High Prevalence of the *SCN5A* E1784K Mutation in School Children With Long QT Syndrome Living on the Okinawa Islands

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Background: Genetic testing for long QT syndrome (LQTS) is now in clinical practice. We conducted molecular genetic analyses to definitively diagnose LQTS and to determine its subtypes for gene-specific treatment. We conducted a retrospective study to determine the characteristics of schoolchildren with LQTS living on the Okinawa Islands.

Methods and Results: The study population included children identified in a school-based electrocardiographic (ECG) screening program for cardiovascular diseases who were referred to Okinawa Children's Medical Center between 2007 and 2012; 23 children met the diagnostic criteria for LQTS. Of them, 17 were genotype-positive and 14 were found to harbor the *SCN5A* E1784K mutation exclusively among the LQTS genotype-positive children. The children were divided into genotype-positive and -negative groups. Clinical characteristics and ECG data were analyzed and compared. The median Schwartz score was 3. The median QT interval was 521 ms.

Conclusions: The major finding is that the prevalent subtype of LQTS in Okinawa is discordant with other cohorts living in other regions of Japan or overseas. We cannot exclude the possibility of the presence of a specific founder mutation in this geographically clustered population, particularly considering that the hospital is the only tertiary heart center for children in Okinawa. However, this uniquely high prevalence of the *SCN5A* E1784K mutation serves as a compelling justification to conduct a larger study. (*Circ J* 2014; **78**: 1974–1979)

Key Words: Arrhythmia; Long QT syndrome; Okinawa; *SCN5A*

The long QT syndrome (LQTS) is an inherited disorder of cardiac repolarization characterized by electrocardiographic (ECG) abnormalities, syncopal attacks, and risk of sudden death from ventricular tachyarrhythmias such as torsade de pointes.^{1,2} Mutations in genes encoding cardiac ion channels and membrane adaptor proteins cause this syndrome. There are 13 distinct LQTS-susceptibility genes and mutations in the 3 most common LQTS subtypes (*KCNQ1*-mediated LQT1, *KCNH2*-mediated LQT2, and *SCN5A*-mediated LQT3) account for approximately 80% of clinically confirmed cases of LQTS.^{3–5}

at a regional tertiary children's medical center on the Okinawa Islands of Japan, and describe the children's clinical characteristics and outcomes.

Methods

Patient Recruitment

Okinawa Children's Medical Center is the only tertiary hospital for children on the Okinawa Islands of Japan. It serves 1.4 million people and is a regional referral center that offers a comprehensive clinical practice of pediatric cardiology. A school-based ECG screening program for cardiovascular diseases aimed at schoolchildren in the 1st, 7th, and 10th grades is conducted all over Japan to identify heart problems. Schoolchildren are also checked for clinical and familial findings associated with LQTS, such as syncope, congenital deafness, and unexplained sudden cardiac death among family members. Children with positive findings are directed to referral

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Genotyping is used for adjunctive diagnosis as well as for gene-specific risk stratification and gene-specific therapy, particularly for LQTS.^{5–8} We report here the overrepresentation of the LQT3 mutation detected by genetic testing conducted

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Table 1. Demographic Data of Schoolchildren With LQTS on the Okinawa Islands

	Total	Gene positive	Gene negative	P value
n	23	17	6	
Age at 1st referral (years)	9.7±3.4	9.4±3.6	10.8±3.4	NS
Sex (M/F)	15/8	11/6	4/2	NS
Follow-up duration, months	37±23	43±23	23±14	NS

Data given as mean±SD. LQTS, long QT syndrome.

hospitals.^{9,10}

The present study population was retrospectively recruited from children who participated in the school-based ECG screening program and were referred to Okinawa Children's Medical Center between April 2007 and March 2013. The diagnosis of LQTS and screening for prolonged QT intervals was based on the judgment of the physician in each hospital that participated in the program in each area. For their final diagnosis, many physicians use a scoring system published in 1993.¹¹ Included were children who met the diagnostic criteria for LQTS ("Schwartz and Moss" score ≥3). This approach is similar to that described in a published study,⁵ although the most recent HRS/EHRA/APHRS expert consensus statement recommends that the score is ≥3.5.¹²

Retrospective review was approved by the Institutional Review Board. The patients' characteristics that were reviewed included sex, age at diagnosis, presence or absence of syncope, seizures, aborted cardiac arrest, family history, and 12-lead ECG. We assigned a cumulative LQTS diagnostic score, which is derived in part from the corrected QT interval (QTc), symptoms, and family history.¹¹ The children were divided into genotype-positive and -negative subgroups (G-pos and G-neg) according to the results of genetic analysis. Clinical characteristics and ECG data were analyzed and compared between the subgroups.

Clinical Testing

Each patient referred to the center for the evaluation of LQTS had their history taken and underwent a physical examination and a supine ECG. The QT interval was measured with a standard 12-lead ECG using lead V5. The ECG measurements were conducted by K. T. who was blinded to each subject's genetic status before making the measurements. QT interval was measured manually and defined as the time interval between QRS onset and the point at which the isoelectric baseline intersected a tangential line drawn at the maximal downslope of the positive T wave. QT interval measurements represented the mean of 3 consecutive beats in lead V5. The QT interval was corrected for rate using the Bazett formula ($QT/\sqrt{RR}$, interval measured in seconds). The LQTS score was determined according to the LQTS diagnostic criteria described earlier. Diagnostic criteria included the QTc interval (450ms), at least 1 symptomatic episode (bradycardia), or a family history of LQTS. A cumulative score ≥3 suggested an intermediate probability of LQTS.

Genetic Testing

Genetic testing was recommended according to the opinion of the chief physician who participated in the present study, and it was performed when the phenotype suggested LQTS according to the Schwartz score and clinical presentation or as detailed in the recent consensus report.¹² After written informed consent was given, genomic DNA was isolated from blood for

Figure 1. Distribution of genotypes among schoolchildren on the Okinawa Islands. LQT, long QT [syndrome].

direct sequencing of the complete *KCNQ1*, *KCNH2* and *SCN5A* genes in the National Cerebral and Cardiovascular Center, Osaka, Japan.

Statistical Analysis

The values of the continuous variables are presented as the mean±standard deviation or median and interquartile range. Categorical variables are represented by frequencies and percentages. Data were compared between the 2 groups using the following tests: t-test for normally distributed continuous variables, Mann-Whitney test for non-normally distributed data, and the chi-square or Fisher's exact test to compare the frequency distribution of categorical variables. Two-tailed $P<0.05$ was considered statistically significant. Analyses were performed using StatView J-5.0 PPC (SAS Institute Inc, Cary, NC, USA).

Results

Study Population

The study population comprised 23 children who met the criteria during the study period. Demographic data at referral are shown in [Table 1](#).

A total of 17 (74%) children were positive in genetic testing (G-pos subgroup; 6 females) and 6 were negative (G-neg subgroup, 2 females). Mean age at referral was 9.7 ± 3.4 years. Total follow-up period for the G-pos and G-neg groups was 43 ± 23 months and 23 ± 14 months, respectively. [Figure 1](#) shows the distribution of genotypes. The G-pos subgroup comprised LQT type 1 (LQT1, $n=2$), LQT type 2 (LQT2,

Table 2. ECG Data and Symptoms at Referral of Schoolchildren With LQTS on the Okinawa Islands

	Total	Gene positive	Gene negative	P value
ECG findings				
Average QTc (ms)	510±44	516±45	495±39	NS
% w/QTc >480 ms	15 (65%)	12 (71%)	3 (50%)	NS
% w/Schwartz score ≥4	8 (35%)	6 (35%)	2 (33%)	NS
Late-appearing T wave	15 (65%)	14 (82%)	1 (17%)	<0.01
Symptoms				
Syncope, n	1	0	1	NS
Bradycardia, n	1	1	0	NS
Epilepsy	1	0	1	NS
Family history				
Positive for LQTS, n	8 (35%)	7 (41%)	1 (17%)	NS

ECG, electrocardiographic; LQTS, long QT syndrome; QTc, corrected QT interval.

Table 3. Symptoms Newly Developed in Schoolchildren With LQTS on the Okinawa Islands During Follow-up Period and Treatment

	Total	Gene positive	Gene negative	P value
Symptoms				
Syncope/presyncope, n (%)	3 (13)	2 (12)	1 (17)	NS
Bradycardia, n	4	2	2	NS
Epilepsy, n	2	1	1	NS
Treatment				
Medications, n (%)	9 (39)	7 (41)	2 (33)	NS
Mex, n	8	7	1	
BB, n	3	3	0	
Antiepileptic, n	2	1	1	
Pacemaker, n	1	1	0	NS

BB, β -blocker; LQTS, long QT syndrome; Mex, mexiletine.

n=1), and LQT type 3 (LQT3, n=14). LQT3 was the most prevalent subtype (82%) in the G-pos subgroup. Further, all patients with LQT3 were found to share the same *SCN5A* c.5350G>A p.E1784K mutation within the sequence that encodes the transmembrane region of the *SCN5A* sodium ion channel.

ECG Data and Clinical Characteristics at Referral

Clinical and ECG data of the subgroups were analyzed, and the comparisons are shown in **Table 2**. The average QTc interval was 510 ms (516 ms vs. 495 ms, NS). The frequency of patients with QTc >480 ms and with a Schwarz and Moss score >4 was not significantly different between the groups.

Although the findings were somewhat subjective for QT morphology, late-appearing T wave was more frequent in the G-pos subgroup (82% vs. 17%, $P<0.01$). There was no Brugada syndrome (BrS)-type ECG in the cohort at referral. No provocative test with sodium-channel blockers was performed. Each child was asymptomatic at presentation except for 1 in the G-neg subgroup; 1 child in the G-pos subgroup exhibited sinus bradycardia, and 1 child in the G-neg subgroup was epileptic. All but 2 children were unrelated. To the best of our knowledge, all parents of the probands were descendants of the Okinawa Islands. There was no identifiable common relative for this cohort after pedigree construction. A familial history of LQT was identified in 35% of the children, and its presence trended toward an increase among the G-pos chil-

dren compared with the G-neg children (41% vs. 17%). Pacemakers were implanted in selected children based on screening of their first-degree relatives (unpublished data).

Clinical Outcome and Treatment During Follow-up

During the study period, no child died from sudden cardiac arrest, although syncope or presyncope occurred (n=2 vs. n=1, NS) (**Table 3**). One child in each subgroup developed epilepsy, which was diagnosed using electroencephalography. Treatment with an antiepileptic drug controlled their symptoms, and 1 child was the subject of another report.¹³ Two children experienced bradycardia on Holter monitoring, and 1 child in the G-pos group required pacemaker therapy for symptomatic sick sinus syndrome. The detailed clinical features of patients with newly developed symptoms during the follow-up period are presented in **Table 4**.

Treatment Nine (39%) of 23 patients received pharmacotherapy (7 and 2 in the G-pos and G-neg subgroups, respectively). The indication for pharmacotherapy in asymptomatic LQTS patients considered at high risk is QTc >500 ms, if the patient also agrees to keep taking the medication. One patient in each group received an antiepileptic agent. Mexiletine was administered to 7 patients in the G-pos subgroup (with β -blockers for 3) and 1 in the G-neg subgroup without β -blocker.

In the G-pos subgroup, QTc significantly decreased (from 553 ms to 491 ms; $P=0.02$) in the 7 patients receiving mexi-

Table 4. Characteristics of Newly Developed Symptoms in Schoolchildren With LQTS on the Okinawa Islands During Follow-up Period

Subtype	Age (years)	Sex	Gene test	QTc at referral (ms)	QTc at follow-up (ms)	Symptoms	Cardiovascular treatment
G-pos	13	F	KCNQ1	531	524	Resuscitation drowning	Mex, BB
G-pos	17	F	E1784K	591	502	Syncope VT	Mex, BB, pacemaker
G-pos	11	F	E1784K	565	423	Epilepsy	Mex
G-neg	12	M	Negative	556	553	Syncope with exertion	Mex
G-neg	10	M	Negative	492	505	Epilepsy	No

VT, ventricular arrhythmia. Other abbreviations as in Tables 2,3.

Figure 2. Changes in the corrected QT intervals (QTc) of pediatric patients in the subgroup positive for the E1784K mutation and receiving mexiletine.

lentine, whereas the change in QTc (from 497 ms to 508 ms) was not significant in the 7 patients receiving no medication (Figure 2). All but 1 child on medication in the G-pos group showed no BrS-type ECG on the third-right precordial leads.

Discussion

The most significant finding of this retrospective study of a small cohort is that the proportion of patients with LQT3 with the *SCN5A* mutation was significantly higher than previously reported for patients living in other regions of Japan or in other countries. Further, the course of LQTS probands with the E1784K mutation was relatively benign during the study period.

Prevalence of LQT3

The children referred to us were screened according to the judgment of the physicians who participated in the program in each area. Therefore, the exact number of the entire population of participants in this study is unknown. According to another study, the prevalence of long QT was 1 in 1,164 among 7th graders aged 12 years.¹⁴

In general, approximately 90% of patients with genotyped LQTS carry a mutation in *KCNQ1*, *KCNH2* (*HERG*), or *SCN5A*, which is responsible for the LQTS subtype.^{5,8} The most prevalent form of LQTS appears to be caused by mutations in *KCNQ1*, which encodes the potassium channel (LQT1).^{7,9,10,15} Mutations in *SCN5A* (LQT3) are responsible for only a small proportion (10–20%) of genotyped patients with LQTS.^{16,17} In sharp contrast to these previous findings, the present study

describes a predominance of LQT3 (82% of genotyped patients with LQTS) among schoolchildren living on the Okinawa Islands. Even more striking is the exclusive presence of the *SCN5A* E1784K mutation that causes LQT3. Yoshinaga et al⁹ recently reported the genetic characteristics of children and adolescents with LQTS diagnosed by school-based ECG screening programs. The incidence of LQT3 was 23% of all subjects in that study population with LQTS. An E1784K mutation was detected only in 1 patient. Blaufox et al published a multicenter study of patients residing in North America that showed that an E1784K mutation is present in 13 (30%) of 43 pediatric patients with LQT3.¹⁸

In patients with the *SCN5A* E1784K mutation, overlap of sinus node dysfunction and BrS is relatively common.¹⁹ Regarding the prevalence of LQT3 in other Asian countries such as Taiwan, China, and South Korea, we speculate that the high prevalence of LQT3 is similar to that of BrS in Asia.²⁰ To the best of our knowledge, only a limited number of reports have addressed the prevalence of LQT3 in Asian countries. For example, the *SCN5A* mutation was detected in 17.5% of all genotyped patients with LQTS residing in South Korea.²¹ The mutation rate of *KCNQ1* (6.4%) and *KCNH2* (6.4%) was lower in the Chinese population compared with those of North America or Europe.²² The true prevalence of LQT3 in Asia is unknown, but we believe that it is reasonable to conclude that LQT3 may be prevalent in China.

The high prevalence of LQT3 in Okinawa may be accounted for, in part, by the potential bias introduced by studying a small number of patients at a single center. A second possible cause is a founder mutation, which is defined as disproportion-

ate genetic representation resulting from an affected common ancestor who established a new population, in contrast to the presence of the same mutation among individuals. Such a regional predominance in frequency is associated with LQT1.^{23–25} There is a report that describes a large Dutch family with a founder mutation that uniquely overlaps those of LQT3, BrS, and progressive cardiac conduction defects.²⁶

The subtropical Okinawa Islands are located 2,000 km south of mainland Japan between the East China Sea and the Pacific Ocean. Although haplotype analysis was not performed, a common ethnic heritage for the inhabitants of the Okinawa Islands is consistent with a founder effect. The study subjects described here are unrelated, except for 2. Therefore, the predominant genotype of the children with LQTS studied here strongly suggests community clustering that may represent a founder effect of the same *SCN5A* mutation.

Clinical Characteristics of Patients and Their Treatment

In the present study, most patients were asymptomatic at initial diagnosis, and the disease may have been relatively benign at this time. However, 2 patients experienced bradycardia during the follow-up period, and 1 required implantation of a pacemaker. Zareba et al reported that a cardiac event will occur after adolescence in patients with LQT3.²⁷ The symptoms of patients with LQT3 generally appear after puberty, and in BrS, the electrophysiological phenotype is most prevalent in the 3rd decade. The developmental characteristics of LQT3 and BrS show age-dependent penetrance.²⁸ The late presentation and frequent asymptomatic status of carriers is consistent with a benign disease with possible post-reproductive pathogenicity in the population of the Okinawa Islands.

To date, 8 of 15 patients in the present study received mexiletine. Only 1 patient exhibited a BrS-type ECG while taking this medication. Bradycardia was detected using the third right-precordial lead in the single patient with a BrS-type ECG. Patients with LQT3 without cardiac events in the first year of life respond extremely well to therapy with β -blockers, left cervical sympathetic denervation, or both.²⁹ Mexiletine is considered the medication of choice for treating LQT3.^{30,31} However, 2 studies recommend caution when treating LQT3 because a patient's response depends on the type of mutation.^{32,33} Further, an in-vivo study showed that patients with the *SCN5A* E1784K mutation respond to mexiletine.¹⁹ The diagnosis of LQT3 does not necessarily indicate treatment with an implantable cardioverter-defibrillator. For this reason, Schwartz et al recommend a staged strategy.²⁹

Study Limitations

This was a small and retrospective cohort study. Although the study groups should include patients with LQT3 as well as those positive and negative for mutation, the distribution of the prevalence of genotype-positive subtypes was unpredictably imbalanced and unique. The prevalence of LQT3 (exclusively the E1784K mutation) was predominantly high in genotype-positive patients; therefore, we conclude that our classification was justified. Moreover, despite the possibility of the enrollment of patients with a specific founder mutation and considering that the hospital is the only tertiary heart center for children in Okinawa, our findings of a unique and highly prevalent *SCN5A* mutation (E1784K) serve as a compelling justification to conduct larger or long-term studies.

Conclusions

We were unable to determine why the prevalence of the *SCN5A*

E1784K mutation was uniquely high among schoolchildren living on the Okinawa Islands. The prognosis of these patients is relatively benign; however, the prognosis for adults is unknown. Because of the geography of Okinawa, its population should be ideal for studies on gene modifiers with a focus on the prevalent *SCN5A* mutation.

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