circadian distribution of cardiac events in patients with structural heart diseases such as old myocardial infarction,[6,9] hypertrophic cardiomyopathy,[11] idiopathic dilated cardiomyopathy,[7] or non-structural heart disease such as Brugada syndrome,[12] those associated with congenital LQT syndrome have remained unknown. We therefore examined circadian and seasonal variations in patients with LQT syndrome in multiple institutions. Our findings indicated specific seasonal and circadian distributions of cardiac events in patients with congenital LQTS that are quite different from those occurring in patients with structural heart disease. **Figure 1** shows that the incidence of cardiac events significantly peaked during the summer in LQT1 and during the summer to autumn in LQT2. Although events in LQT3 did not significantly peak during any particular season, a significant nadir was reached during the winter. Cardiac events were generally associated with more severe symptoms such as syncope, cardiac arrest, and sudden death in the LQT1 and LQT3 groups, but with milder symptoms among the LQT2 group. Triggers for cardiac events among the 3 genotypes were generally similar to those reported by others.[10,13–16] The incidence of events significantly peaked between the morning and afternoon (6:00–17:59) in LQT1, and during the morning (6:00–11:59) in LQT2 (**Figure 2**). More events occurred during the late morning in LQT1 ($P<0.001$), and around the time of awakening in LQT2 ($P<0.001$). Although a significant circadian difference was not found, the frequency of cardiac events was relatively higher during the night-time to early morning in LQT3 compared with other LQT syndromes (**Figure 3**).

Possible Mechanisms for Seasonal Distribution of Cardiac Events

Although the frequency of cardiac events including VT/VF in patients with structural heart disease significantly increases during the winter,[2–4,17,18] the frequency was higher during summer to autumn in patients with LQT1 and LQT2 and lowest during the winter among those with LQT3. Several potential factors could explain the differences in seasonal distribution of cardiac events in patients with long QT syndrome compared with those having structural heart disease. The most likely reason for the highest frequency of cardiac events occurring in LQT1 during the summer is that participation in activities such as swimming and running is higher during the summer, and children might have more opportunities to play outside during the summer in Japan. Athletic and swimming meets are usually held during this season in schools. Sympathetic nerve activities and catecholamine levels are closely related to the occurrence of cardiac events in individuals with LQT1.[19–21] Most cardiac events occurred during exercise in our patients with LQT1, which supports previous findings.[10,13,22,23]

The reason why patients with LQT2 had the highest frequency of cardiac events from summer to early autumn remains unknown. However, seasonal variations in serum potassium levels could be 1 factor, as these levels are significantly lower in summer than in winter.[24] This could be a result of a loss of potassium through profuse sweating or increased water intake. A close correlation has been implied between hypokalemia and LQT2, in which the cell surface density of the voltage-gated K^+ channel, *HERG*, is regulated by a biological factor and the extracellular K^+ concentration, and the administration of oral potassium results in a greater reduction in resting corrected QT (QTc) interval.[25–27]

The frequency of cardiac events was lower in patients with LQT3 during the winter than during other seasons, which is similar to that of Brugada syndrome.[12] LQT3 and Brugada syndromes are both associated with mutations in SCN5A, the gene that encodes the α subunit of the sodium channel. Mutations in SCN5A result in an increase (gain of function) and decrease (loss of function) in the late sodium current (I_{Na}) in patients with LQT3 and Brugada syndrome, respectively, and are reportedly found in 18–30% of clinically diagnosed Brugada syndrome. Some single mutations in the SCN5A gene cause multiple phenotypes such as Brugada syndrome, sick sinus syndrome. and conduction disease in addition to the LQT3 phenotype.[22,28–30] In addition, recent evidence shows considerable clinical overlap, implying a new disease entity known as the overlap syndrome of cardiac sodium channelopathy.[31,32] The seasonal distribution of "multiple" events was similar to those of isolated episodes.

Possible Mechanisms for Circadian Distribution of Cardiac Events

One factor that might explain the varied circadian distribution of cardiac events is the effect of autonomic nervous activity. Sympathetic nerve activity is higher during the daytime and upon awakening.[33–37] Cardiac events in patients with LQT1 are closely related to sympathetic nerve activities and plasma catecholamine levels, which are also higher during the daytime. In addition, daytime provides more opportunities for physical stress, because more exercise is accomplished during the daytime than during the night-time. Thus, the circadian profiles of cardiac events are similar between LQT1 and structural heart disease.

The frequency of cardiac events was significantly higher among patients with LQT2 during the early morning, when the alarm clock rings, or when they awakened, stood upright, walked, or performed daily rituals, such as face washing or brushing teeth. The response to epinephrine test in patients with LQTS reported by Noda et al might explain this circadian profile in patients with LQT2[19] in whom the QTc duration is transiently prolonged just after starting intravenous epinephrine and returns to the baseline level at the steady state. This suggests that cardiac events tend to occur immediately after an initial increase in sympathetic nerve activities or catecholamine levels, and that cardiac responses to epinephrine and or sympathetic nerve activity might be intensified at the time of awakening.

The circadian distribution of cardiac events in patients with LQT3 is difficult to conclude because of the low incidence. However, the tendency is quite similar to that of Brugada syndrome, in which cardiac events occur during the night and while asleep. Increased vagal activity apparently plays a significant role in the genesis of VF in patients with Brugada syndrome. The hereditary association in the seasonal distribution of cardiac events in LQT3 described above might participate in the coincidence of cardiac events between LQT3 and Brugada syndromes.

Darwin et al recently uncovered molecular evidence that links circadian rhythms to vulnerability in ventricular arrhythmias in mice, in which cardiac ion-channel expression and QT-interval duration (an index of myocardial repolarization) exhibit endogenous circadian rhythmicity under the control of the clock-dependent oscillator, kruppel-like factor 15 (Klf15).[38] This factor transcriptionally controls rhythmic expression of Kv channel-interacting protein 2 (KChIP2), a critical subunit required for generating the transient outward potassium current. A deficiency or excess of Klf15 causes a loss of rhythmic QT variation, abnormal repolarization, and enhanced susceptibility to ventricular arrhythmias. These mechanisms might participate in the circadian variation of ventricular arrhythmias

associated with each type of LQT syndrome. Although gene-specific differences might be associated with a discrepancy in the occurrence of cardiac events,[39] further investigations are required.

Clinical Implications

The present results indicate a need for more specific medical therapy, although further assessments are required. For example, amounts of medication should be increased in summer and taken in the morning by patients with LQT1, increased over summer to autumn and taken before falling asleep by patients with LQT2, and increased before falling asleep for patients with LQT3.

Study Limitations

First, the timing and number of events might have been underestimated because they were based on patients' recall and medical records. Not all cardiac events were memorized like those recorded by an implantable cardioverter defibrillator. However, more extreme symptoms such as syncope and cardiac arrest or death were usually memorable and a history was taken from not only the patients but also their families. Thus, underestimation of these more disastrous events was considered to be low. In contrast, the frequency of events such as presyncope could be overestimated because they could arise as a result of causes other than ventricular tachyarrhythmias. However, we defined the symptoms of presyncope as sudden dizziness, palpitations, and chest pain persisting for over 30s without a complete loss of consciousness that were confirmed by ECG recordings as being associated with ventricular tachyarrhythmias at least once, and we attempted to minimize false-positive cases. Second, the influence of drug therapy was not considered in this study, so the precise effect of time- or season-dependent exposure to β-blockers on the distribution of events was not analyzed. However, patients usually take medications in the morning and we did not change the medication according to the season. Third, some patients who had experienced a large number of events might have distorted the results. However, the tendencies of the seasonal and circadian distribution of cardiac events were similar, even when patients with a large number of cardiac events ($\geq$10) were excluded. In addition, the tendency remained similar regardless of the severity of cardiac events (presyncope, syncope, cardiac arrest, and death). Finally, this was a retrospective study, and the population size and the number of events was small, especially among patients with LQT3. In addition, unavoidable bias was conferred by excluding patients with LQTS whose first manifestation of illness was sudden death. Therefore, further studies of a large number of patients (with an implantable cardioverter defibrillator if possible) are required to validate the present findings and to define the underlying mechanisms.

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Disclosures

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Long-Term Follow-Up of a Pediatric Cohort With Short QT Syndrome

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Objectives The purpose of this study was to define the clinical characteristics and long-term follow-up of pediatric patients with short QT syndrome (SQTS).

Background SQTS is associated with sudden cardiac death. The clinical characteristics and long-term prognosis in young patients have not been reported.

Methods This was an international case series involving 15 centers. Patients were analyzed for electrocardiography characteristics, genotype, clinical events, Gollob score, and efficacy of medical or defibrillator (implantable cardioverter-defibrillator [ICD]) therapy. To assess the possible prognostic value of the Gollob score, we devised a modified Gollob score that excluded clinical events from the original score.

Results Twenty-five patients 21 years of age or younger (84% males, median age: 15 years, interquartile range: 9 to 18 years) were followed up for 5.9 years (interquartile range: 4 to 7.1 years). Median corrected QT interval for heart rate was 312 ms (range: 194 to 355 ms). Symptoms occurred in 14 (56%) of 25 patients and included aborted sudden cardiac death in 6 patients (24%) and syncope in 4 patients (16%). Arrhythmias were common and included atrial fibrillation (n = 4), ventricular fibrillation (n = 6), supraventricular tachycardia (n = 1), and polymorphic ventricular tachycardia (n = 1). Sixteen patients (84%) had a familial or personal history of cardiac arrest. A gene mutation associated with SQTS was identified in 5 (24%) of 21 probands. Symptomatic patients had a higher median modified Gollob score (excluding points for clinical events) compared with asymptomatic patients (5 vs. 4, p = 0.044). Ten patients received medical treatment, mainly with quinidine. Eleven of 25 index cases underwent ICD implantation. Two patients had appropriate ICD shocks. Inappropriate ICD shocks were observed in 64% of patients.

Conclusions SQTS is associated with aborted sudden cardiac death among the pediatric population. Asymptomatic patients with a Gollob score of <5 remained event free, except for an isolated episode of supraventricular tachycardia, over an average 6-year follow-up. A higher modified Gollob score of 5 or more was associated with the likelihood of clinical events. Young SQTS patients have a high rate of inappropriate ICD shocks. (J Am Coll Cardiol 2013;xx:xxx) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ECG = electrocardiography

ICD = implantable cardioverter-defibrillator

IQR = interquartile range

QTc = corrected QT interval for heart rate using the Bazett formula

SCD = sudden cardiac death

SQTS = short QT syndrome

SVT = supraventricular tachycardia

VF = ventricular fibrillation

The short QT syndrome (SQTS) is a primary cardiac electrical disease and one of the recent additions of inherited arrhythmias associated with sudden cardiac death (SCD). Although believed to be a rare condition, the entire disease spectrum continues to emerge with newly recognized cases, and as we continue to understand the disease better and to characterize it more fully, a broader disease spectrum may be revealed. The underlying pathophysiological features involve shortening of myocardial repolarization, which creates the electrical substrate for atrial and ventricular tachyarrhythmias (1). The arrhythmogenic potential of a short QT interval was described first by Gussak et al. (2). To date, genetic studies have shown that SQTS is associated with gain-of-function mutations in 3 different potassium channels (3–6) and 3 loss-of-function mutations in the L-type cardiac calcium channel, although forms of short QT interval associated with calcium channelopathies show phenotypic overlap with Brugada syndrome (7,8).

In SQTS, the corrected QT interval for heart rate using the Bazett formula (QTc) in most reported cases to date usually is <340 to 360 ms, with rare exceptions (9). A normal QT interval has been reported as 370 ± 30 ms in children (10) and 385 ± 24 ms in adults (11), with a slightly longer QT interval in post-pubescent females (12). According to population studies (13), a QTc interval of 340 to 360 ms has been proposed as the lower limit of normal. However, as demonstrated with long QT syndrome, there is an overlapping range of QT intervals between affected individuals (14) and apparently healthy subjects (15). It is likely SQTS cases with longer QTc interval exist. In contrast, the presence of a short QT interval in isolation may not always be indicative of SQTS. Thus, Gollob et al. (16) proposed diagnostic criteria for SQTS (Table 1).

The therapeutic approach to SQTS is not well defined. An implantable cardioverter-defibrillator (ICD) may be considered as primary therapy, given the known risk of SCD (17). However, the risk-to-benefit ratio of such an approach remains unknown, particularly in the young. Although hydroquinidine has demonstrated some benefit in a limited number of patients (18,19), there is limited experience with medical therapy.

To date, the long-term prognosis in young SQTS patients has not been reported. We set out to define the clinical characteristics and long-term outcomes of a pediatric cohort diagnosed with SQTS.

Methods

Study population. Pediatric SQTS patients (≤21 years of age at clinical presentation) from 15 centers in North and South America, Europe, and Japan were characterized clinically and were followed up beginning in 2007. Entry criteria included: 1) QT interval of 330 ms or less; or 2) QTc interval of 360 ms or less with 1 or more of the following: syncope, atrial fibrillation, ventricular fibrillation (VF), aborted SCD, positive family history of SQTS or unexplained SCD, or a combination thereof. A total of 28 patients were enrolled, of whom 25 met the inclusion criteria for this study: 1) a Gollob diagnostic score of 3 or more (indicating a moderate to high probability of SQTS); and 2) clinical follow-up longer than 1 year. Patient demographic data were collected. The ECG parameters analyzed included: QT interval, QTc interval, J point-to-T peak interval, and early repolarization. The QT interval was measured manually. The QTc interval was calculated using Bazett's formula. The J point was defined as the end of the QRS interval and the beginning of the ST segment. The T peak was measured at the highest point of the T-wave. Early repolarization was defined as an elevation of more than 0.1 mV of the J point from baseline in at least 2 contiguous

Table 1 SQTS Diagnostic Criteria: Gollob Score

	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	1
Clinical history*	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

High-probability SQTS: ≥4 points, intermediate-probability SQTS: 3 points, low-probability SQTS: ≤2 points. Electrocardiogram must be recorded in the absence of modifiers known to shorten the QT interval. J point-to-T peak interval must be measured in the precordial lead with the greatest amplitude T-wave. Clinical history events must occur in the absence of an identifiable cause, including structural heart disease. Points can be received only for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope. Family history points can only be received once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points.

QTc = corrected QT interval for heart rate using the Bazett formula; SQTS = short QT syndrome; VF = ventricular fibrillation; VT = ventricular tachycardia.

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Table 2 SQTS Diagnostic Criteria: Modified Gollob Score

	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

Electrocardiogram must be recorded in the absence of modifiers known to shorten the QT interval. J point-to-T peak interval must be measured in the precordial lead with the greatest amplitude T-wave. Family history points can be received only once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points.

Abbreviations as in Table 1.

leads in the inferior leads (II, III, aVF), lateral leads (I, aVL, V_4 to V_6), anterior leads (V_1 to V_3), or combinations thereof. The contour of the ST segment was classified as having either upsloping or horizontal (downsloping) morphological features. Patients with ICD were assessed for implant indication, delivered therapies, and device complications. We elected to explore the risk-stratifying value of specific variables within the Gollob scoring system. Thus, the diagnostic Gollob score was modified, by excluding clinical events, into a new prognostic score referred to as the modified Gollob score (Table 2).

Statistical analysis. Continuous variables are presented as mean ± SD or median (interquartile range [IQR]: 25th to 75th percentile). Analyzed continuous variables are presented only as medians with IQR and were analyzed using the Wilcoxon rank sum test. Categorical variables are presented as counts with percentages and were analyzed using the Fisher exact test or the chi-square test. Correlation between continuous data was analyzed using the Spearman correlation coefficient. Two-tailed p values of <0.05 were considered statistically significant. Statistical analysis was performed using SAS software version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results

Clinical data. There were 25 patients and a total of 21 (84%) were male. Their clinical data are presented in Table 3. Patients were followed up for a median of 5.9 years (IQR: 4 to 7.1 years). Patient age at the time of clinical presentation ranged from 1 day to 21 years (13.4 ± 6 years, median: 15 years, IQR: 9 to 18 years), with 9 patients (36%) younger than 12 years.

ECG. The QT interval varied from 160 to 360 ms (279 ± 51 ms, median: 290 ms, IQR: 280 to 300 ms), whereas the QTc interval ranged from 194 to 355 ms (304 ± 41 ms, median: 312 ms, IQR: 286 to 335 ms). The J point-to-T peak interval ranged from 63 to 180 ms (132 ± 35 ms, median: 140 ms, IQR: 119 to 160 ms). Arrhythmias were common: 4 patients had atrial fibrillation, 6 had VF, and 1 had supraventricular tachycardia (SVT) at presentation.

GENETIC TESTING. Genetic testing was undertaken in 21 of the 25 patients, and 5 patients had a confirmed mutation. All gene-positive patients were symptomatic, including a 3-month-old young female with recurrent atrial fibrillation since the age of 4 days and associated sinus and atrioventricular node dysfunction (KCNQ1 V141M). Tables 3 and 4 outline the culprit genes, specific mutations, and associated symptoms and arrhythmias detected in the gene-positive cohort.

FAMILY HISTORY. A personal or familial history of cardiac arrest was present in 16 (84%) of 25 patients. A familial history of SCD, presumed to be arrhythmogenic, was present in 5 symptomatic patients and in 6 asymptomatic patients. These involved 6 siblings (4 young males and 2 young females 2 uncles, and 1 father. The equal distribution of familial SCD among symptomatic and asymptomatic individuals suggests that SCD alone may not predict prognosis, although numbers were relatively small in this study. Among the entire cohort, there was a positive family history for a clinical diagnosis of SQTS in 17 (68%) patients, equally distributed between parents and siblings. Among the patients with atrial fibrillation, only 1 of 4 had a family history of atrial fibrillation. In the patients with VF, only 1 of 6 had a first-degree relative (father) with SCD. Overall, the prevalence of symptomatic family members did not seem to be more common in symptomatic patients, although a much larger cohort would be required to assess confidently whether a symptomatic family member predicts individual risk. Only 4 of 25 patients had no family history of SQTS or SCD.

Symptomatic versus asymptomatic patients. Of the entire cohort, 14 (56%) patients had 1 or more clinical features associated with SQTS, including aborted SCD in 6 (24%), unheralded syncope in 4 (16%), and palpitations with documented atrial fibrillation in 4 (16%). The remaining 11 (44%) patients were asymptomatic, 10 of whom were identified through family screening and the remaining through an incidental ECG finding of a very short QTc interval (292 ms). There was no significant difference in median age between symptomatic and asymptomatic patients (median: 15 years, IQR: 8 to 17 years vs. median: 17 years, IQR: 9 to 18 years, $p = 0.621$). All but 1 of the asymptomatic cases had a family history of SQTS or unexplained SCD.

ECG PARAMETERS. No differences were found in the ECG parameters between asymptomatic and symptomatic patients (Table 3). Although the QTc interval tended to be shorter in symptomatic patients (median: 306 vs. 330 ms), the difference was not statistically significant ($p = 0.207$).

Table 3 Characteristics of All Patients

Variable	Total (n = 25)	Symptomatic* (n = 14)	Asymptomatic (n = 11)	p Value
Patient age at presentation (yrs)	15 (9–18)	15 (8–17)	17 (9–18)	0.621
Age <12 yrs	9 (36%)	4 (28.6%)	5 (45.5%)	0.434
Male	21 (84%)	11 (78.6%)	10 (90.9%)	0.604
Follow-up duration (yrs)	5.9 (4.4–7.1)	5.7 (4.8–7.4)	6.1 (3.2–6.9)	0.460
Symptoms				
Aborted SCD	6 (24%)	6 (43%)	—	
Unheralded syncope	4 (16%)	4 (28.5%)	—	
Palpitations†	4 (16%)	4 (28.5%)	—	
Modified Gollob score	5 (4–5)	5 (4–6)	4 (4–5)	0.044
Genetic mutation				
KCNH2	2 (8%)	2 (14%)	0	
KCNJ2	2 (8%)	2 (14%)	0	
KCNQ1	1 (4%)	1 (7%)	0	
ECG parameters				
QT (ms)	290 (280–300)	280 (200–300)	295 (280–320)	0.333
QTc (ms)	312 (286–335)	306 (252–329)	330 (292–335)	0.207
J point-to-T peak interval (ms)	140 (119–160)	130 (80–160)	140 (120–160)	0.344
J point-to-T peak interval <120 (ms)	7 (28%)	6 (42.9%)	1 (9.1%)	0.090
Early repolarization	12/24 (50%)	6/14 (43%)	6/10 (60%)	0.680
Family history				0.620
SQTS	8 (32%)	4 (28.6%)	4 (36.4%)	
SCD	4 (16%)	3 (21.4%)	1 (9.1%)	
SCD and SQTS	9 (36%)	4 (28.6%)	5 (45.5%)	
Negative	4 (16%)	3 (21.4%)	1 (9.1%)	
ICD	11 (44%)	8 (57.1%)	3 (27.3%)	0.227
Appropriate shocks	2 (18%)	2 (25%)	0	
Inappropriate shock	7 (63.6%)	4 (50%)	3 (100%)	
Complications‡	9 (81.8%)	6 (75%)	3 (100%)	

Values are median (interquartile range) or n (%). *Only patients with aborted sudden cardiac death, syncope, or documented ventricular or atrial fibrillation at presentation or during follow-up were considered symptomatic for short QT syndrome. †Palpitations and atrial fibrillation or supraventricular tachycardia. ‡Including inappropriate shocks.

ECG = electrocardiography; ICD = implanted cardiac defibrillator; J point-to-T peak interval = interval in milliseconds measured on standard electrocardiography ECG from the J-point to the peak T-wave voltage; SCD = sudden cardiac death. Other abbreviations as in Table 1.

There was a trend toward a higher prevalence of short J point-to-T peak interval (<120 ms) in the symptomatic versus the asymptomatic patients (42.9% vs. 9.1%, p = 0.090). Only 1 of the asymptomatic patients had a short J point-to-T peak interval. The presence of early repolarization did not differ between symptomatic and asymptomatic patients. Early repolarization was found in the anterior (n = 2), anterolateral (n = 2), lateral (n = 1), and anteroinferolateral (n = 1) leads in 43% of symptomatic cases. In 60% of asymptomatic cases, early repolarization was found in the inferolateral (n = 3) cases and in the anterior or lateral leads, or both (n = 3). In all cases, early repolarization had an upsloping ST segment pattern (Fig. 1).

GOLLOB DIAGNOSTIC SCORE FOR SQTS. Asymptomatic patients had Gollob scores ranging from 3 to 5 (median: 4, IQR: 4 to 5), whereas most symptomatic patients had higher Gollob scores ranging from 4 to 10 (median: 6, IQR, 6 to 8, p < 0.001).

A modified Gollob score, excluding clinical events, was assigned to each patient. Asymptomatic patients had modified Gollob scores ranging from 3 to 5 (median: 4, IQR: 4 to 5), whereas most symptomatic patients had higher scores ranging from 3 to 8 (median: 5, IQR: 4 to 6, p = 0.044).

ABORTED SCD. Aborted SCD occurred in 6 (24%) of 25 patients. These patients had a longer follow-up duration

Table 4 Genetic Mutations in the Pediatric Cohort

Age (yrs)	Gender	Gene	Mutation	Current	Symptoms	Arrhythmias
3	F	KCNQ1	V141M	IKs	None	Atrial fibrillation, sinus, and atrioventricular node dysfunction
5	F	KCNJ2	M301K	IK1	None	Atrial fibrillation
8	F	KCNJ2	M301K	IK1	None	Atrial fibrillation
14	M	KCNH2	N588K	IKr	Syncope	Ventricular fibrillation
19	M	KCNH2	E50D	IKr	Syncope	None

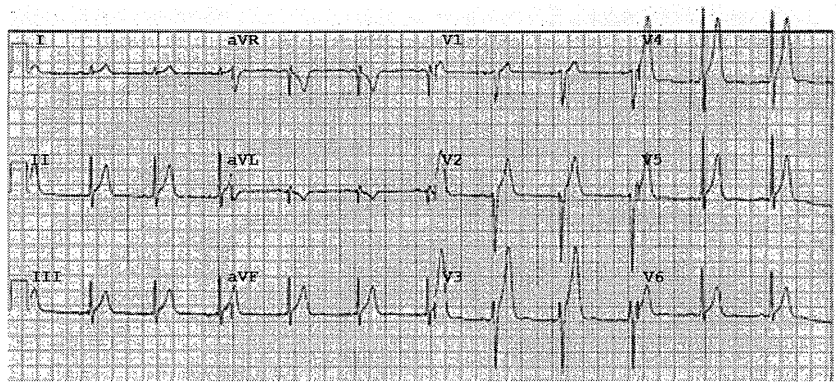

Figure 1 Representative 12-Lead Electrocardiogram of the Short QT Syndrome

Resting electrocardiogram (ECG) of a 15-year-old young male with aborted sudden cardiac death and a short QT interval (QT interval: 280 ms, QT interval corrected for heart rate [QTc]: 325 ms). There are peaked T waves in most of the precordial leads. The J point-to-T peak interval is 140 ms. There is early repolarization with upsloping ST segment in II, III aVF, and V_2 to V_6.

than those without aborted SCD (median: 7.3 years, IQR: 6.3 to 7.8 years vs. median: 5.3 years, IQR: 4.0 to 6.9 years, p = 0.045). A short J point-to-T peak (<120 ms) was more prevalent among the aborted SCD group (67% vs. 16%, p = 0.032) (Table 5). Five of these 6 patients had implantation of an ICD. In one instance, the parents declined an ICD for a 6-month-old young male (at the time of clinical presentation) with an ultra-short QT interval of 160 ms (QTc interval: 241 ms) who, at 80 months of follow-up, had no recurrent symptoms (Fig. 2). A positive family history of SQTS or SCD did not discriminate between aborted SCD and nonaborted SCD patients because of the high prevalence among the entire cohort. Early repolarization with upsloping ST segment in the anteroinferolateral leads was present in only 1 of the 6 patients with aborted SCD.

Therapy. ICD. Implantation of a cardioverter-defibrillator (ICD) was performed in 11 (44%) of 25 patients, in 54 as primary prevention (unexplained syncope in 2). Indications for ICD in the other 7 patients were aborted SCD or VF (n = 5). Two (18%) patients had appropriate shocks: a 14-year-old young male (QT interval: 300 ms, QTc interval: 286 ms) with a history of aborted SCD while receiving quinidine at 9 mg/kg daily and a 14-year-old young male (QT interval: 248 ms; QTc interval: 252 ms) with a history of syncope and VF. The latter had no recurrent ICD appropriate shocks while taking quinidine. Two other patients had no shock and 7 (64%) had 1 or more inappropriate shocks. The underlying cause of inappropriate shocks was atrial fibrillation with rapid ventricular conduction (n = 1), sinus tachycardia (n = 3), SVT (n = 1), and ventricular lead fracture (n = 3), including 1 Sprint Fidelis lead (Medtronic, Minneapolis, Minnesota). There was an additional patient with a ventricular lead fracture 6 years after implantation that did not cause an inappropriate ICD shock. Of patients who received an ICD as primary prevention, 4 had inappropriate shocks.

MEDICAL THERAPY. Medical therapy was initiated in 10 (40%) of 25 patients, 4 of whom received multiple agents. Of the 4 patients with paroxysmal atrial fibrillation, 3 received quinidine therapy that proved unsuccessful in preventing recurrences of the arrhythmia. These patients were quite young, including an infant who also had recurrences while receiving propafenone and sotalol, a 5-year-old in whom flecainide also failed, and an 8-year-old. The remaining patient with atrial fibrillation was a 17-year-old young male (QT interval: 320 ms, QTc interval: 355 ms) (Fig. 3A) who was cardioverted at the time of ICD implantation, but continued to experience recurrences despite therapy with digoxin and propafenone. On treatment with digoxin and dofetilide, there was prolongation of the QT interval and return to sinus rhythm without symptomatic recurrences through follow-up (Fig. 3B). However, ICD interrogation identified asymptomatic, short episodes of atrial fibrillation. Two patients with a history of appropriate ICD shocks also received quinidine therapy. The first patient, a 14-year-old young male with aborted SCD, had a therapeutic shock while receiving quinidine 9 mg/kg daily. We were unable to confirm whether lack of compliance was the issue. The J point-to-T peak interval in this patient was 118 ms. He had a Gollob score of 8 with a QT interval of 300 ms (QTc interval: 286 ms). Genetic testing did not identify any known mutation. The second patient had no recurrent shocks while receiving quinidine therapy.

ARRHYTHMIAS ENCOUNTERED DURING FOLLOW-UP. Of the asymptomatic patients, only a 21-year-old man with an ICD as primary prevention had SVT resulting in inappropriate shocks and requiring ICD reprogramming. He had a modified Gollob score of 4. The other 10 asymptomatic cases with Gollob scores of 3 to 5 remained asymptomatic and arrhythmia-free during follow-up. In the group that was symptomatic at presentation, a 19-year-old man receiving no

Table 5 Comparison of Patients With Versus Without Aborted Sudden Cardiac Death

Variable	Aborted SCD (n = 6)	No Aborted SCD (n = 19)	p Value
Patient age at presentation (yrs)	14 (14–15)	17 (8–18)	0.632
Age <12 yrs	1 (16.7%)	8 (42.1%)	0.364
Male	6 (100%)	15 (79%)	0.540
Follow-up duration (yrs)	7.3 (6.3–7.8)	5.3 (4.0–6.9)	0.045
Genetic mutation (n = 21)			
KCNH2	1 (20%)	1 (6.3%)	
KCNJ2	0	2 (12.5%)	
KCNQ1	0	1 (6.3%)	
Negative	4 (80%)	12 (75%)	
Family history			
SCD and/or SQTS	5 (83.3%)	16 (84.2%)	0.999
ECG parameters			
QT interval (ms)	280 (248–300)	295 (280–320)	0.261
QTc interval (ms)	300 (252–325)	312 (291–335)	0.323
QTc interval < 330 ms	5 (83.3%)	11 (57.9%)	0.364
J point-to-T peak interval	109 (80–140)	140 (120–160)	0.130
J point-to-T peak interval <120 ms	4 (66.7%)	3 (15.8%)	0.032
Early repolarization	1/6 (17%)	11/18 (61%)	0.155
Medical therapy with quinidine	3 (50%)	6 (31.6%)	0.344
Documented arrhythmia on follow-up			
Ventricular fibrillation	1 (16.7%)	0	
Polymorphic VT	1 (16.7%)	0	
Atrial fibrillation	0	3 (15.8%)	
SVT	0	1 (5.3%)	
ICD	5 (83.3%)	6 (31.6%)	0.056
Appropriate shocks	2 (40%)	0	
Inappropriate shock	3 (60%)	4 (66.7%)	
Complications*	5 (100%)	4 (66.7%)	

Values are median (interquartile range) or n (%). *Including inappropriate shocks.
SVT = supraventricular tachycardia. Other abbreviations as in Tables 1 and 3.

medical therapy and with a history of aborted SCD experienced 2 episodes of nonsustained polymorphic ventricular tachycardia that terminated spontaneously. All cases with atrial fibrillation required ongoing therapy with cardioversion, medical treatment with different antiarrhythmic agents, or both. A 3-month-old young female with an ultra-short QT of 200 ms (QTc interval: 275 ms) had a history of marked sinus bradycardia since birth and atrioventricular node dysfunction with a Wenckebach cycle length of 500 ms. The patient demonstrated atrial fibrillation at 4 days of age, requiring cardioversion. A ventricular pacemaker was implanted at 6 days of age. Despite antiarrhythmic therapy, it eventually progressed into permanent atrial fibrillation. A 5-year-old young female with an ultra-short QT of 172 ms (QTc interval: 194 ms) had mechanically induced atrial and VF during insertion of a Swan Ganz catheter.

Discussion

To our knowledge, this is the longest follow-up cohort of patients with SQTS reported in the literature. It also represents the largest series of pediatric SQTS patients, because the average age in this cohort was 13 years.

Our cohort was predominantly male (84%), reflecting a gender-specific prevalence and possible greater vulnerability to SQTS in young males as compared with young females. Eighty-four percent of patients had a personal or familial history of cardiac arrest. More than half of our patients had symptoms, including aborted SCD (24%) and syncope (16%). The most common symptomatic presentation was cardiac arrest. An additional 11 cases (44% of cohort) were identified through cascade family screening. Twenty percent of cases were identified to have disease-causing mutations. Our cohort included a 6-year-old young male with aborted SCD and a QT interval of 160 ms, the shortest QT interval reported to date. In addition, we report 3 children younger than 8 years with recalcitrant atrial fibrillation and ultra-short QT intervals ranging from 172 to 200 ms and 1 patient, an infant with a QT of 200 ms (QTc interval: 275 ms), who had coexisting sinus and atrioventricular node dysfunction. This patient had sinus bradycardia at birth and demonstrated slow atrial fibrillation at 4 days of age. To our knowledge, the latter clinical scenario associated with a V141M mutation in the KCNQ1 gene has not been reported with SQTS. Another unique finding in this young population has been the high incidence of inappropriate shocks, affecting 64% of ICD recipients, which far exceeded appropriate shocks.

A previously reported study presented the clinical characteristics and outcomes in an adult population of SQTS patients (median age: 26 years) (19). Similar to the observations of our pediatric cohort, most clinically affected adults were men (75%), cardiac arrest as a first presentation was relatively common (32%), a family history of SQTS was present in 50% of patients, and disease-causing mutations were found in 23% of probands. In contrast, our pediatric cohort tended to have a shorter QTc interval (average: 304 ms vs. 314 ms), and although adult and pediatric ICD recipients both received a high inappropriate shock rate, this was more common in pediatric patients (64% vs. 33%).

Gollob et al. (16) proposed diagnostic criteria for SQTS. We found that a modified Gollob score, which excluded points for clinical events, may be useful in identifying patients at a higher risk for unexplained syncope, atrial fibrillation, or aborted SCD. Our patients with a history of these clinical events had a median modified score of 5 (range: 4 to 6) as compared with a median of 4 (range: 4 to 5) in patients who remained asymptomatic (except 1 case of SVT). Patients with a modified Gollob score of 3 (or Gollob score of <5) had a good prognosis during follow-up in this study. Only 1 (7%) of 14 symptomatic patients had a low modified Gollob score of 3.

SQTS is considered a rare electrical abnormality, and recognition of this condition as a cause of unexplained SCD in young children is uncommon, although perhaps underrecognized. A reported series of adult patients with idiopathic VF were noted to have a mean QTc value of 371 ms, significantly less than the QTc value of healthy sex- and

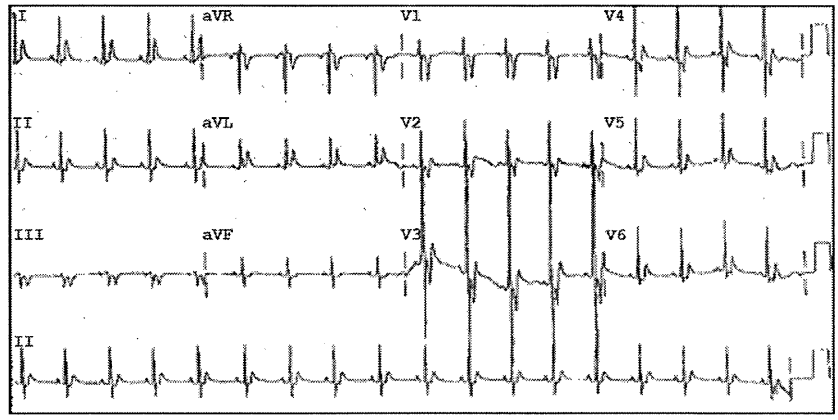

Figure 2 Extreme Abbreviation of QT Interval in a Young, Symptomatic Child

An ultra-short QT interval of 160 ms (QTc interval: 241 ms) in a 6-month-old young male at the time of clinical evaluation after cardiac arrest.

age-matched controls (20). These observations suggest that less extreme values of short QTc interval may be part of the SQTS disease spectrum.

Aborted SCD affected 6 of our patients (24%), 5 of them at 15 years of age or younger. One of the current therapeutic options for patients with SQTS includes implantation of an ICD (21–23). Six of our patients received an ICD for primary prevention; however, 4 experienced 1 or more inappropriate ICD shocks. Previous studies have reported an increased risk for inappropriate ICD therapy because of oversensing of short-coupled and prominent T waves resulting in T-wave oversensing (24). In our young cohort with SQTS, inappropriate shocks far exceeded appropriate shocks. Most of our patients had inappropriate shocks secondary to atrial tachycardias, including sinus tachycardia (n = 3), SVT (n = 1), and atrial fibrillation (n = 1). Inappropriate therapies resulting from rapid atrial arrhythmias may be prevented by programming device therapies for heart rates exceeding 210 beats/min, although a formative assessment is needed to evaluate the efficacy of such an approach. In addition, we observed a high prevalence of ventricular lead fracture of 36% (4 of 11 cases) with most (3 of 4) resulting in inappropriate ICD shocks. The high prevalence of ventricular lead fracture in part may be the result of the patients' young ages at implantation. These points together highlight our concerns regarding the use of ICD therapy in asymptomatic young patients.

We identified a higher prevalence of short J point-to-T peak interval (<120 ms) in symptomatic (42.9%) versus asymptomatic patients (9.1%). However, because of the small number of cases, the difference did not reach statistical significance. Watanabe et al. (25) reported a high prevalence (65%) of early repolarization in patients with SQTS that was associated with arrhythmic events. In their cohort, early repolarization was localized in either inferior leads, lateral leads, or both, but the ST segment contour was not described in their paper. Early repolarization with upsloping morphological features can be a benign ECG finding (26), whereas a horizontal or downsloping ST segment may be associated with VF (27). Early repolarization also was observed in a high percentage of our cohort (50%), and it was localized in anterior, inferior, and lateral leads, or in a combination thereof. This ECG feature was not significantly different between our symptomatic (43%) and asymptomatic (60%) patients. None of our patients with early repolarization had a horizontal or downsloping pattern. Only 1 of our 6 cases of aborted SCD showed early repolarization.

Five of our patients, all symptomatic, had genetic mutations associated with SQTS. The yield of genetic mutation detection was 24% for index patients who underwent genetic testing. This compares with the 23% incidence reported in the literature (16).

Quinidine has been suggested as one of the mainstay therapies for SQTS because of its ability to offset the extreme shortening of repolarization that occurs in SQTS (28). In this cohort, quinidine proved ineffective in managing atrial fibrillation in those patients with frequent recurrences. In addition, while receiving a low dose of quinidine, one patient experienced a therapeutic ICD shock. Therefore, the effectiveness of this antiarrhythmic agent in young SQTS patients awaits further investigation.

Study limitations. Although we describe the largest population of pediatric patients with SQTS with the longest reported clinical follow-up, event rates and risks in later decades of life remain unknown. As a relatively rare or perhaps under-recognized disease, our cohort included only 25 patients. Thus, we must be cautious in reaching conclusions based on such a small group.

Conclusions

SQTS in the pediatric population is associated with a high risk of aborted SCD. The diagnosis seems more common in young males similar to observations in adult SQTS patients. This may reflect protection from ultra-short QT intervals in

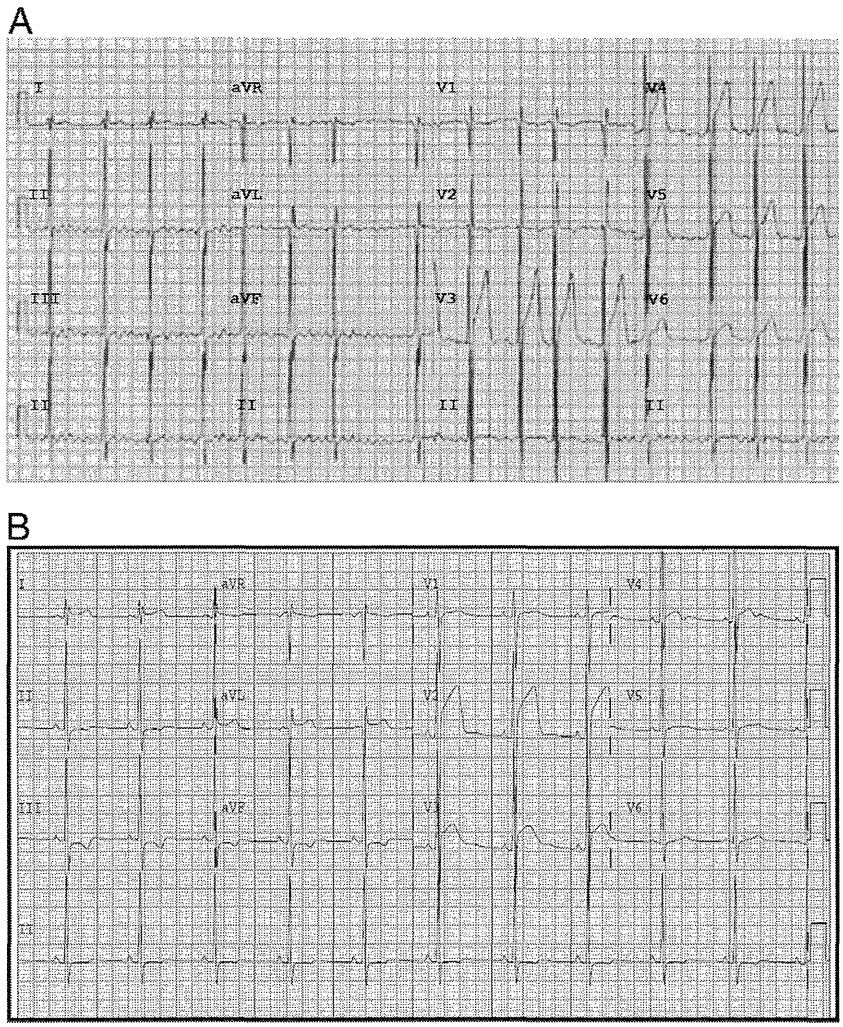

Figure 3 **Atrial Fibrillation and the Short QT Syndrome in a 17-Year-Old Young Male Resulting in Conversion to Sinus Rhythm and Prolongation of the QT Interval With Antiarrhythmic Therapy**

(A) Twelve-lead ECG of a symptomatic 17-year-old young male with atrial fibrillation. There is a short QT interval (QT interval: 320 ms, QTc interval: 355 ms), peaked T waves, and early repolarization. **(B)** After treatment with dofetilide and digoxin, there was prolongation of the QT interval (QT interval: 380 ms, QTc interval: 380 ms). The patient remained asymptomatic and on sinus rhythm except for short bouts of atrial fibrillation.

women because of the QT prolonging effects of estrogen (29). A modified Gollob score may be useful in identifying patients at a higher risk of clinical events and may prove useful for risk stratification, although larger cohort studies are necessary. Although ICD therapy proved useful in some patients, it was fraught with inappropriate shocks. One of 2 appropriate ICD shocks occurred despite a low dose of quinidine. Quinidine monotherapy did not prove to be effective in treating atrial fibrillation.

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Letter to the Editor

SCN5A mutation associated with ventricular fibrillation, early repolarization, and concealed myocardial abnormalities ☆

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There is increasing evidence that early repolarization or J-wave in the inferolateral leads is associated with an increased risk of ventricular fibrillation and sudden cardiac death [1]. Mutations in ATP-sensitive potassium channel gene *KCNJ8* and L-type calcium channel genes including *CACNA1C*, *CACNB2B*, and *CACNA2D1* have been associated with idiopathic ventricular fibrillation with early repolarization [2,3]. Furthermore, we have recently identified mutations in *SCN5A*, which encodes the predominant cardiac sodium channel α subunit, in patients with idiopathic ventricular fibrillation who had early repolarization in the inferior leads and right precordial leads [4]. Mutations in *SCN5A* have also been associated with cardiomyopathy and concealed myocardial abnormalities [5–7]. Here, we describe a case with a mutation in *SCN5A* who had early repolarization in the inferior leads but not in the right precordial leads, ventricular fibrillation, and structural myocardial alteration.

Genetic testing was performed for mutations in ion channel genes including *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, and *KCNJ8*. Mutations identified were screened in 200 ethnically matched controls in our institutions and 5400 individuals on the Exome Variant Server of NHLBI GO Exome Sequencing Project (http://evs.gs.washington.edu/evs/). The functional effects of mutations were assessed using PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/). Right ventricular endomyocardial biopsy sample was stained with hematoxylin-eosin and Masson's trichrome, and examined by light microscopy. Immunostainings for N-cadherin and plakoglobin were also performed in the endomyocardial sample.

A novel missense mutation R1023C in *SCN5A* was identified in a 28-year-old Japanese man (Fig. 1A). The variant occurs at a residue within the highly conserved cytoplasmic linker between domains two and three (Fig. 1B and C). The mutation was absent in 200 controls. There was no variant affecting R1023 in *SCN5A* in 5400 individuals on NHLBI GO Exome Sequencing Project server, suggesting the pathogenicity of the mutation. The mutation was predicted to have damaging effects on protein functions by PolyPhen-2. The patient lost consciousness suddenly without any prior symptoms while lying on a bed after taking dinner. Ventricular fibrillation was recorded and electrical shock was delivered to restore sinus rhythm by emergency medical services. The physical examination and echocardiography were normal. His electrocardiogram showed prolongation of the PR interval and early repolarization in leads II, III, and aVF (Fig. 1D). A diagnostic type 1 Brugada ECG was not seen spontaneously or after the administration of sodium channel blocker pilsicainide (Fig. 1E). Pilsicainide attenuated early repolarization. During electrophysiologic study, His-ventricular interval was 51 ms and ventricular fibrillation was repeatedly induced by two extrastimuli performed from the right ventricular outflow tract (Fig. 1F). Although coronary angiogram revealed no significant stenosis, coronary spasm was provoked in the right and left coronary arteries by intracoronary administration of acetylcholine. Right ventricular endomyocardial biopsy revealed disarrangement of cardiomyocytes and intestinal fibrosis (Fig. 2A and B). Immunohistochemical analysis did not reveal any abnormalities of expression patterns of plakoglobin and cadherin, that are often affected in arrhythmogenic right ventricular cardiomyopathy (Fig. 2C and D). Left ventriculography, delayed enhanced cardiac magnetic resonance

☆ Disclosures: None.

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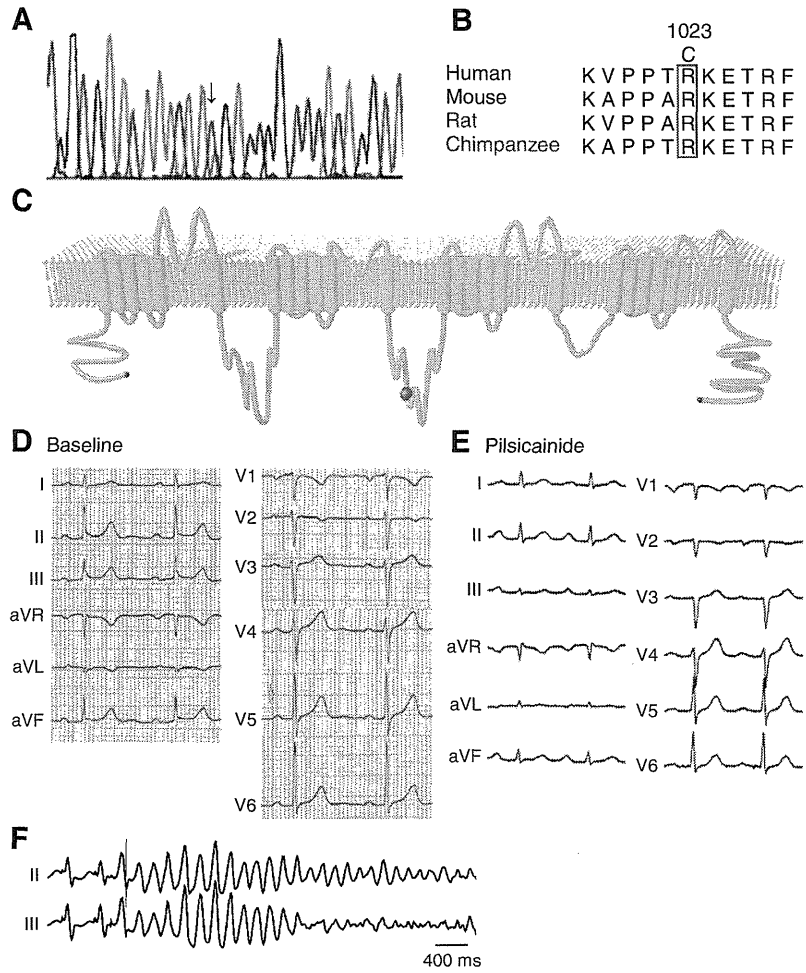

Fig. 1. Genetic and clinical characteristics in a patient with ventricular fibrillation associated with early repolarization. A, The c.3067C→T mutation in *SCN5A* resulting in p.R1023C found in the patient. B, Alignment of amino acids of SCN5A channel across species showing the high conservation of R1023. C, Predictive topology of SCN5A channel. A red circle indicates the location of the mutation. D, Early repolarization was present in the inferior leads. The PR interval was prolonged (250 ms). E, Administration of pilsicainide did not cause J-point elevation or Brugada type electrocardiogram. F, During electrophysiologic study, ventricular fibrillation was repeatedly induced. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

imaging, and thallium/beta-methyliodophenyl pentadecaonic acid (BMIPP) myocardial scintigraphy were normal. He received implantable cardioverter defibrillator. The patient's family history was negative for syncope, sudden cardiac death, and epilepsy. During a follow-up of 8 years, he was free from arrhythmia recurrence or heart failure.

Loss-of-function mutations in *SCN5A* have been associated with the increased susceptibility to arrhythmia syndromes [8]. In our recent study, mutations in *SCN5A* have been identified in patients with idiopathic ventricular fibrillation who had early repolarization in the right precordial leads in addition to the inferior leads, suggesting the similarities to Brugada syndrome [4]. In this report, a novel mutation in *SCN5A* was identified in a patient who had early repolarization in the inferior leads, but not in the right precordial leads. His electrocardiograms did not show J-point elevation or Brugada electrocardiogram in the right precordial leads even after sodium channel blocker challenge, supporting our hypothesis that mutations in *SCN5A* are responsible for idiopathic ventricular fibrillation associated with early repolarization. Evidence that the mutation is predicted to substitute a highly conserved residue across the spices, resulting in altered sodium channel function, and that there is no variant affecting the residue in a large number of controls suggests the disease causative of the mutation. Another mutation R1023H in *SCN5A*, which affects the same residue, has been associated with Brugada syndrome, further supporting the functional importance of the residue [7].

Mutations in *SCN5A* have been associated with myocardial changes in addition to the increased arrhythmia susceptibility. *SCN5A* is one of the causative genes for dilated cardiomyopathy [5], and using mice expressing the human *SCN5A* mutation associated with dilated cardiomyopathy, we have recently shown that reducing cardiac sodium current is the pathogenic mechanism for cardiomyopathy phenotype [9]. In patients with Brugada syndrome who carry a mutation in *SCN5A*, dilatation and contractile dysfunction of both ventricles have been revealed by cardiac magnetic resonance imaging, and concealed myocardial abnormalities have been frequently identified by endomyocardial biopsy [6,7]. In our patient heterozygously carrying the R1023C *SCN5A* mutation, histology showed myocardial abnormalities and intestinal fibrosis. Furthermore, the R1023H *SCN5A* mutation has been associated with cardiomyopathic changes and aneurysms in both ventricles, suggesting that R1023 may have a critical role in cardiac function in addition to that in electrophysiology [7]. Although the high frequency of inferolateral early repolarization in right ventricular arrhythmogenic cardiomyopathy has been reported [10], cardiac magnetic resonance imaging, histology, and immunostaining for plakoglobin were negative for diagnosis of right ventricular arrhythmogenic cardiomyopathy in our patient.

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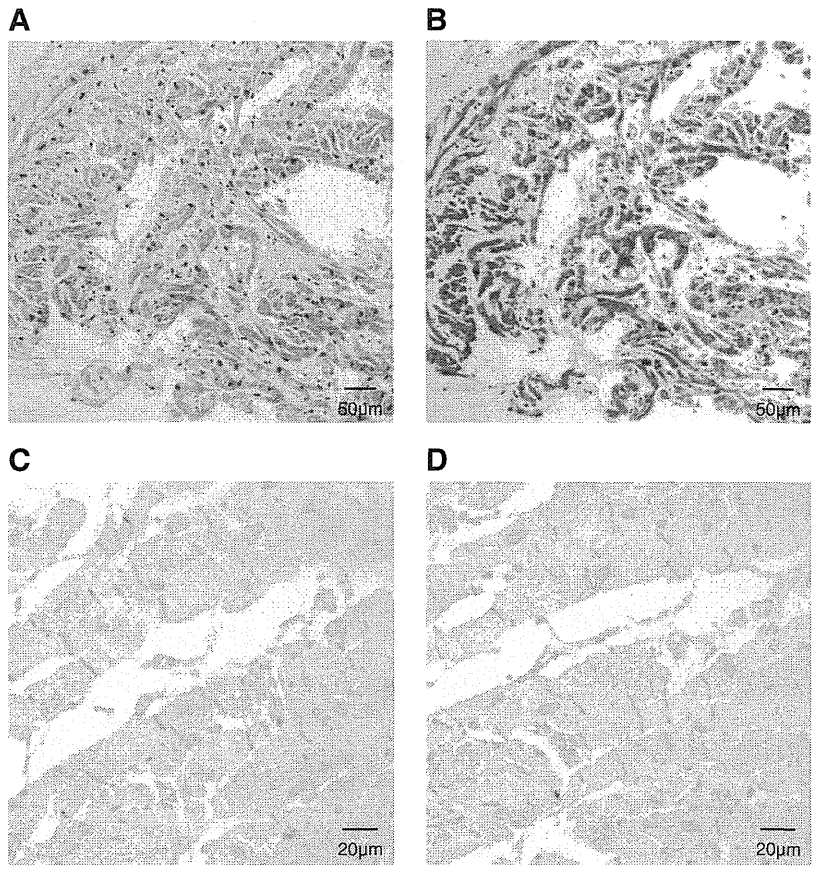

Fig. 2. Photomicrographs of right ventricular endomyocardial biopsy shows disarrangement of cardiomyocytes and intestinal fibrosis (A, hematoxylin and eosin; B, Masson's trichrome). Immunohistochemistry shows normal expressions of (C) plakoglobin and (D) N-cadherin.

In conclusion, our findings support the hypothesis that cardiac sodium channel dysfunction is associated with early repolarization, arrhythmia susceptibility, and myocardial degeneration.

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IR between 2008 and 2011 in groups A, B and C. In group D, there was a significant increase in the mean value of log-transformed HOMA-IR between 2008 and 2011. In contrast, there were no significant differences in the mean values of BMI and WC between 2008 and 2011 in group D (Table 1).

In this study, HOMA-IR significantly increased in all groups (continuous exercise, no exercise, sopped habitual exercise and began habitual exercise), and a significant change in BMI and WC was observed in groups with continuous exercise, no exercise, and sopping habitual exercise, However, no significant change in BMI and WC was observed in subjects who began habitual exercise. Exercise is important to avoid obesity and metabolic syndrome. The author speculates that HOMA-IR, BMI and WC increase by aging, although the absolute value of each indicator is different by exercise. As presented in Table 1, increase of BMI and WC by aging is suppressed for subjects who began habitual exercise, and the significant level of their increase in HOMA-IR by aging is relatively small compared with data from other three groups. Longer follow-up study is needed to observe the further results.

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Clinical characteristics and risk of arrhythmia recurrences in patients with idiopathic ventricular fibrillation associated with early repolarization

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Early repolarization or J-wave has generally been considered benign for decades. However, since we and others have recently reported that early repolarization in the inferior and/or lateral leads of the 12-lead electrocardiogram is associated with pathogenesis in idiopathic ventricular fibrillation [1,2], there has been an increasing interest in the disorder. This study aimed to investigate the clinical and genetic characteristics and to identify risk factors for arrhythmia events in patients with idiopathic ventricular fibrillation associated with early repolarization.

This study included 53 patients (46 men; age, 44±17 years) with idiopathic ventricular fibrillation and early repolarization who were referred to our institutions due to ventricular fibrillation events. All patients gave written informed consent prior to the genetic and clinical investigations. Patients were diagnosed with idiopathic ventricular fibrillation if they had no structural heart disease as identified using echocardiography, coronary angiography, and left ventriculography. Early repolarization was defined as an elevation of

Table 1
Clinical and electrocardiographic characteristics of 53 patients.

Male sex, N (%)	46 (87%)
Age, years	44 ± 17
Family history of sudden death, N (%)	7 (13%)
Activity at initial cardiac arrest, N (%)	
Sleep	14 (26%)
Rest	12 (23%)
Physical effort	10 (19%)
Other activities	17 (32%)
Atrial fibrillation, N (%)	12 (23%)
History of electrical storm,[a] N (%)	9 (17%)
Inducible ventricular fibrillation	15/31 (48%)
Mutation in *SCN5A*, N (%)	4/29 (14%)
Electrocardiography	
Heart rate, beats/min	63 ± 9
PR interval, ms	175 ± 34
QRS duration, ms	95 ± 14
QT interval, ms	384 ± 29
Corrected QT interval, ms[b]	389 ± 25
Prolonged PR interval ≥200 ms, N (%)	12 (23%)
Prolonged QRS duration ≥120 ms, N (%)	3 (6%)
Location of early repolarization,[c] N (%)	
Inferior	37 (70%)
Lateral	37 (70%)
Right precordial	11 (21%)
Multiple locations of early repolarization	28 (53%)

[a] An electrical storm was defined as ≥3 episodes of VF within 24 h.
[b] Corrected QT interval was calculated with Bazett's formula.
[c] Some patients had early repolarization in multiple locations.

the J-point, either as QRS slurring or notching of ≥0.1 mV in ≥2 consecutive leads in the 12-lead electrocardiogram [1]. Patients were excluded if they had a short QT interval (corrected QT interval using Bazett's formula <340 ms) or a long QT interval (corrected QT interval >440 ms). All patients received a sodium channel blocker challenge, and patients who met the diagnostic criteria for Brugada syndrome at baseline or after sodium channel blocker challenge were excluded [3]. Genetic testing was performed for mutations in ion channel genes including *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, and *KCNJ8*, as previously described [4]. The contribution of variables to risk of arrhythmia recurrences was tested with Cox proportional-hazards models using SPSS, version 12.0 (SPSS Inc, Chicago, IL). A two-sided $P<0.05$ was considered statistically significant. Values are expressed as mean ± SD or number (percentage).

The cardiac arrest events occurred during sleep or at rest in about half of the patients (Table 1). An electrical storm defined as ≥3 episodes of ventricular fibrillation within 24 h was observed in 8 patients (21%). A family history of sudden cardiac death was reported in 7 patients (18%). In the 12-lead electrocardiogram, early repolarization was frequently present in the inferior leads and in the lateral leads. In more than half of the patients, early repolarization was found in multiple locations. Although the initial report has described inferolateral early repolarization [1], early repolarization, which is different from Brugada type electrocardiogram, was also present in the right precordial leads in 11 patients (21%). Conduction disease, mostly prolongation of the PR interval, was present in 15 patients (28%). Mutations in *SCN5A* were identified in 4 unrelated patients. Among 46 patients who were followed ≥6 months, arrhythmia recurred in 10 patients (22%) during a follow up of 6.0 ± 5.7 years (incidence, 5.9 per 100 person-years [95% confidence interval, 2.3–9.4]). In univariate analyses, age at arrhythmia onset, a family history of sudden death, and a history of electrical storm were associated with the increased risk of arrhythmia recurrences (Table 2). In multivariate analyses, age, family history, and electrical storm were associated with arrhythmia recurrences (Table 3). Gender, location of early repolarization, activity at the initial event, conduction disorder, and inducibility of ventricular fibrillation were not associated with the risk of arrhythmia recurrences.

Heritability of early repolarization has been reported in the general population [5], and as in other arrhythmia syndromes such as long QT syndrome and Brugada syndrome [6], ion channel genes are responsible for idiopathic ventricular fibrillation associated with early repolarization [4,7–9]. However, compared to the frequency of a positive family history of sudden death, mutations in ion channel genes were less commonly identified in this study similarly to a previous study [8], suggesting that most of the causative genes are missing. Early repolarization is augmented after a pause, and it is attenuated by exercise and isoproterenol, a β-adrenergic agonist [1,10]. Therefore, vagal stimulation has been considered to increase arrhythmia susceptibility. However, in this study, arrhythmia events occurred not only during rest or sleep but also during exercise and daily activity consistent with a previous study [1], although a high

Table 2
Risk factors for arrhythmia recurrence, univariate models.

	Arrhythmia recurrence N = 10	No arrhythmia recurrence N = 36	Hazard ratio (95% CI)	P-value
Male sex, N (%)	8 (80)	33 (89)	1.49 (0.31–7.04)	0.62
Age, years	45 ± 17	47 ± 15	1.71 (1.06–2.77)[a]	0.03
Family history of sudden death, N (%)	3 (30)	2 (5)	4.02 (1.03–15.76)	0.04
Sleeping/rest at initial cardiac arrest, N (%)	6 (60)	17 (46)	2.29 (0.64–8.23)	0.20
Atrial fibrillation, N (%)	4 (40)	7 (19)	2.19 (0.62–7.75)	0.23
History of electrical storm, N (%)	6 (60)	2 (5)	15.87 (3.87–65.05)	<0.001
Inducible ventricular fibrillation	3 (60)	11 (48)	1.36 (0.22–8.40)	0.74
Mutation in *SCN5A*, N (%)	1/8 (13)	3/21 (14)	1.00 (0.13–7.91)	0.99
Electrocardiography				
Heart rate, beats/min	63 ± 9	62 ± 10	1.30 (0.69–2.44)[b]	0.41
PR interval, ms	174 ± 35	176 ± 33	0.93 (0.77–1.12)[b]	0.43
QRS duration, ms	95 ± 14	96 ± 14	0.88 (0.53–1.46)[b]	0.63
Corrected QT interval, ms	390 ± 25	388 ± 27	1.20 (0.94–1.53)[b]	0.14
Conduction disorder[c]	3 (30)	11 (30)	1.32 (0.34–5.16)	0.69
Location of early repolarization, N (%)				
Inferior	6 (60)	28 (76)	0.42 (0.12–1.51)	0.18
Lateral	8 (80)	25 (68)	1.78 (0.38–8.41)	0.46
Right precordial	3 (30)	8 (22)	1.64 (0.42–6.48)	0.48
Multiple locations of early repolarization	5 (50)	21 (57)	0.73 (0.21–2.54)	0.63

[a] Per 10 unit decrement.
[b] Per 10 unit increment.
[c] Conduction disorder includes prolonged PR interval and prolonged QRS duration.

Table 3
Risk factors for arrhythmia recurrence, multivariate models.

	Hazard ratio (95% CI)	P-value
Male sex, N (%)	0.74 (0.09–6.23)	0.78
Age, years	1.83 (1.08–3.11)[a]	0.03
Family history of sudden death, N (%)	6.92 (1.16–41.12)	0.03
History of electrical storm, N (%)	16.06 (3.43–75.15)	<0.001

[a] Per 10 unit decrement.

incidence of cardiac arrest during the nocturnal period has been reported [11]. The heterogenic genetic background may explain the various triggers of the arrhythmia events.

It is important to assess risk of arrhythmia recurrences for appropriate management in patients with arrhythmia syndromes. In a recent population-based study, middle-aged individuals with inferior early repolarization, but not those with lateral early repolarization, have been shown to have an elevated risk of cardiac death [12]. In another study, the risk of electrical storm is increased in patients with idiopathic ventricular fibrillation who have early repolarization in both of the limb leads and the precordial leads [13,14]. However, in our study, the location or the number of leads where early repolarization occurred was not associated with the increased risk of arrhythmia recurrences. The amplitude and morphology of early repolarization have been associated with the risk of arrhythmia events [12,15,16], but it may be difficult to use for risk stratification because of variability of early repolarization [1].

Among clinical characteristics, age at arrhythmia onset, a history of electrical storm of ventricular fibrillation, and a family history of sudden death were associated with the increased risk of arrhythmia recurrences in this study. It seems reasonable that patients with severe diseases such as young onset and repetitive arrhythmias are at high risk for arrhythmia recurrences. In fact, a history of electrical storm has been associated with a high frequency of arrhythmia events in Brugada syndrome, another form of idiopathic ventricular fibrillation [17]. However, inconsistent with our results, a previous study has indicated that the frequency of family history is similar between patients with multiple episodes of ventricular fibrillation and those without [1], although the reason of this discrepancy is unclear.

In conclusion, we have shown clinical and electrocardiographic characteristics in idiopathic ventricular fibrillation associated with early repolarization and have identified the risk factors for arrhythmia recurrences.

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Regulatory mechanisms underlying the modulation of GIRK1/GIRK4 heteromeric channels by P2Y receptors

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Abstract The muscarinic K^+ channel ($I_{K,ACh}$) is a hetero-tetramer composed of GIRK1 (Kir3.1) and GIRK4 (Kir3.4) subunits of a G protein-coupled inwardly rectifying channel, and plays an important role in mediating electrical responses to the vagal stimulation in the heart. $I_{K,ACh}$ displays biphasic changes (activation followed by inhibition) through the stimulation of the purinergic P2Y receptors, but the regulatory mechanism involved in these modulation of $I_{K,ACh}$ by P2Y receptors remains to be fully elucidated. Various P2Y receptor subtypes and GIRK1/GIRK4 (I_{GIRK}) were co-expressed in Chinese hamster ovary cells, and the effect of stimulation of P2Y receptor subtypes on I_{GIRK} were examined using the whole-cell patch-clamp method. Extracellular application of 10 μM ATP induced a transient activation of I_{GIRK} through the $P2Y_1$ receptor, which was completely abolished by pretreatment with pertussis toxin. ATP initially caused an additive transient increase in ACh-activated I_{GIRK} (via M_2 receptor), which was followed by subsequent inhibition. This inhibition of I_{GIRK} by ATP was attenuated by co-expression of regulator of G-protein signaling 2, or phosphatidylinositol-4-phosphate-5-kinase, or intracellular phosphatidylinositol 4,5-bisphosphate loading, but not by the exposure to protein kinase C inhibitors. $P2Y_4$ stimulation also persistently suppressed the ACh-activated I_{GIRK}. In addition, I_{GIRK} evoked by the stimulation of the $P2Y_4$ receptor exhibited a transient activation, but that evoked by the stimulation of $P2Y_2$ or $P2Y_{12}$ receptor showed a rather persistent activation. These results reveal (1) that $P2Y_1$ and $P2Y_4$ are primarily coupled to the G_q-phospholipase C-pathway, while being weakly linked to $G_{i/o}$, and (2) that $P2Y_2$ and $P2Y_{12}$ involve $G_{i/o}$ activation.

Keywords GIRK1/GIRK4 · P2Y receptors · I_{GIRK} · PIP_2 · Patch clamp · CHO

Abbreviations

ACh	Acetylcholine
$I_{K,ACh}$	Muscarinic K^+ channel
PLC	Phospholipase C
PKC	Protein kinase C
PIP_2	Phosphatidylinositol 4,5-bisphosphate
PTX	Pertussis toxin
PI4P-5K	Phosphatidylinositol-4-phosphate-5-kinase
CHO	Chinese hamster ovary
AC	Adenylyl cyclase
WT	Wild type
GFP	Green fluorescent protein
ATP	Adenosine triphosphate
UTP	Uridine triphosphate
RGS_2	Regulator of G-protein signaling 2
GIRK	G protein-activated inward rectifier K^+ channel

Jie Wu and Wei-Guang Ding have contributed equally to this work.

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Introduction

The muscarinic K^+ channel ($I_{K,ACh}$) is a heterotetramer that comprises Kir3.1 and Kir3.4 subunits (encoded by GIRK1 and GIRK4, respectively) of G protein-coupled inwardly rectifying channel. $I_{K,ACh}$ plays an important role in mediating negative inotropic, chronotropic, and dromotropic responses to the vagal neurotransmitter acetylcholine (ACh) in the heart [20]. Previous reports indicate that adenosine 5′-triphosphate (ATP) produces dual effects on $I_{K,ACh}$: a transient activation followed by a persistent inhibition, in guinea pig atrial cells [13, 24, 44]. Like other neurotransmitters such as ACh [34, 35] and adenosine [21, 24], ATP activates the membrane receptors coupled to the $I_{K,ACh}$ channel proteins through a pertussis toxin (PTX) sensitive heterotetrameric G protein, thus leading to the dissociation of the heterotrimeric G-protein complex into its α and $\beta\gamma$ subunits that can interact with the channel and cause an increase in open-state probability of the channel [5, 24, 42]. Conversely, $I_{K,ACh}$ is persistently inhibited by ATP following the transient activation. Previous studies using guinea pig atrial cells [25, 44] demonstrated that the inhibition of $I_{K,ACh}$ by ATP is associated with activation of the P2Y receptors that are coupled to a PTX-insensitive G protein leading to activation of G_q-phospholipase C (PLC) signaling pathway. However, the modulatory mechanism underlying the inhibition of $I_{K,ACh}$ by P2Y receptor subtype stimulation has yet to be fully elucidated.

P2Y receptors belong to G protein-coupled P2 purinergic receptors that can be activated by purine or pyrimidine nucleotides. Eight P2Y receptor subtypes ($P2Y_{1,\ 2,\ 4,\ 6,\ 11,\ 12,\ 13}$ and $_{14}$) have been cloned from mammalian cells, and all of them are expressed in heart tissues and associated with the extracellular signaling pathway [3, 10, 30, 37]. Several studies have so far indicated that ATP elicits diverse functional responses in various types of tissues including cardiac cells [10, 26, 27]. However, the functional coupling correlates of the involved P2Y receptor subtypes in cardiac cells is still a topic of debate and remains difficult in native cell due to the restricted availability of subtype-selective ligands and/or blockers.

The present study was undertaken to further explore the inhibitory mechanism of $I_{K,ACh}$ using Chinese hamster ovary (CHO) cells heterologously co-expressed with GIRK1/GIRK4 and different P2Y receptor subtypes. The result reveals that stimulation of $P2Y_1$ or $P2Y_4$ receptor subtype markedly inhibited ACh-activated I_{GIRK} currents by G_q-PLC pathway signaling, although the two receptors were also weakly coupled to $G_{i/o}$ protein to transiently activate I_{GIRK}. On the contrary, $P2Y_2$ and $P2Y_{12}$ receptor subtypes were coupled with $G_{i/o}$ protein to persistently activate I_{GIRK}.

Materials and methods

Heterologous expression of cDNA in CHO cells

Full-length cDNA encoding rat GIRK1 subcloned into the pCI expression vector was a kind gift from Dr. LY Jan (Department of Physiology and Biochemistry, Howard Hughes Medical Institute, University of California). Full-length cDNA encoding rat GIRK4 subcloned into the pCDNA3 expression vector was kindly provided by Dr. JP Adelman (Department of Molecular and Medical Genetics, Oregon Health and Sciences University). Full-length cDNA encoding rat type I phosphatidylinositol-4-phosphate-5-kinase (PI4P-5K) subcloned into pCDNA3 expression vector was generously donated by Dr. Y Oka (Third Department of Internal Medicine, Yamaguchi University School of Medicine, Japan). Full-length cDNA encoding human M_2, α_1, $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_{12}$ receptors and regulator of G protein signaling 2 (RGS_2) subcloned individually into $pCDNA3.1^+$ were all obtained from the University of Missouri–Rolla cDNA Resource Center (Rolla, MO). The experimental cDNAs were transiently transfected into CHO cells together with green fluorescent protein (GFP) cDNA [0.5 μg GFP +1 μg GIRK1+1 μg GIRK4+1 μg P2Ys (or α_1)+1 μg M_2] by using Lipofectamine (Invitrogen Life Technologies, Inc. Carlsbad, CA, USA) according to the manufacturer's instructions. Two micrograms of PI4P-5K or RGS_2 cDNA was co-transfected in subset experiments. The transfected cells were cultured in DMEM/Ham's F-12 medium (Nakalai Tesque Inc., Kyoto, Japan) supplemented with 10% fetal bovine serum (GIBCO) and antibiotics (100 U/ml penicillin and 100 μg/ml streptomycin) in a humidified incubator with 5% CO_2 and 95% air at 37°C. The cultures were passaged every 4 to 5 days using a brief trypsin–EDTA treatment. The trypsin-EDTA treated cells were seeded onto glass coverslips in a petri dish for later patch-clamp experiments.

Solutions and chemicals

The pipette solution contained (mM) 70 potassium aspartate, 40 KCl, 10 KH_2PO_4, 1 $MgSO_4$, 3 Na_2-ATP (Sigma), 0.1 Li_2-GTP (Roche Diagnostics GmbH, Mannheim, Germany), 5 EGTA, and 5 Hepes, and pH was adjusted to 7.2 with KOH. The extracellular solution contained (mM) 140 NaCl, 5.4 KCl, 1.8 $CaCl_2$, 0.5 $MgCl_2$, 0.33 NaH_2PO_4, 5.5 glucose, and 5.0 Hepes, and pH was adjusted to 7.4 with NaOH. Agents added to the extracellular solutions included ACh (Sigma Chemical Co., St. Louis, MO, USA), ATP (Sigma), uridine triphosphate (UTP, Sigma), bisindolylmaleimide 1 (BIS-1, Sigma), chelerychrine (CHE, Sigma), and phenylephrine (PHE, Sigma). ACh, ATP, UTP, and PHE were dissolved in the distilled water to yield 10 mM or 30