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, clinical and genetic counseling, and introduction of 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)

Key Words: Long QT syndrome; Short QT syndrome

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 pointes type of ventricular tachycardia on the surface ECG (Fig 1).^{1,2} 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.³ 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 2000.⁴

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)^{5–13} (Table 1).

In 2004, Brugada et al¹⁴ 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).

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 1,200.¹⁹ The disease is usually inherited as an autosomal dominant trait with incomplete penetrance and variable expression.²⁰ 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 K channel currents or an increase in the inward 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 (penetrance, gene-specific clinical manifestations²¹), risk stratification (assessment of malignant vs benign mutations²²), 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 expression²⁰ or in patients with a *forme fruste* phenotype.^{23,24} Molecular genetic examination does strengthen the clinically overt or suspicious diagnosis. However, the genetic variant identified in

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Fig 1. Distinctive ECG features and family tree associated with long QT syndrome (LQTS). (A) Torsades de pointes type of ventricular tachycardia in a patient with genotyped LQT2. Torsade de pointes frequently appeared during sleep. (B) Family analysis associated with the patient. The proband (arrow) was diagnosed as LQT2 with the G572S mutation, which is located in the S5-pore site for the KCNH2 channel. Heterozygous mutation carriers are indicated by filled symbols, and the numbers below the symbols are the QTc interval at rest. Although the index patient and her father, both carrying the G572S mutation, had syncope at rest, the other 2 mutation carriers remained asymptomatic. The proband had 2 uncles, 1 of whom (open symbol) was genetically negative, and the other (half-tone filled) was clinically LQTS, although the genetic data were not available.

Table 1 Gentic Classification of LQTS

Subtypes	Genetic locus	Genes	Ion channel
<i>Congenital LQTS (Romano-Ward syndrome)</i>			
LQT1	11 (11p 15.5)	KCNQ1	<i>I_{Ks}</i>
LQT2	7 (7q 35-36)	KCNH2	<i>I_{Kr}</i>
LQT3	3 (3p 21-24)	SCN5A	<i>I_{Na}</i>
LQT4	4 (4q 25-27)	Ankyrin-B	[Ca ²⁺] _i
LQT5	21 (21q 22.1-q22.2)	KCNE1	<i>I_{Ks}</i>
LQT6	21 (21q 22.1-q22.2)	KCNE2	<i>I_{Kr}</i>
LQT7	17 (17q 23)	KCNJ2	<i>I_{K1}</i>
LQT8	12p 13.3	CACNA1C	<i>I_{Ca-L}</i>
LQT9	3 (3p 25)	CAV3	<i>I_{Na}</i>
LQT10	11q 23.3	SCN4B	<i>I_{Na}</i>
<i>Congenital LQTS (Jervell and Lange-Nielsen syndrome)</i>			
JLN1	11 (11p 15.5)	KCNQ1 (homozygous)	<i>I_{Ks}</i>
JLN2	21 (21q 22.1-q22.2)	KCNE1 (homozygous)	<i>I_{Ks}</i>

LQTS, long QT syndrome.

Table 2 Gentic Classification of SQTs

Subtype	Gene	Mutations	QTc	Functions	Reference
SQT1	KCNH2	N588K	286	Impaired inactivation of <i>I_{Kr}</i>	14
SQT2	KCNQ1	V141M	AF	Accelerated activation of <i>I_{Ks}</i>	15
				Hyperpolarized shift of the activation curve	
		V307L	302	Faster activation	16
SQT3	KCNJ2	D172N	315	Larger <i>I_{K1}</i> currents	17
SQT4	CACNB2b	S481L	330–370	loss-of-function in L-type Ca channel	39
				Brugada phenotype	
SQT5	CACNA1C	A39V	346–360	loss-of-function in L-type Ca channel	39
		G490R		Brugada phenotype	

SQTs, short QT syndrome; AF, atrial fibrillation.

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^{25–27} 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.

Fig2. Schematic presentation of ion currents governing the action potential duration in the ventricle. Action potential duration (APD) varies depending on the subtle balance between inward and outward currents. An increase in the inward Na^+ and Ca^{2+} currents (blue and yellow arrows) or a decrease in the outward K^+ current (red arrow) prolongs the APD and causing long QT syndrome (Left panel). Conversely, an increase in the outward K^+ currents shortens the APD, causing short QT syndrome (Right panel).

SQTS

SQTS constitutes a new primary electrical abnormality associated with sudden cardiac death^{4,28}. The family first reported by Gussak et al⁴ consisted of patients with a constantly-shortened QT interval and paroxysmal atrial fibrillation, and one member had died of sudden cardiac death²⁸. 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^{11,28–32}.

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 death³³. Atrial fibrillation is a characteristic complication^{4,15,33} and Giustetto et al³⁴ 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 infancy³⁴. Although arrhythmogenic triggers in SQTS are incompletely understood, bradycardia may predispose to ventricular tachycardia because the shortened QT interval would become obvious at a lower heart rate³³. 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 al¹⁴ identified the first missense mutation in *KCNH2*, N588K, which causes a substitution of lysine for asparagines 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 *I_{Kr}*.

The second mutation in SQTS was found in *KCNQ1*, which encodes the slow component of the delayed rectifier potassium channel (*I_{Ks}*) (SQTS type 2, SQT2)¹⁶. *KCNQ1* is also a gene responsible for LQTS (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 fibrillation¹⁵.

The latest mutation in SQTS was identified in *KCNJ2* (type 3, SQT3)¹⁷. Again, *KCNJ2* is responsible for Andersen syndrome (LQT7), encoding the inward rectifier K channel (*I_{K1}*). 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 *I_{K1}*. 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 phase¹⁷.

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 SQT1^{14,35} (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 SQT3¹⁷.

Regarding the arrhythmogeneity in SQTS, Antzelevitch et al have presented the first experimental evidence for the role of transmural dispersion of repolarization (TDR)³⁶. They used a pharmacological method with pinacidil, a strong activator of the cardiac ATP-sensitive K channel (*I_{K-ATP}*), to mimic a “gain-of-function” in outward K currents in a canine arterially-perfused 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 patients³⁷. Quinidine can prolong the QT interval and protect against ventricular fibrillation in SQT1 by suppressing *I_{Kr}*, whereas class Ic and III antiarrhythmic drugs (eg, flecainide, sotalol, and ibutilide) are ineffective against ventricular fibrillation³⁸.

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 α_1 and α_2b 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.

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