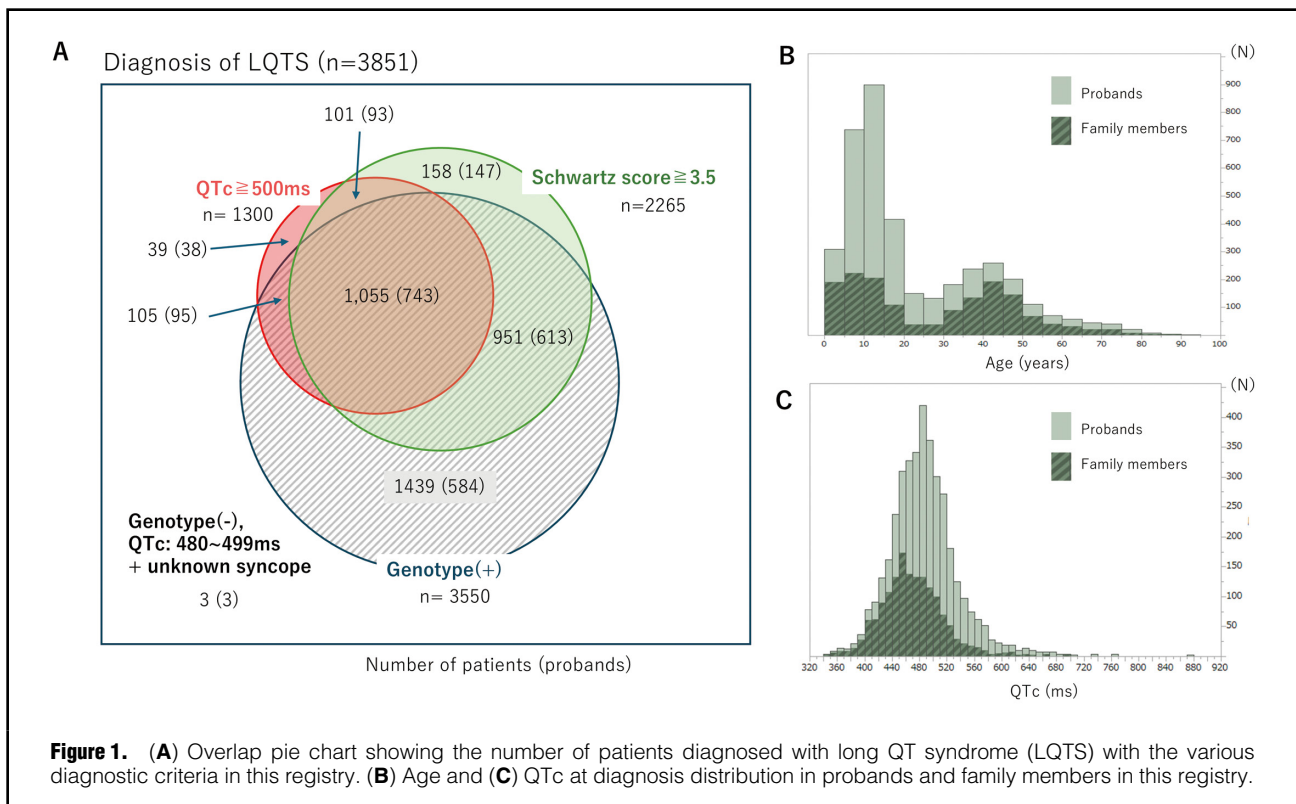


Figure 1. (A) Overlap pie chart showing the number of patients diagnosed with long QT syndrome (LQTS) with the various diagnostic criteria in this registry. (B) Age and (C) QTc at diagnosis distribution in probands and family members in this registry.

acteristics between probands and family members were compared using Student's t-test or the Wilcoxon rank-sum test for continuous variables, and the Chi-squared test or Fisher's exact test for categorical variables, as appropriate. Differences among patients in the major 3 LQTS genotypes, namely *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3), were compared using analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables, and the Chi-squared test or Fisher's exact test for categorical variables, as appropriate. We described QTc (ms) at diagnosis using violin plots for better visualization of the distribution of QTc among genotypes. We used ANOVA to compare mean QTc values among genotypes and Tukey's honestly significant difference test for multiple comparisons. The cumulative incidences of the primary and secondary outcomes were calculated using the Kaplan-Meier method. The follow-up period was defined as from birth to the age of initial diagnosis. The primary endpoint was the time from birth until the first syncope event up to age 70 years, and the secondary endpoint was VF or CPA up to age 70 years. All reported P values are 2-tailed, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS version 9.4 and JMP version 14 (SAS Institute Inc., Cary, NC, USA).

Results

LQTS Diagnosis

In total, 4,006 patients with LQTS were recorded in this registry from 19 institutions in Japan. Of these 4,006 patients, 155 who were not compatible with the diagnostic criteria for LQTS were excluded,³ leaving 3,851 patients who met the LQTS diagnosis in this study. **Figure 1A** shows

the number of patients in whom LQTS was diagnosed using the different diagnostic criteria. Specifically, 1,300 patients had a QTc ≥ 500 ms on ECG, and 1,160 (89.2%) of these patients were genotype positive; another 2,265 patients had a Schwartz score ≥ 3.5 , with 2,006 (88.6%) being genotype positive. However, 1,439 patients did not completely meet these diagnostic criteria (QTc ≥ 500 ms or Schwartz score ≥ 3.5) and were diagnosed with LQTS on the basis of a positive genetic test; almost 60% of these patients were family members of the probands.

As shown in **Figure 1B**, the age of the probands peaked before 20 years, but the age distribution was extremely broad, indicating that LQTS can be diagnosed not only in children/adolescents but also in adults and older populations.¹⁵ Conversely, the age of family members (**Figure 1B**) showed a bimodal distribution because, in many familial cases, a child (proband) was first diagnosed with LQTS and the parents or siblings were then diagnosed with LQTS by cascade screening.

As indicated in **Table 1**, 1,161 (30%) patients had a history of syncope, with 1,146 being aged ≤ 70 years old, of whom a higher proportion were probands (40%) than family members (14%). Not all syncope in this registry was due to TdP; however, 16% of probands experienced TdP. Furthermore, 322 (8.5%) patients had a history of VF/CPA at age ≤ 70 years, with a significantly higher proportion among probands than their families (12.6% vs. 2.0%). Thus, some probands could be diagnosed with LQTS when they experienced a cardiac event such as syncope, TdP, or VF/CPA.

The QTc was longer in probands than in the family members, but its distribution was also broad (**Figure 1C**). Moreover, the presence of other ECG parameters, such as

Table 1. Clinical Characteristics of Patients With LQTS at Diagnosis

	Overall (n=3,851)	Probands (n=2,316)	Family members (n=1,535)	P value
Age at diagnosis (years)	14 [9–36]	13 [9–24]	27 [9–43]	<0.001
Female sex	2,283 (59.3)	1,435 (62.0)	848 (55.2)	<0.001
Symptom				
Syncope	1,161 (30.2)	938 (40.5)	223 (14.5)	<0.001
First syncope at age ≤70 years	1,146 (29.8)	924 (39.9)	222 (14.5)	<0.001
VF/CPA	333 (8.6)	300 (13.0)	33 (2.1)	<0.001
First VF/CPA at age ≤70 years	322 (8.5)	291 (12.6)	31 (2.0)	<0.001
ECG parameters				
RR (ms)	890±191	903±184	870±199	<0.001
QT (ms)	455±65	470±63	434±61	<0.001
QTc (B) (ms)	486±49	497±48	469±44	<0.001
T wave alternans	112 (2.9)	92 (4.0)	20 (1.3)	<0.001
Notched T wave	966 (25.1)	664 (28.7)	302 (19.7)	<0.001
TdP	391 (10.2)	367 (15.9)	24 (1.6)	<0.001
Bradycardia	316 (8.2)	246 (10.6)	70 (4.6)	<0.001
Deafness	23 (0.6)	17 (0.7)	6 (0.4)	0.175
Treadmill exercise testing				
QTc 4 min after exercise testing (ms)	503±53	505±53	496±49	0.034
Family history				
Definitive LQTS		942 (40.7)	N/A	
SCD at age <30 years		190 (8.2)	N/A	
Schwartz score	3.8±2.0	4.3±2.0	3.0±1.8	<0.001

Continuous variables are presented as the mean±SD or median [interquartile range]. Categorical variables are presented as n (%). CPA, cardiopulmonary arrest; ECG, electrocardiogram; LQTS, long QT syndrome; QTc, QT corrected for heart rate; SCD, sudden cardiac death; VF, ventricular fibrillation.

TWA, notched T wave, and bradycardia for age, was also higher among probands than their family members. Therefore, the Schwartz score was significantly higher among probands than their family members (Table 1).

Genotype Identification

Genetic testing was performed in 3,770 (97.9%) patients. Among the probands, 2,250 (97.2%) underwent genetic testing, with 670 (29.8%) undergoing NGS; after testing, 2,035 (90.4%) probands were diagnosed as genotype-positive LQTS. Conversely, among family members (n=1,535), 1,520 (99.0%) underwent genetic testing, with 1,448 (95.3%) undergoing Sanger sequencing targeting the variant that had already been identified in the probands (Table 2; Figure 2A).

Finally, in total, there were 1,710 (45.3%) patients with *KCNQ1* variants (LQT1; including 8 homozygous for a *KCNQ1* variant), 1,293 (34.3%) with *KCNH2* variants (LQT2), 314 (8.3%) with *SCN5A* variants (LQT3), 4 (0.1%) with *KCNE1* variants (LQT5), 1 (0.03%) with a *KCNE2* variant (LQT6), 100 (2.7%) with *KCNJ2* variants (LQT7; Andersen–Tawil syndrome [ATS]), 58 (1.5%) with *CACNA1C* variants (LQT8; including 5 with Timothy syndrome [TS]), and 13 (0.3%), all probands, with *CALM1* (n=3) and *CALM2* (n=10) variants enrolled in this registry. Moreover, 47 patients had more than 2 variants (double or compound heterozygous) of the LQTS genes. Variants not related to LQTS (i.e., *ANK2*, *RYR2*, *KCNJ5*, *HCN4*, and *MYBPC3*) were identified in 7 patients, and 3 patients had structural abnormalities of chromosome 7. Finally, P/LP variants in the LQTS genes were not identified in 220 patients (genotype unknown; Table 2; Figure 2B).

Genotype-Phenotype Association

The QTc distribution at diagnosis for each genotype is shown in Figure 3. Among genotyped LQTS patients, QTc was significantly longer for those with the *CALM1,2* genotype than for those with the major 3 LQTS genotypes (i.e., *KCNQ1*, *KCNH2*, and *SCN5A*). In contrast, the QTc was shorter (and nearly normal) in those with the *KCNJ2* genotype compared with the other genotypes.

Kaplan–Meier analysis was used to investigate the cumulative incidence of the first cardiac event, such as syncope (Figure 4A) and VF/CPA (Figure 4B), for each genotype. Patients with *CALM1,2* variants had the worst prognosis among all the genotypes. However, when *CALM*-LQTS was excluded from consideration, syncope events in the other genotyped patients also increased after adolescence. In particular, the incidence of syncope after puberty was higher among patients with LQT2 than among those with other types of LQTS.

Furthermore, the frequency of VF/CPA in patients with *KCNH2* (LQT2), *SCN5A* (LQT3), and *CACNA1C* (LQT8 or TS) was nearly 20% when they reached middle age if they were untreated, which is higher than among those with *KCNQ1* (LQT1) and *KCNJ2* (LQT7 or ATS) variants.

Genotype-Phenotype in LQT1–3

The 3 major genes (i.e., *KCNQ1*, *KCNH2*, and *SCN5A*) were found in 3,317 (86%) patients. We therefore focused on patients with LQT1–3. As indicated in Table 3, the age at diagnosis was younger for those with LQT1 and LQT3 than for those with LQT2. Female sex was more common in the LQT1 and LQT2 groups than in the LQT3 group (60.9% and 60.6% vs. 46.8%, respectively). Syncope events

Table 2. Genetic Testing and LQTS Genotype				
	Overall (n=3,851)	Probands (n=2,316)	Family members (n=1,535)	P value
Genetic testing performed	3,770 (97.9)	2,250 (97.2)	1,520 (99.0)	
Sanger only	3,009 (79.8)	1,561 (69.4)	1,448 (95.3)	<0.0001
NGS only	222 (5.9)	194 (8.6)	28 (1.8)	
NGS+Sanger	505 (13.4)	476 (21.2)	29 (1.9)	
Unknown/others	34 (0.9)	19 (0.8)	15 (1.0)	
Genotype				<0.001
KCNQ1	1,710 (45.4)	948 (42.1)	762 (50.1)	
KCNH2	1,293 (34.3)	737 (32.8)	556 (36.6)	
SCN5A	314 (8.3)	186 (8.3)	128 (8.4)	
KCNE1	4 (0.1)	4 (0.2)	0 (0.0)	
KCNE2	1 (0.03)	1 (0.04)	0 (0.0)	
KCNJ2	100 (2.7)	60 (2.7)	40 (2.6)	
CACNA1C	58 (1.5)	40 (1.8)	18 (1.2)	
CALM1	3 (0.1)	3 (0.1)	0 (0.0)	
CALM2	10 (0.3)	10 (0.4)	0 (0.0)	
CALM3	0 (0.0)	0 (0.0)	0 (0.0)	
TRDN	0 (0.0)	0 (0.0)	0 (0.0)	
Double or compound hetero	47 (1.3)	36 (1.6)	11 (0.7)	
Others ^A	10 (0.3)	10 (0.4)	0 (0.0)	
Unknown	220 (5.8)	215 (9.6)	5 (0.3)	

Unless indicated otherwise, data are given as n (%). ^AOther genotypes included *ANK2* (n=3), structural abnormalities of chromosome 7 (n=3), *RYR2* (n=1), *KCNJ5* (n=1), *HCN4* (n=1), and *MYBPC3* (n=1). Double or compound hetero, double or compound heterozygous variants in long QT syndrome [LQTS]-associated genes; NGS, next-generation sequencing.

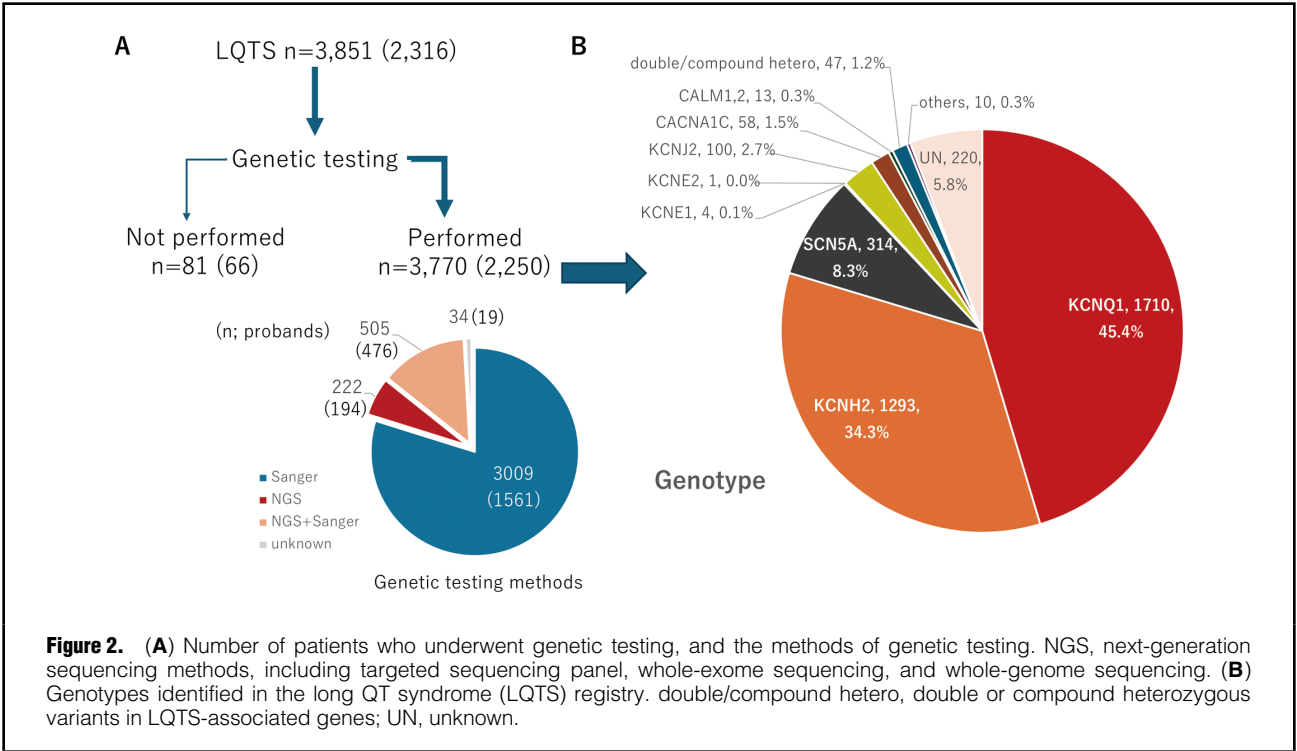


Figure 2. (A) Number of patients who underwent genetic testing, and the methods of genetic testing. NGS, next-generation sequencing methods, including targeted sequencing panel, whole-exome sequencing, and whole-genome sequencing. (B) Genotypes identified in the long QT syndrome (LQTS) registry. double/compound hetero, double or compound heterozygous variants in LQTS-associated genes; UN, unknown.

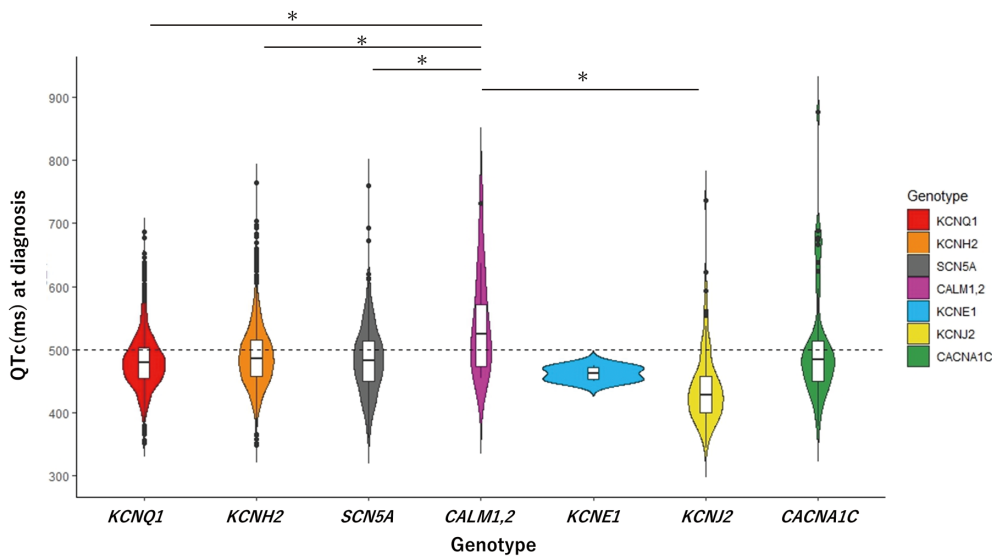


Figure 3. Violin plot of QTc at diagnosis for each long QT syndrome (LQTS) genotype. *P<0.01 (ANOVA with Tukey's honestly significant difference test).

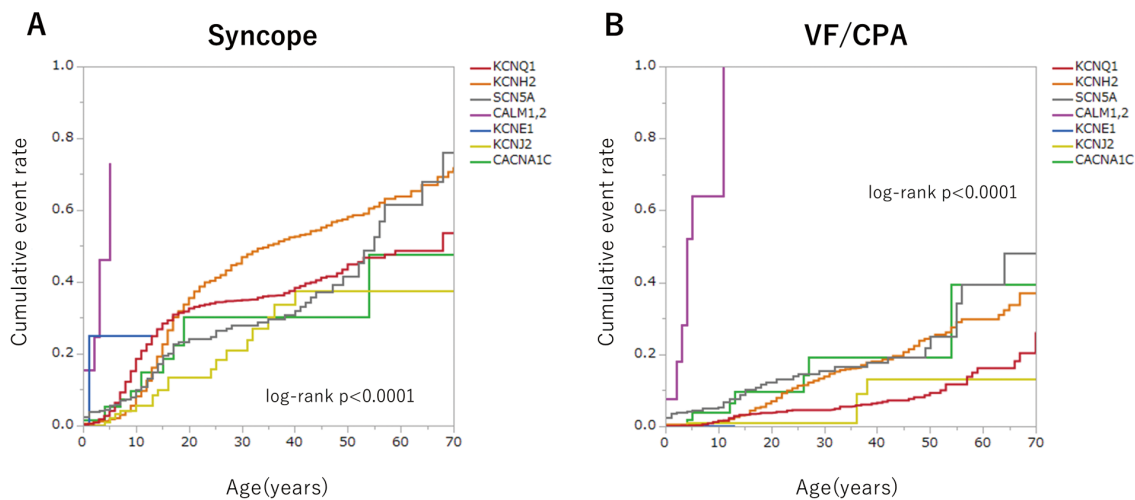


Figure 4. Kaplan-Meier curves for (A) the first syncope event and (B) the first ventricular fibrillation (VF) or cardiopulmonary arrest (CPA) event.

at age ≤70 years were more common in the LQT2 group than in the LQT1 and LQT3 groups. However, the occurrence of VF/CPA at age ≤70 years was higher in the LQT3 and LQT2 groups than in the LQT1 group. With regard to ECG parameters, the QTc at diagnosis was longer in the LQT2 group than in the LQT1 and LQT3 groups. In addition, a notched T wave and TdP were more often observed and a family history of LQTS was more common in the LQT2 group than in the LQT1 and LQT3 groups. Conversely, the QTc at 4 min after exercise testing was significantly longer in the LQT1 group than in the LQT2 and LQT3 groups, and the incidence of

bradycardia and TWA was higher in the LQT3 group than in the other 2 groups. Together with clinical parameters, the ECG findings contributed to a higher Schwartz score in the LQT2 group than in the LQT1 and LQT3 groups (Table 3). Triggers for the first syncope event are shown in Figure 5A. In the LQT1 group, many (70%) syncope events occurred during exercise and/or swimming. In contrast, exercise as a trigger of first syncope was rare in the LQT2 and LQT3 groups, as reported previously.⁵ In the LQT2 group, 23% of syncope events occurred during some emotional stress or arousal stimuli, but they occurred more

	LQT1 (KCNQ1; n=1,710)	LQT2 (KCNH2; n=1,293)	LQT3 (SCN5A; n=314)	P value
Age at diagnosis (years)	13 [8–37]	17 [11–38]	13 [8–34]	<0.001
Female sex	1,041 (60.9)	784 (60.6)	147 (46.8)	<0.001
Symptom				
Syncope	473 (27.7)	481 (37.2)	78 (24.8)	<0.001
First syncope at age ≤70 years	464 (27.2)	478 (37)	77 (24.5)	<0.001
Age at first syncope (years)	10 [7–14]	16 [12–25]	13.5 [7–27.5]	<0.001
VF/CPA	78 (4.6)	151 (11.7)	41 (13.1)	<0.001
First VF/CPA at age ≤70 years	73 (4.3)	146 (11.5)	41 (13.2)	<0.001
Age at first VF/CPA (years)	17 [10–46]	23 [16–38]	12 [1–25]	0.001
ECG parameters				
RR (ms)	885±176	906±198	913±222	0.003
QT (ms)	450±56	464±71	459±75	<0.001
QTc (B) (ms)	481±43	490±51	484±56	<0.001
T wave alternans	30 (1.8)	40 (3.1)	24 (7.7)	<0.001
Notched T wave	122 (7.2)	629 (48.7)	53 (16.9)	<0.001
Bradycardia	100 (5.9)	97 (7.5)	60 (19.1)	<0.001
Deafness	14 (0.8)	6 (0.5)	0 (0.0)	0.160
TdP	67 (3.9)	235 (18.2)	36 (11.5)	<0.001
Treadmill exercise test				
QTc(B) 4 min after exercise test (ms)	521±47	489±44	471±46	<0.001
Family history				
LQTS	1,094 (64.1)	889 (68.8)	188 (60.1)	0.002
SCD	104 (6.1)	149 (11.5)	41 (13.1)	<0.001
Schwartz score	3.5±1.9	4.3±2.1	3.5±2.2	<0.001

Continuous variables are presented as the mean±SD or median [interquartile range]. Categorical variables are presented as n (%). TdP, torsade de pointes. Other abbreviations as in Table 1.

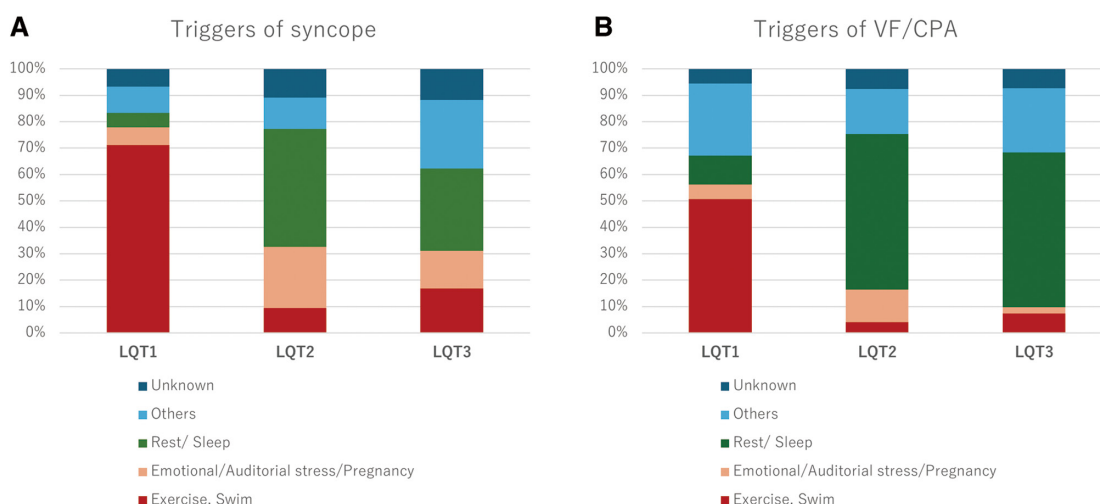


Figure 5. Triggers of the first cardiac event occurring at age ≤70 years in patients with LQT1, LQT2, and LQT3: (A) syncope and (B) ventricular fibrillation (VF) or cardiopulmonary arrest (CPA).

(44%) often during sleep or when waking up in the morning, similar to findings in the LQT3 group. These results mirror the triggers for VF/CPA (Figure 5B): almost half the VF/CPA events in the LQT1 group occurred during exercise, whereas more than half the events in the LQT2 and LQT3

groups occurred during rest or sleep.

Variants in LQT1–3

In total, 243 variants were identified in 948 LQT1 probands (Supplementary Table 2), including 719 (75.8%) patients

with missense variants, 106 (11.2%) with splicing errors, 49 (5.2%) with frameshifts, 34 (3.6%) with nonsense variants, 30 (3.2%) with deletions, 4 with insertions/deletions, 2 with duplications, and 4 with copy number variants. Among 737 LQT2 probands, 417 variants were identified (Supplementary Table 3), including missense variants in 425 (57.7%) patients, splicing errors in 29 (3.9%), frameshifts in 201 (27.3%), nonsense variants in 53 (7.2%), deletions in 20 (2.7%), insertions/deletions in 2, duplications in 5, and copy number variants in 1. There were 74 variants identified in 186 LQT3 probands (Supplementary Table 4), including 174 (93.6%) patients with missense variants, 9 (4.8%) with deletions, and 2 with duplications (1 unknown). None of the LQT3 patients had splicing errors, or nonsense and frameshift variants.

According to the Franklin ACMG classification, patients with P/LP variants were higher in the order of *KCNQ1* (95.3%), *KCNH2* (88.1%), and *SCN5A* (76.3%). Using ClinVar, there was still a high proportion of P or LP variants (67.6% in *KCNQ1*, 53.2% in *SCN5A*, but only 36.2% in *KCNH2*), but many variants were classified as conflicting with pathogenicity, as a variant of unknown significance (VUS), or were not provided in ClinVar (Supplementary Figure).

Discussion

Major Findings

This study enrolled 3,851 patients with LQTS, comprising 2,316 probands and 1,535 families, in Japan; as of January 2025, this was the largest LQTS cohort in any study, not only in Japan but also worldwide.^{16,17} As detailed in this registry, genetic testing was performed in 3,770 (98%) patients, with 1,710 LQT1, 1,293 LQT2, and 314 LQT3 patients and families identified in total. The number of LQT1 and LQT2 patients enrolled in this registry is also higher than in previous international LQTS studies. Most notably, this registry also identified some minor genotypes, such as *KCNE1*, *CACNA1C*, *KCNJ2* and *CALM1,2* genes, as well as detailed variant information for LQT1–3. Recently, comprehensive genetic testing for all LQTS-associated genes has become available as a routine diagnostic tool, and our data including all genotyped LQTS patients will be helpful for clinical practice.

Genetic Background in LQTS

In LQTS, the causative gene has been identified in 70–80% of patients with a clinical diagnosis of congenital LQTS. Because this registry enrolled patients who had already been diagnosed with congenital LQTS, it is impossible to determine directly how many genotype-positive cases there were among patients clinically diagnosed (or suspected) with LQTS. However, in total, 2,111 of 2,409 (87.6%) patients with clinically confirmed LQTS (QTc $\geq$ 500 ms and/or Schwartz score $\geq$ 3.5) were genotype positive (Figure 1A). Moreover, among the genotype-positive patients (n=3,550), most affected genes were identified as either *KCNQ1*, *KCNH2*, or *SCN5A* (total n=3,317; 93.4%).

In addition to these 3 genes, *CALM1–3* encoding calmodulin, a Ca²⁺-binding protein, is also an important causative gene for LQTS.^{12,13} The Japanese Circulation Society/JCC/JSPCCS 2024 guideline on genetic testing and counseling strongly recommends genetic testing in LQTS for genes that are certain to cause LQTS (i.e., *KCNQ1*, *KCNH2*, *SCN5A* and *CALM1–3*).³ In our LQTS registry,

there were 13 patients with *CALM*-LQTS (3 *CALM1* and 10 *CALM2*). All 13 patients were probands and their QTc was significantly longer than for the other genotypes, except for *CACNA1C* (Figure 3); in addition, most individuals had experienced a lethal cardiac event at age <20 years (Figure 4B). The severe prognosis of *CALM*-LQTS patients is similar to that reported in the international registry data for calmodulin mutations,¹⁸ which cause several arrhythmic disorders in addition to LQTS, such as catecholaminergic polymorphic ventricular tachycardia (CPVT) and idiopathic VF, that may be called “calmodulinopathies.” Fukuyama et al. have already reported some calmodulinopathies in Japanese children (n=10), including 5 with LQTS, 3 with CPVT, and 2 with overlapping phenotypes.¹⁹

TRDN variants are a possible cause in homozygous patients with recessive LQTS, but there were no *TRDN* homozygous variants in our registry. In addition, *KCNQ1* and *KCNE1* are thought to cause Jervell and Lange-Nielsen syndrome, and *KCNE1* and *KCNE2* are associated with acquired LQTS.^{3,13} In our LQTS registry, there were 8 patients with *KCNQ1* homozygous variants and 4 with *KCNE1* heterozygous variants. The D85N variant of *KCNE1* is a susceptibility variant that affects QT prolongation,²⁰ but is not included in the genotypes in our registry because it is essentially a benign variant (Japanese minor allele frequency=0.01 on the 8.3KJPN Japanese whole-genome reference panel). These susceptibility gene variants are also an issue for future studies.

Other LQTS or LQTS-related diseases include TS and non-TS (LQT8) or ATS (LQT7). Several investigators have already reported the genetic and clinical aspects of ATS in Japan,^{21–23} and in an international cohort.²⁴ Moreover, Fukuyama et al. reported on LQT8 in Japan.^{25,26} In our registry, there were 5 patients with TS, 53 with non-TS LQT8, 100 with ATS, and 47 with double or compound heterozygous variants.

Furthermore, a phenotypic overlap of LQT3 with Brugada syndrome is observed in some carriers of variants in the Na channel gene *SCN5A*.²⁷ In our LQTS registry, there were 16 patients (median age 30 years, 75% male) with phenotypic overlap of LQTS with Brugada syndrome. These patients had a variant in the *SCN5A* (n=12), *KCNQ1* (n=2), *KCNH2* (n=1) and *CACNA1C* (n=1) genes, but in most cases (n=10; 63%) the variant was c.5350G>A p.E1784K in *SCN5A*. Details of each genotyped LQTS and other phenotypes, such as calmodulinopathy, TS, non-TS LQT8, ATS, and overlap with Brugada syndrome, were not investigated in this study, but they will be identified in future studies.

Genotype-Phenotype Association in LQT1–3

Since 1985, when Schwartz²⁸ and Moss et al.² first reported more than 100 patients with LQTS, many LQTS registry studies have revealed considerable information about the genotype–phenotype association in LQTS. Most of these studies have focused on LQT1–3, investigating triggers of cardiac events,^{5,17} age and sex differences in arrhythmic risk,^{6,29,30} genotype and variant location-specific risk stratification,^{8,9,31} and genotype-specific pharmacological therapy.^{32–34}

The results of our LQTS registry are similar to those of studies in previous international cohorts. The primary difference is that the present study is not an international study, but a domestic study in Japan (albeit a multicenter

registry in Japan), so most of the participants were Japanese. Thus, the frequency of gene variants reflects race-specific differences. For example, the *KCNQ1* A344A splicing variant is the most commonly found variant in LQT1 in the Japanese population.³⁵ Furthermore, in terms of the triggers of cardiac events (e.g., syncope or VF/CPA), rest or sleep (including waking up in the morning) was the most common in LQT2 patients (Figure 5A), and was found more often than emotional or auditory stress, as previously reported. This was particularly true for VF/CPA, with 59% of events occurring during rest or sleep, and was similar in the case of LQT3 (Figure 5B).

Previous studies on LQTS enabled early diagnosis, risk stratification, and appropriate medical therapies for most LQTS patients and families. The prognosis for patients with LQTS has improved significantly since the first reports.³⁶ However, some severe cases of LQTS, particularly in women with the LQT2 genotype, are refractory to β -blocker treatment, and alternative medication or non-pharmacological therapies other than β -blockers have not been fully elucidated. To begin with, the rate of β -blocker adherence is lower among Japanese patients with LQTS than in the Europe.³⁷ It is still unclear to what extent the diagnosis and treatment of LQTS based on current practical guidelines actually contribute to improving a patient's prognosis and preventing SCD. It is therefore essential to follow the prognosis of patients enrolled in our registry.

Study Limitations

This study has some limitations. First, this study was a retrospective study, and has some selection bias because many of the patients with LQTS were enrolled from institutions that treated many cardiovascular diseases and arrhythmias in children or adults, but not from general hospitals or clinics. Therefore, there was a high rate of genetic testing and there may be more severe cases included than for actual LQTS.

Second, this study has only provided clinical and genetic data at diagnosis, and has not included follow-up results after diagnosis. The quality of life, transitional care, and long-term prognosis of patients with congenital LQTS after diagnosis are not well understood. The effects of exercise restriction and allowing competitive sports for genotypes other than LQT1 are also not known.³⁸ To clarify these unresolved issues in LQTS, further investigations are needed into follow-up results of all patients after LQTS diagnosis.

Conclusions

The phenotype of patients with LQTS differs according to genotype, as well as age, sex, and probands/families, thus comprehensive genetic testing, including for non-major LQTS genes, is important for diagnosis and risk stratification of LQTS. The evidence from this registry study is expected to play an important role in the future treatment of LQTS and other inherited arrhythmias.

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Disclosures

W.S. is a member of *Circulation Journal's* Editorial Team. The remaining authors have no conflicts of interest to declare.

IRB Information

This study was approved by the Ethics Committee of the National Cerebral and Cardiovascular Center (Reference no. R22006-5).

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Supplementary Files

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