Disorders of Cardiac Repolarization
— Long QT and Short QT Syndromes —

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The long and short QT syndromes are heterogeneous diseases characterized by abnormal ventricular repolarization and episodes of syncope and/or life-threatening cardiac arrhythmias. Several disease-causing genes have been identified, including those encoding cardiac ion channel-composing proteins. The clinical determination of genotype offers a striking benefit: diagnosis, prediction of clinical phenotype, risk stratification, and therapy. Genetic testing is of special importance for the genotyped patient’s family members to prevent unexpected cardiac death. By means of recently advanced methodology in molecular genetics and electrophysiology it is expected that novel genes responsible for these disease entities will be identified. (*Circ J 2007; Suppl A: A-50–A-53*)

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The long QT syndrome (LQTS) is a primary electrical disease characterized by an abnormality in myocardial repolarization that leads to the prolongation of QT interval, morphological changes in T waves and torsades de points type of ventricular tachycardia on the surface ECG (*Fig 1*). The association between prolongation of the QT interval and cardiac sudden death was implicated soon after the introduction of ECG recording in the clinical setting. In contrast, the short QT syndrome (SQTS) has been ignored for a long time and the first report relating short QT interval with an increased risk for ventricular fibrillation and cardiac sudden death appeared in 2000.

In the late 1990s, the advent of the molecular genetic era provided new insights into the mechanisms underlying LQTS, showing that mutations in genes encoding ion channels or their accessory proteins and other membrane proteins cause the disease. These genetic variants alter the function of ion channels governing the repolarization process of the ventricle. To date, 10 distinct genes responsible for LQTS have been identified, including those for Andersen (LQT7) and Timothy (LQT8) syndromes on chromosomes 11q15.5 (*KCNQ1*; LQT1), 7q35-36 (*KCNH2*; LQT2), 3p21 (*SCN5A*; LQT3), 4q25-27 (*ANKB*; LQT4), 21q22 (*KCNE1*; LQT5), 21q22 (*KCNE2*; LQT6), 17q23 (*KCNJ2*; LQT7), 12p13.3 (*CACN1c*; LQT8), 3p25 (*CAV3*; LQT9) and 11q23.3 (*SCN4B*; LQT10)*Table 1*).

In 2004, Brugada et al* reported the first mutation associated with SQTS. It was a *KCNH2* mutation, N588K, involving a substitution of lysine for asparagine in position 588 of *KCNH2*. Since then 3 disease-causing genes for SQTS have been identified, including genes encoding cardiac ion channel-composing proteins on chromosomes 7q35-36 (*KCNH2*; SQT1)*14 11q15.5 (*KCNQ1*; SQT2)*15,16 and 17q23 (*KCNJ2*; SQT3)*17*Table 2*.

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LQTS

The estimated prevalence of LQTS in the general population is 1 in 5,000*18* During an ECG checkup of Japanese school pupils, its prevalence was 1 in 2,000*19* The disease is usually inherited as an autosomal dominant trait with incomplete penetrance and variable expression. LQTS has played a key role as a “Rosetta Stone” in the understanding of the general mechanism of ion channel disease. *Fig 2* is a schematic explanation of how a functional alteration in ion channels causes prolongation or abbreviation of the QT intervals on ECG. Electrophysiological assays using a heterologous expression system have shown that some mutations in the aforementioned genes induce a gain or loss-of-function in a respective ion channel and thereby modulate the repolarization process. For example, a reduction in outward Na+ or Ca2+ channel currents would delay repolarization of the action potential, and therefore prolong the QT interval on the surface ECG.

Now that we know most of the genes responsible for repolarization disorder and the resultant clinical phenotypes, molecular testing for mutation screening of disease genes has become feasible. The availability of genetic testing offers the possibility of identifying genetically affected individuals who are, in other words, potential victims of cardiac sudden death. The clinical determination of genotype offers a striking benefit, including diagnosis (family screening and preclinical diagnosis), prediction of clinical phenotype (penetrate, gene-specific clinical manifestations), risk stratification (assessment of malignant vs benign mutations), clinical and genetic counseling (restriction of physical activity, family planning etc), and therapy (prevention of sudden death by implantable defibrillator (ICD)).

One of the most important aims of genetic testing is to achieve a preclinical diagnosis of LQTS, particularly in family members with incomplete disease expression or in patients with a *forme fruste* phenotype. Molecular genetic examination does strengthen the clinically overt or suspicious diagnosis. However, the genetic variant identified in
an individual does not directly explain the clinical phenotypes. Mutation carriers may have either no disease phenotype (incomplete penetrance) or present with various degree of clinical manifestations, ranging from asymptomatic with relatively prolonged QT interval and no arrhythmias to those experiencing cardiac arrest even under β-blocker therapy or after ICD implantation. Thus, inheriting a mutation does not always mean that the individual will present a clinical manifestation of LQTS, but apparently “healthy” mutation carriers have inherited the risk for developing the clinical phenotype. Because congenital LQTS affects the young, all efforts should be made to genotype them for appropriate management of both the patient and the family members who may be at highest risk of sudden death. These efforts are justified by timely therapy with β-blockers and/or ICD in association with careful clinical follow-up to avoid hypokalemia, bradycardia and drugs that prolong the QT interval\textsuperscript{125–27} and family education, including the use of an automated electrical defibrillator at home.

Through the elucidation of pathophysiological mechanisms underlying the congenital LQTS during the past decade, we have witnessed the most rapid and fruitful progress in powerful scientific tools: molecular genetics and cellular physiology. We are expecting to identify novel additional genes responsible for the disease.
SQTS

SQTS constitutes a new primary electrical abnormality associated with sudden cardiac death.28 The family first reported by Gussak et al.28 consisted of patients with a constantly-shortened QT interval and paroxysmal atrial fibrillation, and one member had died of sudden cardiac death.28 Subsequently, the short QT interval was shown to be associated with sudden cardiac death without structural heart disease.14–17 The syndrome is now considered as a new cardiac ion channel disease.1,28–32

The diagnostic criteria for SQTS currently include (1) QTc interval <330 ms, (2) ventricular tachycardia without structural heart disease, and (3) a family history of sudden cardiac death.33 Atrial fibrillation is a characteristic complication.15,33 and Giustetto et al.34 demonstrated that 31% of patients with this syndrome had documented atrial fibrillation, even in young subjects. His group also reported that SQTS could be related to death in early infancy.34 Although arrhythmogenic triggers in SQTS are incompletely understood, bradyarrhythmia may predispose to ventricular tachycardia because the shortened QT interval would become obvious at a lower heart rate.33 The induction rate of ventricular tachycardia during electrophysiological examination is apparently very high in SQTS patients33 but the issue remains unclear because information is still limited.

Three responsible genes have been reported to date (Table 2), indicating that SQTS has a genetically heterogeneous background. Brugada et al.14 identified the first missense mutation in KCNH2, N588K, which causes a substitution of lysine for asparagine in position 588 located in the S5-pore loop (SQTS type 1, SQT1). KCNH2 is known as the gene responsible for LQT2, but in contrast to the case in LQTS, N588K in SQTS was found to cause a remarkable gain-of-function in Ifκs.

The second mutation in SQTS was found in KCNQ1, which encodes the slow component of the delayed rectifier potassium channel (Ifκs) (SQTS type 2, SQT2)16 KCNQ1 is also a gene responsible for LQT3 (LQT1). A missense mutation (V307L) was identified in an index patient with short QT interval and ventricular fibrillation, and it causes a substitution of leucine for valine in position 307 of the KCNQ1 pore site. Another missense KCNQ1 mutation (V141M) was found in a baby with both shortened QT interval and atrial fibrillation.15

The latest mutation in SQTS was identified in KCNJ2 (type 3, SQTS).17 Again, KCNJ2 is responsible for Andersen syndrome (LQT7), encoding the inward rectifier K channel (Iκ1). The missense KCNJ2 mutation (D172N), causing a substitution of aspartic acid for asparagine in position 172, was shown to induce a gain-of-function of Iκ1. Surface ECG features differ among the 3 subtypes of SQTS. In fact, the T wave in SQT3 associated with the KCNJ2 mutation is asymmetrical, with a remarkably rapid terminal phase.17

All genetic mutations in SQTS cause a gain of the outward K currents governing the ventricular repolarization, and therefore shortening the QT interval (Table 2). However, the mechanism of inducing the “gain-of-function” differs: (1) impaired inactivation in SQT114,35 (2) accelerated activation and hyperpolarized shift of the activation curve15 or faster activation16 in SQT2, and (3) larger outward currents and depolarized shift of the peak current in SQT3.37

Regarding the arrhythmogeneity in SQTS, Antzelevitch et al. have presented the first experimental evidence for the role of transmural dispersion of repolarization (TDR).16 They used a pharmacological method with pinacidil, a strong activator of the cardiac ATP-sensitive K channel (IκATP), to mimic a “gain-of-function” in outward K currents in a canine arteriofemoral wedge preparation. Pinacidil caused a heterogeneous abbreviation of the action potential duration in 3 principal cell types spanning the ventricular wall, indicating that TDR could lead to an increased vulnerability to polymorphic ventricular tachycardia.

ICD implantation is the first-line therapy for SQTS patients.37 Quinidine can induce a gain of function in the QT interval and protect against ventricular fibrillation in SQT1 by suppressing Iκc, whereas class Ic and III antiarrhythmic drugs (eg, flecainide, sotalol, and ibutilide) are ineffective against ventricular fibrillation.38

Clinical information on SQTS remains scarce because the patients are very rare compared with those with LQTS. However, there is no doubt that SQTS is strongly associated with an abnormality of the genes encoding cardiac ion channels. Strategies used in the study of LQTS would therefore be useful for further clarification of SQTS.

Note:

After submitting the manuscript, a report on novel mutations causative of SQTS appeared regarding cardiac L-type Ca channel genes: CACNB2b and CACNA1C encoding ɑ1 and ɑ2s subunits of Ca channel39 (SQT 4 and 5 in Table 2). Functional analyses revealed that 2 mutations of CACNA1C (A39V and G490R) and one CACNB2b (S481L) caused a loss-of-function in Ca channel currents. The probands’ phenotypes carrying these mutations of Ca channel genes were characterized by cardiac sudden death, atrial fibrillation and Brugada type ECG patterns.

References

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