Clinical characteristics and genetic background of congenital long QT syndrome diagnosed in fetal, neonatal and infantile life. A nation-wide questionnaire survey in Japan

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Abstract

Background: Data on the clinical presentation and genotype-phenotype correlation of patients with congenital long QT syndrome (LQTS) diagnosed at perinatal through infantile period are limited. A nation-wide survey was conducted to characterize how LQTS detected during those periods is different from that in childhood or adolescence.

Methods and Results: Using questionnaires, 58 cases were registered from 33 institutions. Diagnosis (or suspicion) of LQTS was made during fetal life (n=18), neonatal period (n=31, 18 of them at 0 to 2 days of life) and beyond the neonatal period (n=9). Clinical presentation of LQTS included sinus bradycardia (n=37), ventricular tachycardia/torsades de pointes (VT/TdP) (n=27), atrioventricular block (AVB) (n=23), family history of LQTS (n=21), sudden cardiac death (SCD)/aborted cardiac arrest (ACA) (n=14), convulsion (n=5), syncope (n=5) and others. Genetic testing was available in 41 (71%) cases, and the genotype was confirmed in 29 (71%) cases, consisting of LQT1 (n=11), LQT2 (n=11), LQT3 (n=6), and LQT8 (n=1). VT/TdP and AVB were almost exclusively observed in patients with LQT2, LQT3, and LQT8, as well as in those with no known mutation. In LQT1 patients, clues to diagnosis were mostly sinus bradycardia or family history of LQTS. SCD/ACA (n=14) was noted in four cases with no known mutations as well as in four genotyped cases, although the remaining six did not undergo genotyping. Their subsequent clinical course after ACA was favorable with administration of beta-blockers and mexiletine, and with PMI/ICD.

Conclusion: Patients with LQTS who showed life-threatening arrhythmias at perinatal periods were mostly those with LQT2, LQT3 or no known mutations. Independent of the genotype, aggressive intervention resulted in effective suppression of arrhythmias with only 7 deaths recorded.

Key words: arrhythmia, long QT syndrome, genes, death (sudden)
Introduction

Congenital long QT syndrome (LQTS) is an inherited disorder characterized by polymorphic ventricular tachycardia (VT), or torsades de pointes (TdP), syncope and sudden cardiac death.\(^1\) LQTS is often diagnosed in children from school age to young adulthood,\(^2\) and sometimes during fetal, neonatal and infantile life.\(^3\)\(^-\)\(^5\) Previous case reports suggest that the latter cases are at higher risk of development of life-threatening arrhythmias necessitating emergency treatment\(^3\)\(^-\)\(^5\) and show higher mortality rate than the former age groups.\(^3\)\(^,\)\(^5\)\(^-\)\(^11\) For example, recent progress in molecular biology has clarified that LQTS partly contributes to sudden infant death syndrome (SIDS).\(^12\)\(^,\)\(^13\) Unfortunately, prenatal diagnosis of LQTS has been extremely difficult to confirm except for a limited number of cases for which prenatal gene screening\(^14\) or fetal magnetocardiography (fMCG)\(^15\)\(^-\)\(^17\) was applied.

Thus, the clinical presentation, the genotype-phenotype correlation and the outcome of patients with fetal, neonatal or infantile presentation of LQTS remain to be elucidated. The purposes of this study were first, to report the findings of a nationwide survey conducted to define the clinical characteristics and the genotype-phenotype correlation, and second, to report the outcome of patients with LQTS diagnosed before birth and in the first year of life.

Methods

Population

The population included in the study was fetuses, neonates and infants (<1 year of age) diagnosed with LQTS based on ECG findings including prolonged QTc >0.46 sec (using Bazett’s formula), with or without VT/TdP, who had no structural heart disease, family history of LQTS, or had undergone genetic testing. Those with normal QTc duration and no
gene mutation known to cause LQTS were excluded. Patient data were collected using questionnaire. The form was sent to those councilors of the Japanese Society of Pediatric Cardiology and Cardiac Surgery who responded to a preliminary survey that they had one or more cases of LQTS diagnosed during fetal, neonatal and infantile life. The items obtained from the responders are presented in Table 1.

The study protocol was approved by the Ethics Committee of the University Hospital of Tsukuba, and informed consent was obtained from each patient, or parents if the patient was under 15 years of age, by a coordinator in charge in each institution before the patient’s data were registered.

**Genetic analysis and genotype-phenotype correlation**

Genetic analyses were performed in four established laboratories in Japan. DNA was isolated from blood samples in each patient. Screening for mutations of at least three major genes causing LQTS (*KCNQ1, KCNH2, SCN5A*) was performed using polymerase chain reaction (PCR)/single-strand conformation polymorphism (SSCP) or denatured high-performance liquid chromatography analysis (dHPLC). For aberrant PCR products, DNA sequencing was conducted with a DNA sequencer (ABI 3700 and ABI 3130xl, Applied Biosystems, Foster City, CA). For those subjects in whom genotype was confirmed and those who underwent genetic analysis but found to have no mutation, genotype-phenotype correlations (or mutation negative- phenotype correlations) with the aforementioned items (Table 1) were investigated.

**Statistical analysis**

All statistical calculations were conducted using the R software. Quantitative variables (HR and QTc) are presented as mean±standard deviation (SD), and categorized variables (presence of FH, sinus bradycardia, VT/TdP and AVB) as proportions (percentages).
One-way ANOVA was applied for comparisons of continuous variables, followed by pairwise comparisons with Bonferroni adjustment of p values between four groups (LQT1, LQT2, LQT3 and mutation-negative groups). The equality of proportions for categorical variables among the four groups was examined by the chi-square test (global test). When there was a significant difference in proportions, we performed pairwise comparisons between pairs of proportions with correction for multiple testing using Bonferroni inequality of p-values. Tests were two-sided, and a p value less than 0.05 was considered significant.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Population

A total of 58 cases (all Japanese, males 30, females 28) were registered from 33 institutions. Forty-one were born during the last 10 years (between 1999 and 2008), 14 between 1989 and 1998, 1 in 1986, and 2 in 1984. LQTS was diagnosed or suspected during fetal life at 18-40 weeks of gestation in 18 individuals, during neonatal life at 0-28 days in 31 and in infancy (<1 year) at 1-9 months in 9.

Clinical features

For 18 fetuses with LQTS, clinical presentation (or clues to diagnosis or suspicion of LQTS) included bradycardia (15 cases), AVB (8 cases), VT/TdP (7 cases), and family history of LQTS (6 cases), including one family with a history of a previous intrauterine death (items overlapped in some cases). Two fetuses were confirmed to be LQTS by fetal magnetocardiography (fMCG), with QTc values of 570 and 680 on fMCG, and 590 and 700
on ECG soon after birth, respectively (these two cases have been reported previously). No fetal death was noted in this group.

For 31 neonates with LQTS, the most frequent feature was sinus bradycardia (17 cases) followed by VT/TdP (15 cases), positive family history of LQTS (15 cases), including one with previous intrauterine death and one with infantile death, AVB (10 cases), syncope (5 cases), convulsion (5 cases) and others (items overlapped in some cases). Among the 31 neonatal cases, 18 (70%) were diagnosed within 2 days of life, 8 of them had some significant fetal presentation (4 bradycardia or bradyarrhythmias, 4 tachyarrhythmias and 1 hydrops), retrospectively.

As described above, the number of patients with LQTS diagnosed during infancy beyond the neonatal period was only 9. The clinical presentation of these patients included sinus bradycardia (5 cases), SCD/ACA (5 cases), AVB (5 cases), VT/TdP (5 cases) and other miscellaneous abnormalities.

The ECG on diagnosis, or immediately after birth for fetal cases, showed that the HR and QTc interval (corrected using Bazett’s formula) ranged from 50 to 187 (102±28) bpm, and from 360 to 774 (563±70) msec, respectively.

**Genotype-phenotype correlation**

Among 41 patients who underwent genetic testing, mutations were identified in 29 (71%) cases; including *KCNQ1* gene mutations (LQT1) in 11, *KCNH2* mutations (LQT2) in 11, *SCN5A* mutations (LQT3) in 6 and *CACNA1C* (LQT8) in 1. Twelve patients also underwent genotyping but no mutation was found. Table 2 lists the demographic and clinical features of these subjects (Ref. 16, 17, and 23 reported the same Cases 2, 12 and 27 in Table 2) and of those with no known mutations.
The remaining 17 subjects (6 fetuses, 8 neonates, 3 infants) did not undergo genetic analysis due to lack of such analysis at that time, death soon after birth or refusal by parents. Five of them experienced SCD/ACA (Table 3), including one-day-old neonate who showed AVB and died at 57 days of age in 1984. This case was later assumed to be LQT8 based on characteristic phenotypes such as syndactyly. AVB and VT/TdP were observed in 7 and 5 cases, respectively, in this group.

Although HR and QTc values were not different among LQT1, LQT2, LQT3 and mutation-negative groups, the incidence of VT/TdP was higher in LQT2 and LQT3 compared with LQT1 (Table 4). The incidence of AVB tended to be higher in LQT3 compared with LQT1 although statistically insignificant. On the other hand, the presence of family history of LQTS was more frequent in LQT1 than the mutation-negative group. The incidence of sinus bradycardia was comparable between the four groups (Table 4).

Table 3 lists cases with SCD/ACA; only 4 genetically-confirmed cases were included, and 4 were mutation-negative, although the remaining 6 cases did not undergo genotyping. These individuals showed bradycardia (97 ± 31 bpm; 10/14 showed HR less than 110 bpm) and markedly prolonged QTc (617 ± 81 msec).

**Treatment**

With regard to the treatment of fetal VT/TdP, antiarrhythmic agents were administered transplacentally in 4 of 18 fetal cases (propranolol in 3 cases, lidocaine in 1, mexiletine in 1, flecainide in 1, and magnesium in 1), using the method described in detail in our previous report.17 None of the 4 cases was genetically-confirmed prenatally. When two or three of the following findings; sinus bradycardia, VT, and AVB, were observed in a structurally normal heart, LQTS was strongly suggested, and beta-blockers, sodium channel blockers (lidocaine, mexiletine) and magnesium (Mg) were selected as typical antiarrhythmic agents, instead of
amiodarone or sotalol, which may prolong the QT interval. These drugs were used in combination until VT/TdP was controlled, and proved effective in all 4 cases. However, preterm delivery was conducted in 2 cases both at 33 weeks of gestation due to recurrent VT/TdP and depression of fetal physical activity in one, and to fetal hydrops and distress in the other. In the remaining 14 cases, pharmacotherapy was initiated following confirmation of the type of arrhythmias after birth. However, no fetal death was noted.

For 15 neonatal cases who presented with VT/TdP (including those who did not undergo genotyping), acute pharmacotherapy consisted of two or more of the following drugs; beta-blockers, mexiletine, lidocaine, Mg, phenytoin, and others, except for two cases who were treated with phenytoin alone and one with mexiletine alone. Most of these cases were judged to respond the combination therapy. In 5 neonates in whom LQT3 was strongly suggested based on a typical ECG finding called late appearing T wave, mexiletine was first administered but proved insufficient, and beta-blockers were also added in all 5.

For those with LQTS presenting in infancy, 6 cases received acute pharmacotherapy (two or all of propranolol, mexiletine and Mg). No additional agent was administered. Thus, in all age groups, the acute therapy for VT/TdP consisted of a single drug to which one or more drugs was then added until the arrhythmia was controlled, independent of the genotype. Actually, the genotype was not identified during the acute phase in most cases. Furthermore, genotyping was not conducted in those 17 cases who presented before 1999.

Maintenance therapy consisted mainly of beta-blockers (or no therapy) for LQT1 and mostly of mexiletine/beta-blockers for LQT2 and LQT3 (Table 2). Beta-blockers were added in 8 LQT2 cases after confirmation of the genotype. In all 6 LQT3 cases, mexiletine was maintained (combined with beta-blockers) from acute through chronic phase after determination of the genotype.
Nine patients underwent pacemaker implantation (PMI), 5 with ventricular pacing mode (VVI) and 1 with atrial pacing mode (AAI), from age 1-day to 8 years due to severe bradycardia caused by AVB, inducing VT/TdP. In 6 cases, VT was completely suppressed after PMI. Only two patients had implantable cardioverter defibrillator (ICD) at ages 4 (LQT3) and 25 months (mutation negative), respectively, due to recurrent VT/TdP with satisfactory results.

**Outcome**

During the follow up period of 8 days to 23.5 years (median, 4.25 years), 7 SCD and 7 ACA were registered (age at SCD or ACA, range, 8 days to 10 years, median 10.5 months); 6 did not have genetic testing, while 4 showed no mutation. Only 4 of them were genetically-confirmed (Table 3). One case was later suspected to be LQT8 based on the phenotype including syndactyly. Among the 14 SCD/ACA cases, 12 had been under pharmacotherapy, 5 with both beta-blockers and sodium channel blockers, 2 had had PM or ICD. Four cases developed significant neurological deficits after cardiorespiratory resuscitation.

**Discussion**

The noteworthy finding of the present study was that 49 out of 58 cases (84%) were diagnosed at fetal or neonatal period, although this survey covered the entire infantile period. Remarkably, two-thirds of the neonatal cases were diagnosed within 2 days of life; this period should be recognized as the most vulnerable period. The number of cases diagnosed after the neonatal period was only 9. Considering that the average age at appearance of
symptoms in LQT2 and LQT3 is after school age, we speculate a considerable number of patients are considered to go through infancy uneventfully.

Garson et al. reported 287 patients with LQTS aged less than 21 years; their mean (± SD) age at presentation was 6.8 ± 5.6; and 9% presented with cardiac arrest, 26% with syncope, and 10% with seizures. Although 20% of their subjects were less than 1 month of age, they did not investigate that age group separately. In the present study, confined to the subjects aged less than 1, clinical features were largely different; that is, the incidence of malignant arrhythmias and bradycardia was high whereas that of syncope and seizures was low.

As for genotype-phenotype correlations, Zareba and colleagues investigated child and adult LQTS and reported that LQT1 was associated with the highest risk of first cardiac event among the three most typical genotypes (LQT1-3). By the age of 15, syncope, ACA or SCD was noted in 53% of their patients with LQT1 compared with 29% of LQT2 and 6% of LQT3, although cardiac events occurred in LQT3 were more lethal compared with those in LQT1 or LQT2. In contrast, the present study demonstrated that patients complicated by VT/TdP or AVB were almost exclusively those with LQT2 or LQT3 (and LQT8). LQT3 patients in the present study showed the most severe clinical course similar to those in later-presenting LQT3. Further, patients with LQT1 mostly showed uneventful clinical course apart from sinus bradycardia, and the reason for diagnosis was bradycardia or prolonged QT interval itself on ECG identified on family screening. Another remarkable feature in our young age group was that a considerable number of patients with malignant arrhythmias were mutation-negative as far as LQT1-3 genes were typically examined. This suggests that this age group includes individuals with rare known mutations that were not examined in the present study as well as those with currently unidentifiable mutations.
Notably, many patients in the present study showed sinus bradycardia, although HR was not significantly different among LQT1, LQT2 and LQT3. Sinus bradycardia has been considered a significant presentation of LQTS, especially in fetal-neonatal period, and often a clue to the diagnosis of LQTS. The present study verified that sinus bradycardia is common among all types of LQTS in this age group, especially in fetal-neonatal periods.

Another remarkable feature of the present study was the high incidence of AVB (55% in LQT2, 83% in LQT3), compared with 5% or less in child or adult LQTS. It is intriguing that mutations in our LQT2 patients were almost exclusively located at the pore region of HERG gene (amino acid residues 550 through 650), as mutations in that region are related to high risk for cardiac events. Lupoglazoff et al. reported similar phenotype tendency for neonates with LQTS; that AVB is associated with LQT2 and sinus bradycardia with LQT1. Most of their LQT2 cases also had a mutation in the pore region of the HERG gene, although this was not mentioned in their report. AVB in neonates with a SCN5A mutation have also been reported in single case reports. Considering the implication of sodium channel dysfunction in many other hereditary arrhythmias, the association between LQT3 and AVB is an important finding.

SCD/ACA was seen in 14 cases (24% of all subjects) (7 SCD, 7 ACA), even though 12 of them were under treatment with beta-blockers, mexiletine, or both when the events occurred (Table 3). The direct trigger of SCD/ACA remains to be determined, but the mean QTc interval of those patients was apparently prolonged (617 ± 81 msec), and patients with no gene test (6 cases) were included as well, possibly making the selection of drugs inappropriate, such that only beta-blockers were given to a possible LQT3 patient. Furthermore, 4 other cases had no known mutation on genotyping. It is possible that the cryptogenic mutations unidentifiable in the current era could be resistant to many drugs.
**Therapy**

Since individuals with LQT3 showed serious clinical disorders, they were treated aggressively with multiple antiarrhythmic drugs including mexiletine, beta-blockers, lidocaine, magnesium and PM/ICD, and only one definite LQT3 patient showed ACA. For LQT2, malignant arrhythmias were a little more controllable with the same kind of pharmacotherapy than for LQT3. Again, only one definite LQT2 patient showed ACA. Thus, no death was ultimately observed in LQT2 and LQT3. This favorable clinical course might be derived from implicit strategy prevalent among pediatric cardiologists in our country that early-onset LQTS should be treated with the combination of beta-blockers and mexiletine at the start of therapy because the genotype is not easy to confirm immediately. In other words, treatment strategies in Japan have been driven more by the clinical symptoms than by the genotype. Nevertheless, the response to the multiple antiarrhythmic pharmacotherapy and the long-term outcome presented in this study are encouraging.

It should be noted that the number of patients who underwent PMI/ICD was small in the present cohort compared with other reports.\(^5,6\) It is known that TdP tends to follow prolonged RR interval in LQT2 and LQT3, where conduction disturbances or sinus node dysfunction are common features.\(^25,26\) Thus, PMI/ICD should be considered without delay even when the patient who shows drug-resistant, bradycardia-induced VT/TdP is a small baby.\(^27\)

**Study limitations**

Because of the retrospective nature of the present survey using questionnaire, the extent of clinical data that could be obtained varied among cases. Although approximate tendency in genotype-phenotype correlations for infants with LQT1, LQT2 and LQT3 was determined, most cases registered in the present study did not undergo genetic analysis for genes other
than the three typical types. One case with LQT8 was registered in addition to LQT1-3, but no cases with the other types (LQT4-7) were found. Also, decision of treatment strategy depended on the in-charge physician in each case without the use of a uniform protocol for VT/TdP and/or AVB, making it difficult to evaluate the effects of pharmacotherapy and to determine the event rate beyond infancy for each genotype other than the last outcome, alive or death. Therefore, we should wait for accumulation of more cases for establishment of the genotype-specific strategy.

Conclusion

Our nation-wide survey indicates that early-onset malignant LQTS are mostly those with LQT2 and LQT3 among the three major genes, and the most vulnerable age to life-threatening arrhythmias is from 0 to 2 days of age. A combination pharmacotherapy with a beta-blocker and mexiletine sometimes combined with Mg and PMI/ICD is recommended as the initial therapy. Prospective study of a large number of patients with LQTS diagnosed from fetal to infantile periods and further application of gene testing are needed to establish the most appropriate treatment strategies for those patients.

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Disclosures

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Table 1 Questionnaire items

1. Patient: serial number in each institution, initials, birth year and month, gender
2. Age at diagnosis or suspicion (including gestational age for a fetus)
3. Clinical symptoms: fetal arrhythmias, fetal heart failure, syncope, convulsion, heart failure, aborted cardiac arrest, others
4. ECG findings and arrhythmias (HR, QTc on ECG at presentation, sinus bradycardia, VT/TdP, AVB, other arrhythmias)
5. Family history of LQTS or other arrhythmias or sudden cardiac death (which member, and their outcome?)
6. Genotype
7. Treatment (acute therapy and maintenance therapy)
   pharmacotherapy (which drug, dose, age at initiation, and duration)
   device therapy (PMI, ICD) and age at application
8. Duration of follow-up
9. Outcome (alive or death, and neurological sequels of cardiac arrest)
## Table 2. Clinicogenetic details.

<table>
<thead>
<tr>
<th>Case</th>
<th>LQT type</th>
<th>Mutation</th>
<th>Age at diagnosis /gender</th>
<th>Clinical presentation</th>
<th>FH</th>
<th>HR (bpm)</th>
<th>QTc (msec)</th>
<th>Sinus brady</th>
<th>VT/ TdP</th>
<th>AVB</th>
<th>Acute therapy</th>
<th>Maintenance therapy</th>
<th>PM /ICD</th>
<th>Follow-up</th>
<th>outcome</th>
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<td>561</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<td>+</td>
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<td>4y5m</td>
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<tr>
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<td>-</td>
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<td>-</td>
<td>60</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>Lido, Mg, BB, Mexil, Pacing</td>
<td>BB, Mexil</td>
<td>PM 3y</td>
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</tr>
<tr>
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<td>Gly628Ser</td>
<td>Fetus, M</td>
<td>VT/TdP, AVB</td>
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<td>50</td>
<td>631</td>
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<td>Lido, Mg, BB, Mexil, Pacing</td>
<td>BB, Mexil</td>
<td>PM 3y</td>
<td>68m</td>
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<td>del(7)(q32qter)</td>
<td>Fetus, F</td>
<td>TdP</td>
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<td>90</td>
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<td>convulsion VT</td>
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<td>78</td>
<td>570</td>
<td>+</td>
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<td>+</td>
<td>Lido, Mg, BB, Mexil, Pacing</td>
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<td>Lido, Mg, BB, Mexil, Pacing</td>
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<td>+</td>
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<td>612</td>
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<td>98</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>Asn633Ser</td>
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<td>AVB</td>
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<td>+</td>
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<td>15y4m</td>
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<td>21</td>
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<td>+</td>
<td>+</td>
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<td>convulsion, VT/TdP, AVB</td>
<td>+</td>
<td>115</td>
<td>670</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>BB</td>
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<td>11y4m</td>
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<td>TdP, AVB</td>
<td>+</td>
<td>115</td>
<td>550</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>BB, Mexil</td>
<td>11y4m</td>
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<td>Syncope, TdP</td>
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<td>598</td>
<td>+</td>
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<td>-</td>
<td>BB</td>
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<td>AVB</td>
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<td>ACA</td>
<td>-</td>
<td>111</td>
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<td>550</td>
<td>+</td>
<td>-</td>
<td>BB</td>
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<td>TdP</td>
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<td>111</td>
<td>550</td>
<td>+</td>
<td>-</td>
<td>BB</td>
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<td>4m</td>
<td>alive</td>
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<td>Ala561Val</td>
<td>Neonate, M</td>
<td>TdP</td>
<td>-</td>
<td>111</td>
<td>550</td>
<td>+</td>
<td>-</td>
<td>BB</td>
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<td>4m</td>
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<td>TdP</td>
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<td>111</td>
<td>550</td>
<td>+</td>
<td>-</td>
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<td>4m</td>
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<td>+</td>
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<td>+</td>
<td>-</td>
<td>BB</td>
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<td>Neonate, M</td>
<td>TdP</td>
<td>-</td>
<td>111</td>
<td>550</td>
<td>+</td>
<td>-</td>
<td>BB</td>
<td>-</td>
<td>BB</td>
<td>4m</td>
<td>alive</td>
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</tr>
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<td>39</td>
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<td>Ala561Val</td>
<td>Neonate, M</td>
<td>TdP</td>
<td>-</td>
<td>111</td>
<td>550</td>
<td>+</td>
<td>-</td>
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<td>Ala561Val</td>
<td>Neonate, M</td>
<td>TdP</td>
<td>-</td>
<td>111</td>
<td>550</td>
<td>+</td>
<td>-</td>
<td>BB</td>
<td>-</td>
<td>BB</td>
<td>4m</td>
<td>alive</td>
<td></td>
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</tbody>
</table>
ACA, aborted cardiac arrest; AVB, atrioventricular block; BB, β-blocker; brady, bradycardia; FH, family history; G, gestational age; HR, heart rate; ICD, implantable cardioverter defibrillator; Lido, lidocaine; Mexil, mexiletine; Mg, magnesium; Nifed, Nifedipine; PAC, premature atrial contraction; Pheny, phenytoin; PM, pacemaker; SCD, sudden cardiac death; TdP, torsade de pointes; VT, ventricular tachycardia. Cases 2, 12, and 27 were reported in Ref. 16, 17, and 23, respectively.
Table 3. Clinicogenetic details of cases with sudden cardiac death or aborted cardiac arrest.

<table>
<thead>
<tr>
<th>Case</th>
<th>Case # in Table 2</th>
<th>Genotyping</th>
<th>Age at diagnosis</th>
<th>Age at SCD or ACA</th>
<th>HR (bpm)</th>
<th>QTc (msec)</th>
<th>Maintenance therapy until SCD/ACA</th>
<th>Acute therapy for SCD/ACA event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>LQT3 (Ala1186Thr)</td>
<td>Fetus (28w)</td>
<td>1y10m (aborted)</td>
<td>78</td>
<td>679</td>
<td>Mexil</td>
<td>Mexil, DC</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>No gene test</td>
<td>Fetus (31w)</td>
<td>8d</td>
<td>60</td>
<td>570</td>
<td>-</td>
<td>Lido, Isp, Pacing, DC</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>No gene test</td>
<td>Fetus (36w)</td>
<td>57d</td>
<td>90</td>
<td>600</td>
<td>BB, Mexil</td>
<td>DC</td>
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<tr>
<td>4</td>
<td>29</td>
<td>LQT8 (Gly406Arg)</td>
<td>Neonate (0d)</td>
<td>1y5m (aborted)</td>
<td>141</td>
<td>581</td>
<td>BB, Nifed</td>
<td>Mexil, Mg</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>Negative result</td>
<td>Neonate (0d)</td>
<td>4y</td>
<td>100</td>
<td>647</td>
<td>Mexil</td>
<td>DC</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>Negative result</td>
<td>Neonate (0d)</td>
<td>&lt;1m (aborted)</td>
<td>111</td>
<td>638</td>
<td>Mexil</td>
<td>Lido, Mexil, BB, Pheny</td>
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<tr>
<td>7</td>
<td>17</td>
<td>LQT2 (Ala561Val)</td>
<td>Neonate (1d)</td>
<td>10y (aborted)</td>
<td>86</td>
<td>520</td>
<td>BB, Mexil</td>
<td>Lido, Mexil, Mg, DC</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>No gene test (possible LQT8)*</td>
<td>Neonate (1d)</td>
<td>57d</td>
<td>70</td>
<td>640</td>
<td>BB</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>No gene test</td>
<td>Neonate (4d)</td>
<td>5y4m</td>
<td>60</td>
<td>590</td>
<td>- (refused)</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>No gene test</td>
<td>Infant (1m)</td>
<td>2y</td>
<td>130</td>
<td>640</td>
<td>BB, Mexil</td>
<td>Lido, Mg</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>No gene test</td>
<td>Infant (1m)</td>
<td>1y10m</td>
<td>60</td>
<td>740</td>
<td>BB, Mexil, PM</td>
<td>Lido, Mexil, BB, Mg, Pacing</td>
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<tr>
<td>12</td>
<td>10</td>
<td>LQT1 (Gly643Ser)</td>
<td>Infant (1m)</td>
<td>1m (aborted)</td>
<td>109</td>
<td>554</td>
<td>Mexil</td>
<td>Lido</td>
</tr>
<tr>
<td>13</td>
<td>39</td>
<td>Negative result</td>
<td>Infant (2m)</td>
<td>4m (aborted)</td>
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<td>470</td>
<td>BB, Mexil, ICD</td>
<td>(aborted by ICD)</td>
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<tr>
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<td>40</td>
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<td>2m (aborted)</td>
<td>100</td>
<td>774</td>
<td>Mexil</td>
<td>Mexil</td>
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</table>

ACA, aborted cardiac arrest; BB, beta-blocker; G, gestational age; HR, heart rate; ICD, implantable cardioverter defibrillator; Isp, isoproterenol; Lido, lidocaine; Mexil, mexiletine; Mg, magnesium; Nifed, nifedipine; Pheny, phenytoin; SCD, sudden cardiac death; *LQT8 was retrospectively possible because phenotype included syndactyly.

Median 10.5m 97±31 617±81
Table 4. Comparison of parameters among the groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LQT1 (n=11)</th>
<th>LQT2 (n=11)</th>
<th>LQT3 (n=6)</th>
<th>Negative (n=12)</th>
<th>global test</th>
<th>pairwise comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>109 ± 12 (n=10*)</td>
<td>95 ± 34</td>
<td>100 ± 31</td>
<td>104 ± 32</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>560 ± 24 (n=10*)</td>
<td>538 ± 74</td>
<td>592 ± 79</td>
<td>575 ± 86</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Proportion with family (%)</td>
<td>82</td>
<td>27</td>
<td>50</td>
<td>17</td>
<td>P&lt;0.05</td>
<td>LQT1–Negative, P&lt;0.05</td>
</tr>
<tr>
<td>Proportion with sinus bradycardia (%)</td>
<td>73</td>
<td>82</td>
<td>83</td>
<td>75</td>
<td>NS</td>
<td></td>
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<tr>
<td>Proportion with VT/TdP (%)</td>
<td>0</td>
<td>91</td>
<td>100</td>
<td>42</td>
<td>P&lt;0.05</td>
<td>LQT1–LQT2, P&lt;0.001</td>
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<tr>
<td>Proportion with AVB (%)</td>
<td>9</td>
<td>55</td>
<td>83</td>
<td>25</td>
<td>P&lt;0.05</td>
<td>(LQT1–LQT3, P=0.068)</td>
</tr>
</tbody>
</table>

Data are mean±SD or proportion (percentage).
One-way ANOVA was used to compare mean values of HR and QTc. Chi-square test was used to test differences in proportions of subjects with family history, sinus bradycardia, VT/TdP, and AVB among the four groups. Pairwise comparisons were conducted using Bonferroni adjustment and Bonferroni inequality of p-value.
HR, heart rate; NS, not significant; TdP, torsade de pointes; VT, ventricular tachycardia; Negative, gene mutation-negative group.
*: number of cases is 10 because data were not available in one case.
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