REVIEW ARTICLE

Long QT Syndrome

LI ZHANG MD[1,2], ZAKIR SHAIK[1] MD, SERGIO DUBNER[3 MTSAC] MD, ANDRÉS RICARDO PÉREZ RIERA MD[4], EDGARDO SCHAPACHNIK[5] MD, GANXIN YAN MD PHD[1,6], PETER KOWEY MD[1,6]

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Address for reprints:
Li Zhang, MD
Director, Cardiovascular Outcomes Research
Main Line Health Heart Center
Lankenau Hospital Wynnewood, PA U.S.A.
Phone number: 1-484-476-2694 / Fax 1-484-476-1658
e-mail: ldlzhang@gmail.com

SUMMARY

Long QT syndrome (LQTS) is a heart rhythm disorder characterized by QT prolongation and T wave abnormalities associated with increased susceptibility to torsade de pointes (TdP) that can lead to cardiac events (CE: syncope, cardiac arrest and sudden death). The prevalence of congenital LQTS is estimated as 1:2500 caused by mutations of genes encoding or regulating cardiac sodium, potassium, and calcium ion channels. To date 14 subtypes including 12 in Romano-Ward syndrome and 2 in Jervell and Lange-Nielsen syndrome caused by 12 genes with >1200 mutations have been identified. Most of the known mutations encode potassium ion channels. The disease severity is influenced by the mutation type, location and ion channel biophysical properties. Clinically LQTS-related symptoms are related to age, gender and the degree of QT prolongation. The CE rate is the highest among teenagers and young adults. Females are more problematic than males. The longer QT interval, the higher is the CE rate. Among genotyped individuals LQT1-3 account for 90-95%. Gene-specific ECG phenotype is present in LQT1-3 and 7. The triggers to CEs also differ by genotype. Recognizing gene-specific clinical features and ECG patterns can improve diagnostic accuracy. Family screening, serial ECG follow-up, and stress testing are important not only for the diagnosis of probands, but also for identifying additional affected family members. As the mainstay therapy to all subtypes, β-blocker medication is the most effective to LQT1. Left cardiac sympathetic denervation (LCSD) is known to raise the threshold for ventricular fibrillation and has shown the promise to reduce the CE rate. The minimum invasive approach can provide safer and faster recovery than the traditional LCSD. Implantable cardioverter defibrillators (ICD) provide the best protection against life-threatening arrhythmias. However, risk stratification for ICD applications is necessary since up to 50% of LQTS never experience CEs in their life time. Acquired LQTS is much more common in the general population and females are more susceptible to QT prolonging drugs and electrolyte imbalance induced TdP. Removing the cause is the best way to redress acquired LQTS. Avoiding QT prolonging drugs and gene-specific triggers can lower the CE rate in congenital LQTS as well.

OUTLINE

From genes to patients, this article provides an overview of current understanding of long QT syndrome (LQTS) in both congenital and acquired forms. In the congenital form, 14 subtypes of LQTS including 12 in Romano-Ward syndrome and 2 in Jervell and Lange-Nielsen syndrome caused by 12 genes encoding cardiac sodium, potassium and calcium ion channel subunits are described. Among them LQT1-3 are the common genotypes that account for 90-95% of gene carriers. The clinical course, findings in genotype-phenotype correlation studies, diagnostic and treatment strategies are discussed. In the acquired form, several common causes especially drug-induced LQTS with the underpinning QT prolonging mechanism are provided. With better understanding of the natural course, improved diagnostic methodology/technology and effective therapeutics, the prognosis is optimistic. LQTS is treatable and sudden death can be prevented.

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Key words > Long QT syndrome - Sudden cardiac death - Arrhythmias, cardiac

[1] Main Line Health Heart Center, Lankenau Hospital, Wynnewood, Pennsylvania, USA
[2] Institute of Molecular Medicine, Peking University, Beijing, China
[3] Electrophysiology Service, Clínica and Maternidad Suizo Argentina, Buenos Aires, Argentina
[4] Electro-Vectorcardigraphic Section, ABC Faculty of Medicine, Foundation of ABC, São Paulo, Brazil
[5] Dr. Cosme Argerich Hospital, Buenos Aires, Argentina
[6] Jefferson University School of Medicine, Philadelphia, Pennsylvania, USA

MTSAC Full Member of the Argentine Society of Cardiology

Abbreviations >

AKAP	Akinase anchoring protein	**NMD**	Nonsense-mediated decay
ANKB	Ankyrin B	**nNos**	Neuronal nitric oxide synthase
APD	Action potential duration	**PKA**	Kinase A
AT-PASE	Adenosine triphosphatase	**PMLA4b**	Plasma membrane Ca-ATPhase subtype4b
ATS1	Type 1 Andersen-Tawil syndrome	**PP1**	Phosphatase 1
CAV3	Caveolin 3	**PUCs**	Premature ventricular contractions
CE	Cardiac events	**RWs**	Romano-Ward syndrome
DAD	Delayed-afterdepolarization	**SAH**	Subarachnoid hemorrhage
EAD	Early-after-depolarization	**TdP**	Torsade de Pointes
ICD	Implantable cardioverter defibrillator	**TDR**	Transmural dispersion of repolarization
JLN1	Type1 JLNS	**TS**	Timothy syndrome
JLN2	Type2 JLNN	**TS1**	Type-1TS
JLNS	Jervell and Lange-Nielsen syndrome	**TS2**	Type-2TS
LCSD	left cardiac sympathetic denervation	**VF**	ventricular fibrillation
LQTS	Long QT syndrome		

INTRODUCTION

Long QT syndrome (LQTS) is a heart rhythm disorder. (1-4) Patients with LQTS have a propensity to polymorphic ventricular arrhythmias, typically torsade de pointes (TdP). (5-10) In most cases TdP is self-terminating. However, under certain circumstances, TdP can deteriorate into ventricular fibrillation (VF), causing cardiac arrest and ultimately sudden death. (11) Physical and emotional stress can trigger life-threatening arrhythmias in LQTS. (12-14)

Collectively LQTS is categorized as a channelopathy (15-17) Channelopathies are diseases caused by disturbed function of ion channel subunits or the proteins that regulate them (18) Ion channels have specific ion selectivity and allow the passage of charged ions, such as sodium, potassium and calcium, across the cell membrane. The precision and timeliness of the passage of these charged ions mediated by their specific ion channel proteins provide the molecular biophysical basis for cardiac electrical activity. The P-QRS-T waves are the summations of cardiac ion channel activities registered on the body surface ECG (19-21) Expression of abnormal sodium, calcium, or potassium channels results in aberrant ionic fluxes that can delay ventricular repolarization, manifest as a prolonged QT interval (21) Investigations in LQTS has provided a wealth of information about fundamental mechanisms underlying human cardiac electrophysiology. LQTS can be divided into congenital and acquired forms.

I. Congenital LQTS

Most of congenital LQTS are familial. Very few are due to spontaneous de novo mutations or mosaic mutations. Cardiac events (CE: syncope, cardiac arrest or sudden death) occur most frequently in young otherwise healthy individuals without structural heart abnormalities. The prevalence of LQTS is estimated as 1:2500 (22)

Autosomal dominant inheritance is the most common form, called Romano-Ward syndrome (RWS) and caused by heterozygous mutations in at least 12 different genes (Table 1) (23). Six of the genes encode cardiac potassium channels and most of the known mutations are located in the potassium channel genes. Potassium channels are made up of several protein subunits. Each subunit is produced from a particular gene. Each channel includes four α (alpha) subunits, which are usually identical, and several β (beta) subunits. α subunits form the hole (pore) through which potassium ions can flow (Figs. 1-2). β subunits help regulate the channel function and interact with various proteins inside and outside the cell. (Figs. 2-3) (24) Four genes encode or regulate cardiac sodium channels and one gene encodes a cardiac calcium channel (Figs. 1-3).

Autosomal recessive inheritance is a rare form, associated with congenital deafness (Jervell and Lange-Nielsen syndrome, JLNS). (1, 25) Two subtypes (JLN1 and JLN2) have been identified based on the disease-causing genes that encode one potassium ion channel (Table 1).

Genotype

LQT1 is the most common genotype in RWS, caused by mutations of *KCNQ1* (26) *KCNQ1* encodes α-subunit of a voltage-dependent potassium channel expressed in various cell types including cardiac myocytes and epithelial cells. In the heart, *KCNQ1* protein assembles with *KCNE1* protein to form Kv7.1, a channel complex constituting the slow component of the delayed rectifier current $I_{Ks.}$ (27) The majority of *KCNQ1* mutations are single nucleotide changes causing single amino acid substitutions in the channel protein (missense mutations). (28) The LQT1-causing mutations have dominant-negative loss-of-function properties. (29) Secondly, I_{Ks} is an adrenergic-sensitive potassium current. CE in LQT1 patients are mostly

Table 1. Genetic basis of 12 subtypes of inherited LQTS

Type	Prevalence (among genotyped)	Chromosome / Gene	Protein	Protein function	Mutation effect
Romano-Ward syndrome (autosomal dominant inheritance)					
LQT1	45-50%	11p15.5 / KCNQ1	$K_v7.1$	α-subunit of I_{Ks} channel	I_{Ks} ↓
LQT2	40-45%	7q35-36 / KCNH2	$K_v11.1$	α-subunit of I_{Kr} channel	I_{Kr} ↓
LQT3	3-8%	3p21-24 / SCN5A	$Na_v1.5$	α-subunit of Na^+ channel	$I_{Na.L}$ ↑
LQT4	<1%	4q25-27 / ANK2	Ankyrin B	Adapter protein	unclear
LQT5	<1%	21q22.1 / KCNE1	minK	β-subunit of I_{Ks} channel	I_{Ks} ↓
LQT6	<1%	21a22.1 / KCNE2	MiRP1	β-subunit of I_{Kr} channel	I_{Kr} ↓
LQT7	<2%	17q23 / KCNJ2	Kir2.1	α-subunit of I_{K1} channel	I_{K1} ↓
LQT8	<1%	12p13 / CACNA1C	$Ca_v1.2$	α-subunit of Ca^{2+} channel	$I_{Ca.L}$ ↑
LQT9	<0.5%	3p25 / CAV3	Caveolin-3	co-localizes with $Na_v1.5$ at sarcolemma	I_{Na} '!
LQT10	<0.1%	11q23.3 / SCN4B	â-4	β-subunit of Na^+ channel	I_{Na} '!
LQT11	<0.1%	7q21-22 / AKAP9	Yotiao	Mediate I_{Ks} channel phosphorylation	I_{Ks} ↓
LQT12	<0.1%	20q11.2/ SNTA1	α1-syntrophin	Regulates Na^+ channel function	I_{Na} ↑
Jervell, Lange-Nielsen syndrome (autosomal recessive inheritance)					
JLN1	<0.5%	11p15.5 / KCNQ1	$K_v7.1$	α-subunit of I_{Ks} channel	I_{Ks} ↓
JLN2	<0.5%	21q22.1 / KCNE1	minK	β-subunit of I_{Ks} channel	I_{Ks} ↓

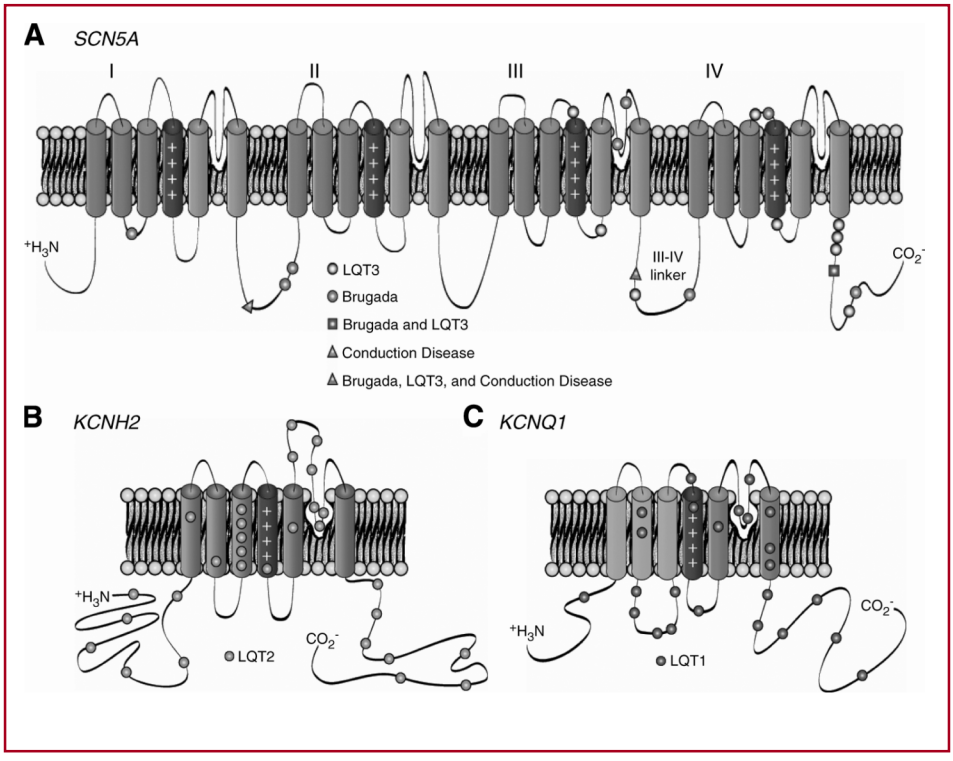

Fig 1. Structural models of Pore forming (α) subunits of cardiac sodium (Na_v) and potassium (K_v) channels linked LQTS
Part A: Depicting four domains (I-IV) of SCN5A linked to LQT3. Part B & C: Depicting subunits linked to LQT2 and LQT1, respectively.
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triggered by physical stress, notably diving or swimming. (13) Exercise aggravates QT prolongation. (30) As anticipated LQT1 patients respond very well to β-blocker treatment. (31)

LQT2 is the second common genotype in RWS, caused by the mutations in *KCNH2* or human ether-a-go-go related gene (hERG) that encodes α-subunit of Kv11.1 channel specifically for the rapidly activating

delayed rectifier K+ current (I_{Kr}) in the heart.(32) *KCNH2* mutations cause loss of Kv11.1 channel function. Different LQT2 mutations cause hERG channel dysfunction by different mechanisms and five mechanisms have been classified, including disruption of Kv11.1 channel synthesis (class 1), protein trafficking (class 2), gating (class 3), permeation (class 4), and degradation of PTC-containing mRNA transcripts by nonsense-mediated mRNA decay (class 5). (33) Class 2 mechanism, the trafficking defects (34, 35) causing reduced delivery of channel protein to the cell surface membrane, is the most common mechanism in hERG dysfunctions. (36, 37)

LQT3 is less common than LQT1 and LQT2, caused by mutations of *SCN5A* that encodes the pore forming á-subunit (Figs. 1-3) of Na^+ channels ($Na_v1.5$), referred to as I_{Na}. (38-41) Voltage-gated Na^+ channels are transmembrane proteins that produce fast inward I_{Na} currents responsible for the depolarization phase of the cardiac action potential. (24, 42) Na^+ channels play fundamental roles in the initiation, propagation, and maintenance of normal cardiac rhythm. (24, 43, 44) Depolarizing current through the channel late in the action potential is thought to prolong the action potential duration (APD). The late current is due to failure of the channel to remain inactivated and hence enter a bursting mode in which significant current can enter when it should not. (24, 38-42)

Differed by mutant $Na_v1.5$ channel biophysics, a gain-of-function mechanism is seen in LQT3 (38-41) and sudden infant death syndrome (SIDS).(45-46) Loss-of-function mutations result in Brugada syndrome (47, 48) and cardiac conduction disease. (49-51) It is of interest that both gain-of-function and loss-of-function can cause sinus node dysfunction, (52) atrial standstill, (53) atrial fibrillation (54-56) and dilated cardiomyopathy. (57) The overlap syndromes of cardiac sodium channel diseases reflect a wide spectrum of phenotypes seen in patients with *SCN5A* mutations. (58-60)

LQT4 is rare, caused by ankyrin B (*ANKB*) mutations. The phenotype is not as unique as seen in LQT1, LQT2, or LQT3 and QT prolongation is not a hallmark of this entity. A more accurate term for LQT4 is *ANKB* syndrome. (61-65) Ankyrins are adapter proteins (Fig. 3) that bind to several ion channel proteins, such as chloride-bicarbonate exchanger, sodium-potassium adenosine triphosphatase (ATPase), the voltage-sensitive sodium channel, the sodium-calcium exchanger (NCX, or I_{Na-Ca}), and calcium-release channels including those mediated by the receptors for inositol triphosphate [IP3] or ryanodine. Mutations in this gene interfere with several of these ion channels. (62-65) Such complexity results in a wide spectrum of ECG phenotype presentations, mainly sick sinus syndrome, atrial fibrillation, T-U wave abnormalities and exercise induced ventricular

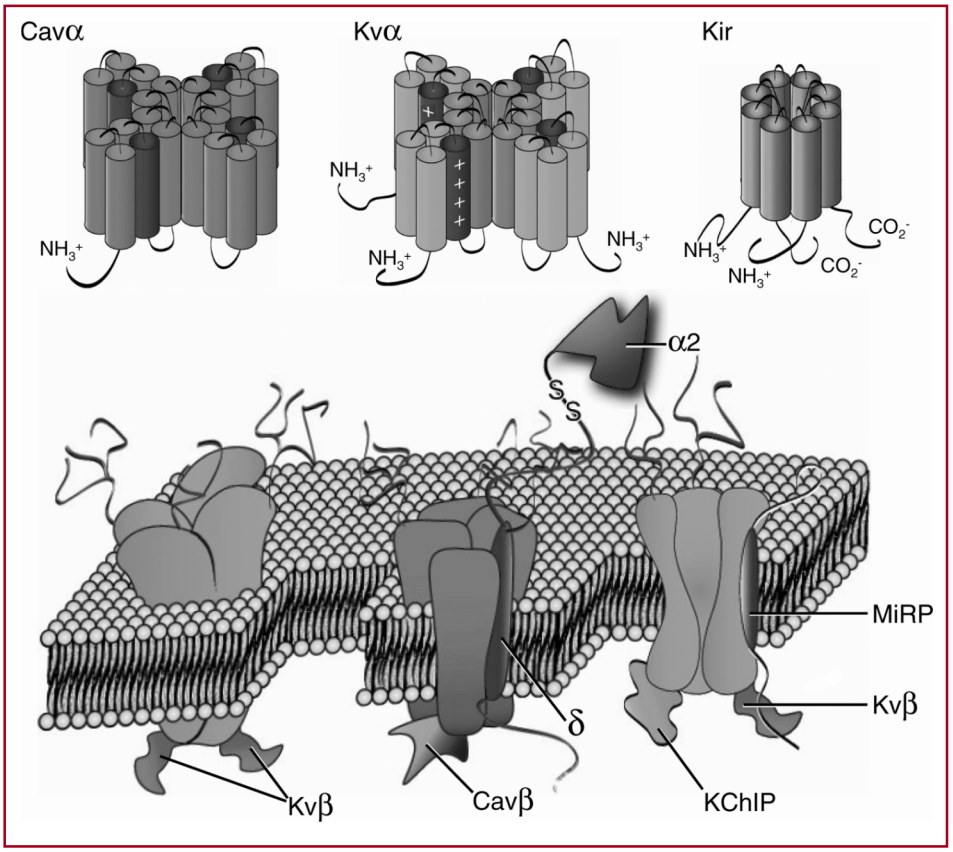

Fig 2. Structural model of cardiac Ca_v (and Na_v), K_v, and Kir channels
Top: Four domains (I-IV) of Ca_v (Na_v) individual α-subunits forming Ca_v (Na_v) channels, four domains of individual α-subunits forming K_v and Kir channels.
Bottom: Depiction of cardiac Na_v, Ca_v, and K_v channels composed of pore forming α-subunits and variety of accessory subunits.
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arrhythmia. The majority of these patients do not show a prolonged QT interval.

LQT5 is caused by mutations of the *KCNE1*, a member of *KCNE* gene family, that encodes mink, a â-subunit of K_v7.1 that assembles with α-subunit to form I_{Ks}(Figs. 2-3). *KCNE1* is a modifier gene to K_v7.1 and Kv11.1 channel functions. *KCNE1* mutations can result in loss-of-function of I_{Ks} and I_{Kr}, thereby reduce outward potassium currents causing delayed repolarization. (66-69)

LQT6 is due to mutations of *KCNE2,* the second member of *KCNE* gene family encoding minK related peptide (MiRP) that coassembles with hERG protein (Fig. 2) to form Kv11.1 channel. Like other *KCNE* isoforms *KCNE2* is also a modifier gene. Mutations in MiRP result in loss-of-function of hERG, therefore reduce I_{Kr} and prolong the QT interval. (258, 70-72) *KCNE2* can affect biophysical properties of K_v7.1 as well.

LQT7 is also referred as type-1 Andersen-Tawil syndrome (ATS1) caused by *KCNJ2* mutations. (73-75) *KCNJ2* encodes α-subunit of Kir2.1 isoform of Kir2X channels (76) (Fig. 2) that conduct inward rectifier potassium currents I_{K1}.(77) Message and protein expression studies indicate that Kir2.1 is the most abundant Kir2X subfamily member in human ventricle. (78) I_{K1} plays a key role in the final phase of repolarization and maintaining the resting membrane potential. (77) *KCNJ2* mutations cause dominant negative effects of Kir2.1 channel function when co-expressed with wild type subunit. (79) The prominent U wave and QU interval prolongation are the signature changes of ATS1. Perhaps long QU syndrome is a more accurate description of LQT7 since the majority of ATS patients do not show a prolonged QT interval. (80) Patients with ATS1 are usually in short statue and associated dysmorphic features such as low set of ears and a small chin. The dysmorphic facial features constitute a distinctive trait of ATS, indicating Kir2.1 protein may play a major role in developmental signaling. About 50% of patients have periodic paralysis,(80) in which potassium-sensitive is the most common type.

LQT8 is also referred as Timothy syndrome (TS), a rare type of LQTS caused by *CACNA1C* mutations. *CACNA1C* encodes α-subunit (Fig. 2) of the voltage-gated calcium channel (Cav1.2) that conducts L-type calcium currents $I_{Ca\text{-}L}$. Two subtypes of TS were reported by Splawski, et al. (81, 82) Type-1 TS (TS1) is caused by a missense mutation (G406R) in exon 8a, an alternative splicing form of exon 8. Most children with TS1 were due to the de novo mutation. In one child parental mosaicism was demonstrated. (81) TS1 children presented with multiorgan dysfunction including markedly prolonged ST-segment and QT interval, lethal arrhythmias, syndactyly, congenital heart disease, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism. (81) The average age of death due to complications of multiorgan dysfunction is 2.5 years. In type-2 (TS2) two mutations G406R and G402S in exon 8 of *CACNA1C* were identified in two unrelated children showing a severe LQTS phenotype but without syndactyly. (82) One child also had severe mental retardation and nemaline rod skeletal myopathy. Functional expression revealed that the G406R mutation slowed deactivation thus prolonged APD (83) G402S reduced channel inactivation that yielded maintained depolarizing L-type calcium currents. (82)

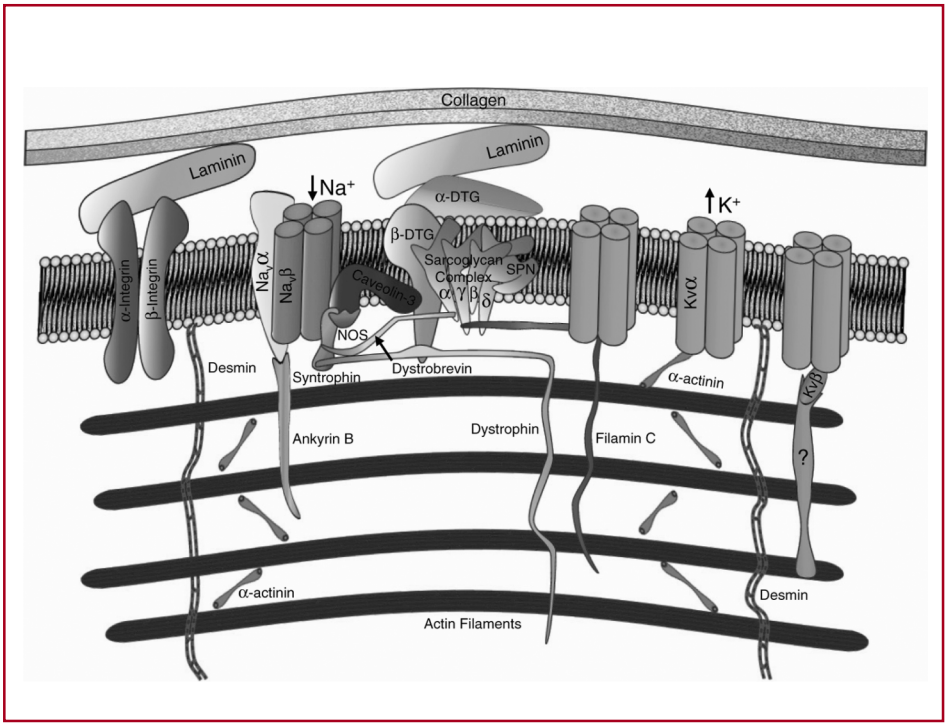

Fig 3. Structural model depicting the protein-protein interactions involved in regulating/modulating the expression, distribution, and function of cardiac ion channels. The α and β subunits of Na_v channel interact with actin cytoskeleton via syntrophin-dystrophin and ankyrin B and with extracellular matrix via sarcoglycan complex. Caveolin-3 directly interacts with neuronal nitric oxide synthase (nNOS). The K_v channel's α and β subunits interact with actin cytoskeleton via actin binding proteins filamin and α-actinin and through PDZ domain containing scaffolding proteins. *Reproduced with permission from Publisher and Jeanne Nerbonn,PhD., the author of Molecular Physiology of Cardiac Repolarization, Physiol Rev 85: 1205–1253, 2005*[24]

LQT9 is caused by mutations in caveolin 3 (*CAV3*) gene.(84) CAV3 encodes for the adapter protein (Fig. 3). Functional studies showed that the mutant *CAV3* results in 2-3 fold increase in $I_{Na,L}$ compared with wild type.(84)The gain-of-function mutations in *CAV3* are also associated with SIDS. (85)

LQT10 is caused by mutations in *SCNB4*, a gene encoding one of four α subunits of voltage-gated Na^+ channel (Figs. 2-3). These α subunits interact with voltage-gated α subunits to change sodium channel kinetics. The encoded transmembrane protein forms inter-chain disulfide bonds with *SCN2A*. Mutation in this gene can cause long QT syndrome. (86)

LQT11 is caused by the mutation of Yotiao, an A-kinase anchoring protein (AKAP). (87) It mediates the formation of a macromolecular complex consisting of the I_{Ks} channel, kinase A (PKA), and phosphatase 1 (PP1). Mutations that disrupt this protein complex do not allow the channel to be regulated in response to stress and can cause death. A heterozygous mutation S1570L in the AKAP9 gene is found in one single Caucasian family with LQTS. (87)

LQT12 is due to syntrophin (*SNTA1*) mutation A390V. (88) The mechanism of LQTS is via the activation of neuronal nitric oxide synthase (nNOS)-*SCN5A* macromolecular complex. A390V can disrupt the binding with plasma membrane Ca-ATPase subtype 4b (PMCA4b) and release inhibition of nNOS, causing S-nitrosylation of *SCN5A* that is associated with increased late sodium current, resulting in a characteristic biophysical dysfunction for sodium-channel seen in LQT3. These results establish a *SNTA1*-based nNOS complex attached to *SCN5A* as a key regulator of sodium current and suggest that *SNTA1* should be considered a LQTS-susceptibility gene. (88)

JLNS and other compound mutation-caused LQTS are rare. Both compound heterozygous and homozygous mutations of *KCNQ1* and *KCNE1* are reported to cause type-1 JLNS (JLN1) and type-2 JLNS (JLN2) that are associated with congenital deafness (89-93) Compound mutations without deafness have also been reported.(94, 95) As anticipated >1 mutations caused LQTS usually present with severe clinical presentations such as markedly prolonged QT interval, and T wave abnormalities associated with a high risk of arrhythmic sudden death. (1, 25)

Most LQTS mutations identified are missence mutations. (28, 96) It is anticipated that more mutations will be identified in the known genes and the list of LQTS genotypes will continue to grow upon new gene discoveries. DNA sequences in the noncoding regions cannot be overlooked because intronic variants can cause LQTS. (97) Moreover, up to 10% of patients have large gene deletions or duplications among major known LQTS susceptibility genes that cannot be detected by sequencing-based mutation screening. (98)

Genotype-phenotype correlation

Among genotyped patients, LQT1, LQT2, and LQT3 account for 90-95% (99) and LQT4 to LQT12 are rare. A series of genotype-phenotype correlation studies have been conducted in regard to mutation types and locations, triggers of cardiac events and ECG characteristics. Recognizing genotype-phenotype characteristics of common genotypes of LQTS can improve diagnostic accuracy, guide targeted genotyping, facilitate gene-specific treatment and improve risk stratification.

1. Effects of mutation type and location
   The type and location of mutations may play an important role in the magnitude of repolarization abnormality, leading to occurrences of life threatening cardiac arrhythmias.
   LQT1%The multi-center/multi-national LQTS registry study has shown that LQT1 patients with transmembrane mutations or mutations causing dominant-negative suppression of ion currents have longer QT intervals and a higher likelihood of developing life-threatening ventricular arrhythmias than patients with C-terminal mutations or mutations resulting in haploineffi-ciency. (100) It is possible that I_{Ks} channels with transmembrane mutations may have reduced responsiveness to regulator-adrenergic signaling of the ion conduction pathway with more impairment of shortening of the QTc with exercise related tachycardia than mutations in the C-terminus region. (101)
   LQT2% Recently Shimizu et al (102) reported that LQT2 patients with missense mutations either at the transmembrane pore (S5-loop-S6) or at the N-terminus region of the hERG gene carry a higher risk of syncope or cardiac arrest (hazard ratio: 2.87 and 1.86, respectively). Those with the same type of mutation but at the transmembrane nonpore location have a lower risk. Among C-terminal mutations, LQT2 patients with non-missense mutations were at significantly higher risk than patients with missense mutations at the same region. Mutations located in a-helical domains are associated with a higher risk of cardiac events than mutations located in β-sheet domains.
   LQT3% Previous studies suggest that the Δ KPQ mutation, located in the intracellular loops, and operating through both faster recovery from inactivation and an increase in residual sodium current, is associated with a significantly higher risk for cardiac events than the C-terminus D1790G mutation that has distinct biophysical function effects on steady-state inactivation and intracellular calcium homeostasis. (103) Depending on the outcome of the altered biophysical behavior of the sodium current, some SCN5A missense mutations can produce malignant phenotype and the severity is age-specific. (104)

2. Gene-specific triggers to cardiac events
   It has been well-documented that in LQT1 patients cardiac events are often triggered by exercise and swimming in particular. Of the patients who experienced cardiac events while swimming, 99% were LQT1. (105) In LQT2 patients only 13% occurred during exercise, most triggered by emotional stress.
   Startle response with loud noise is hazardous to LQT2 patients. (106) In LQT3, sudden death most commonly occurs during sleep.

3. Genotype-specific ST-T-U wave patterns
   The T wave morphology is abnormal in the majority of LQTS patients. Genotype-specific repolarization wave patterns have been identified in LQT1 to LQT3 and LQT7.
   In 1995 Moss, et al (107) first identified three distinct T wave patterns associated with LQT1-3. Zhang et al (108) subsequently identified 10 ST-T wave repolarization patterns including 4 in LQT1, 4 in LQT2 and 2 in LQT3. LQT1 infants present a unique ST-T pattern classified as an infantile ST-T wave. The typical LQT1 ECG patterns in adults are featured by monomorphic T wave (Fig. 4) patterns in broad-based, normal-appearing or late-onset normal-appearing T waves. The normal appearing T wave is most common. Bifid T wave is a hallmark of LQT2 (Fig. 4). Bifid T waves can be obvious or subtle. Sometimes the second component of T wave is merged with U wave in precordial leads V2-3. Sometimes bifid T waves become very subtle that the top of the T wave become flat or rounded. In LQT3 the late-onset peaked/biphasic T waves are most common (Fig. 4). Typical ECG patterns are present in the majority of LQT1-3 mutation carriers. The ECG patterns are atypical in patients with compound mutations.
   Characteristic ECG patterns are also found in ATS1 (LQT7). (80) The majority of *KCNJ2* mutation carriers present with abnormal T-U morphology featured by a prolonged terminal T wave downslope, wide T-U junction, biphasic and enlarged U waves. Frequent premature ventricular contractions (PVCs) in bigeminy and bidirectional ventricular tachycardia (VT) are common in ATS1. Interestingly, ventricular arrhythmias in ATS1 are originated from the left ventricle exclusively.

LQTS-specific arrhythmia

The arrhythmias in most of LQTS come in an "all-or-none" fashion. The signature arrhythmia of LQTS is TdP (Fig. 5). (5) Increased dispersion of ventricular repolarization and/or the development of early- or delayed-afterdepolarizations (EAD, DAD) by various causes can trigger TdP in the setting of an underlying long QT interval. (109, 110) The common ECG

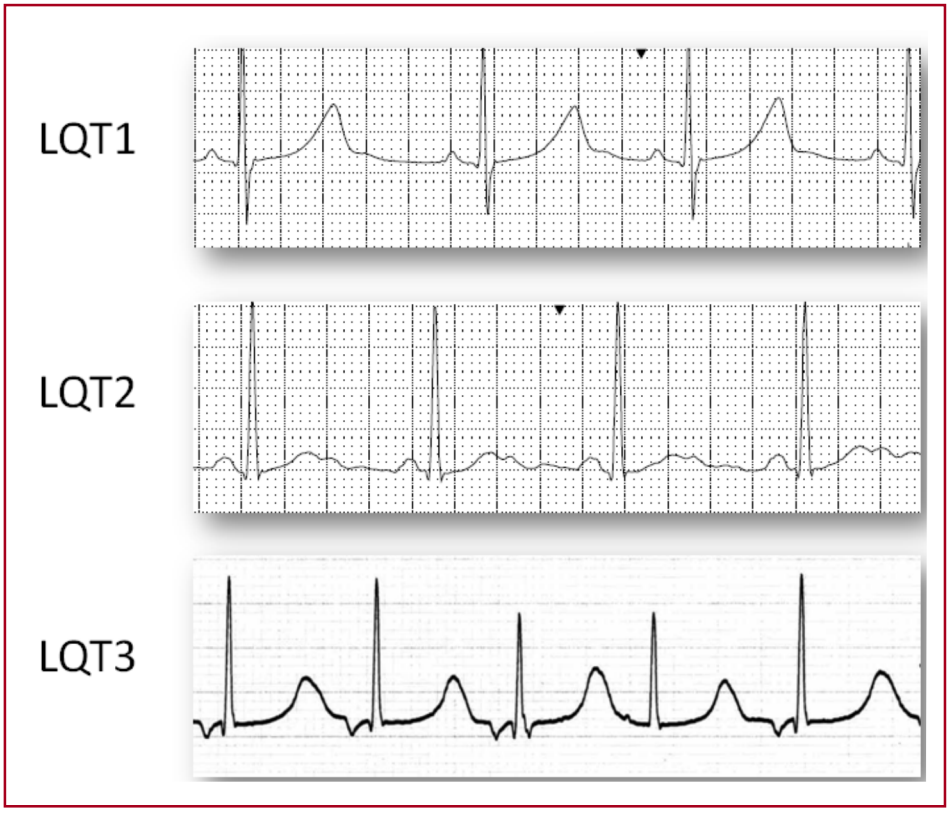

Fig 4. Gene-specific T wave patterns in common LQTS genotypes. There are 10 ECG ST-T patterns typical to LQT1-3. Among them three representative ECG patterns are illustrated.
LQT1- The ECG tracing (25 mm/s) was taken from a 21-year-old LQT1 female who had recurrent syncope and a family history of premature sudden death. The QT interval is markedly prolonged (QTc 540 ms) and the T wave is monomorphic and smooth (normal-appearing T wave).
LQT2- The bifid T wave is of low amplitude and following a visible U wave. The QTc is markedly prolonged (521 ms). This tracing was taken from an asymptomatic 12-year-old girl carrying a *KCNH2* mutation.
LQT3- The Late-onset T waves with visible amplitude alternations were recorded from a symptomatic 6-year-old boy carrying a de novo SCN6A mutation. The QT is dramatically prolonged (QTc 590 ms).

Fig 5. The signature arrhythmia of LQTS
The underlying cause of syncope in LQTS is usually torsade de pointes (TdP), a polymorphic ventricular tachycardia characterized by a pattern of twisting points. TdP in drug-induced LQTS usually starts with a short-long-short pattern of RR cycles. In this case, a short coupled PVC couplet is followed by a compensatory pause and then another PVC falls on the downslope of the T wave of the preceding sinus beat to start TdP. The QRS is wide with morphology and amplitude varied from beat to beat. The QRS axis switches in opposite direction around a virtual isoelectric baseline every 4-8 beats. In most cases TdP is short lived and terminates spontaneously. However it has a tendency to recur and sometimes it can degenerate into ventricular fibrillation, causing cardiac arrest and sudden death.

features of TdP include a markedly prolonged QT interval in the last sinus beat preceding the onset of the arrhythmia (pause-dependent), progressive twisting of the QRS complex polarity around an imaginary baseline, a complete 180-degree twist of the QRS complexes in 10 to 12 beats (150-300 bpm), and a changing amplitude of the QRS complexes in each cycle in a sinusoidal fashion.(10) Noda et al (111) observed three different initiating patterns in 24 congenital LQTS who had 111 TdPs recorded on ECG: (1) "pause-dependent" pattern (23 patients, 72 TdP, 65%); (2) "increased sinus rate" pattern (8 patients, 28 TdP, 25%) defined as a gradual increase in sinus rate with or without T-wave alternans; and (3) "changed depolarization" pattern (5 patients, 11 TdP, 10%) defined as a sudden long-coupled PVC or fusion beat followed by short-coupled PVC, suggesting differential mechanisms of initiation of TdP for each mode. Tan. et al (112) reported that pause-dependent TdP is predominantly seen in LQT2, which is also the case in drug-induced LQTS. In LQT1, a sudden intense adrenergic stimulation can precipitate TdP. In most cases TdP is short lived, terminating spontaneously thus may go unrecognized. However, it has a tendency to recur in rapid succession and can cause syncope. When TdP degenerates into VF, cardiac arrest or sudden death will be the outcome.

Natural history of the inherited LQTS

A much higher mortality reported in the earlier studies was drawn from smaller samples, mostly consisting of LQTS probands. A series of evidence-based studies conducted by International LQTS Registry investigators suggest that the risk of developing cardiac events in RWS is age-related, influenced by gender and the degree of QT prolongation. (113-115) The likelihood of developing cardiac events in infants is low in general. However, symptomatic LQTS babies bear a much higher risk of developing recurrent life-threatening events and the prognosis is poor, (116) especially in TS, JLNS and compound LQTS mutation carriers. In LQT1-3 children age 7 years and above, adolescents and young adults are the high risk groups. (117-118) Boys have higher risks than girls before age 13. Women at childbearing age, (114) especially those during postpartum, are more symptomatic. (119) A markedly prolonged QT interval is an independent risk factor for cardiac events. (120) In contrast to younger patients, a reduced frequency of cardiac events is seen in LQT1-3 patients age > 40. However, the mortality is still significantly higher than the age-matched non-LQTS elders.(121) Probands (the index case of each family) usually present with a much severe phenotype than the affected family members. (121) About 40-50% of LQT1-3 patients never develop cardiac events in their life time. Most asymptomatic LQTS individuals are not probands. Being asymptomatic does not guarantee his/her affected offspring will be risk free.(122) In RWS families, an offspring has a 50% probability of inheriting a mutant gene from his or her parent who carries a single mutation. In JLNS

families, congenital deafness occurs only in individuals carrying compound mutations (either heterozygous or homozygous) in *KCNQ1* (JLN1) or *KCNE1* (JLN2). (25) The prognosis is poor in patients with compound mutations. Their offspring have a 100% chance of inheriting a heterozygous mutation and is expected to present with a RWS phenotype. Heterozygous mutation carriers in JLNS families do not show deafness and usually present with a mild QT prolongation or even without a LQTS ECG phenotype (silent mutation carrier). Overall the cumulative rate of developing cardiac arrest and sudden death from birth to age 40 years is 5-8% in LQT1-3. Despite a high arrhythmia burden, the mortality in LQT7 is also low (3-5%).

Natural protection by genetic modifiers

Theoretically, dysfunction of the defective ion channel protein is the outcome of gene mutation. Why do 50% of LQTS mutation carriers never experience cardiac events in life? The mechanism of self-protection to prevent the worst outcome in LQTS is still largely unknown. More than 30% of the LQT2 mutations result in premature termination codons (PTCs). Degradation of PTC-containing mRNA transcripts by nonsense-mediated mRNA decay (NMD) pathway can reduce mutant mRNA level and therefore eliminate the abundance of truncated proteins. Gong, et al (33) first reported in a large LQT2 family with C-terminus nonsense mutation that underwent NMD. All gene carriers except the proband presented with a mild phenotype. The proband on the other hand had two events of cardiac arrest at age of 30 to 40 years. The 1st event occurred when she was on a potassium depleting diet and the second happened while on a QT prolonging drug. It appears that risk factors such as the use QT prolonging drugs, electrolyte imbalance and gene-specific triggers can overwhelm the natural self-protection to initiate catastrophic arrhythmias in LQTS.

II. Acquired LQTS

Far more common than the congenital form is acquired LQTS that can also lead to TdP, cardiac arrest, and sudden death. They can be divided into several categories.

Drug-induced LQTS

Drug-induced LQTS is characterized by a prolonged QT interval after using one or more QT prolonging drug(s) and associated with an increased risk of TdP. (34) Most drugs that block the Kv11.1 (hERG) channel can prolong the QT interval. (7, 123, 124) However, only those producing inhomogeneous delay of repolarization are highly "TdP-genic". Many individuals developing drug-induced LQTS have underlying risk factors. A detailed drug list can be found at www.QTdrugs.org. Females are more susceptible than males to drug-induced TdP. (125, 126)

The molecular mechanisms of QT prolonging drugs include direct block of hERG channels (127) and inhibition of hERG protein trafficking to the cell surface. (128)

1. Type-1 mechanism: direct I_{Kr} blocking is the most common, seen in a large number of structurally diverse therapeutic compounds including many antiarrhythmics, antihistamines, antipsychotics and antibiotics. The susceptibility of hERG blocking by small organic molecules is attributed to several unique structural features of the hERG channel. (129) 1) The high-affinity drug-binding site of hERG is located in the central cavity of the channel pathway (pore), which holds hydrated K^+ ions on their approach to the selectivity filter once the cytoplasmic activation gate is opened. Consequently, most blockers bind only after the channel has opened, allowing their access to the central cavity of hERG. 2) Another crucial component of high-affinity drug binding originates from two concentric rings of aromatic amino acid side chains stacked on top of each other in the central cavity (Fig 6). Sanguinetti and Mitcheson (130) suggested that the surprising diversity and high affinity of hERG blockers depend to a large extent on hydrophobic interactions between the drug molecule and Phe656 residues and a cation-π interaction between a positively charged tertiary amine present in most blocking molecules and the π-electrons of Tyr652. Both Phe656 and Tyr652 are located in the S6 transmembrane domain and their side chains project directly into the central cavity of hERG. (131)
2. Type-2 mechanism: the inhibition of hERG protein trafficking (132) is seen in a number of agents, including Hsp90 function inhibitors such as geldanamycin, radiciol, 17-AGG, the metalloids arsenic trioxide and potassium antimony tartrate, as well as small organic molecules such as pentamidine, probucol and fluoxetine. The latter blocks hERG and disrupt its trafficking at the same time.

The severity of proarrhythmia at a given QT interval varies from drug to drug and from patient to patient. Unfortunately, the extent of QT prolongation and risk of TdP with a given drug may not be linearly related to the dose or plasma level of the drug as the metabolic factors are different individually (e.g. gender, electrolyte level). Furthermore, there is no linear relationship between the degree of drug induced QT prolongation and the likelihood of the development of TdP. The unintentional use of QT prolonging drugs has been recognized as a risk factor to trigger fatal cardiac events in patients with inherited LQTS. (31, 133)

Electrolyte imbalance

1. Hypokalemia (serum level <3.5 mmol/L), a depletion or insulin-induced shifts of K^+ from the extracellular compartment into cells, is the most common electrolyte imbalance related LQTS. Digestive or kidney disorders, and certain diuretics

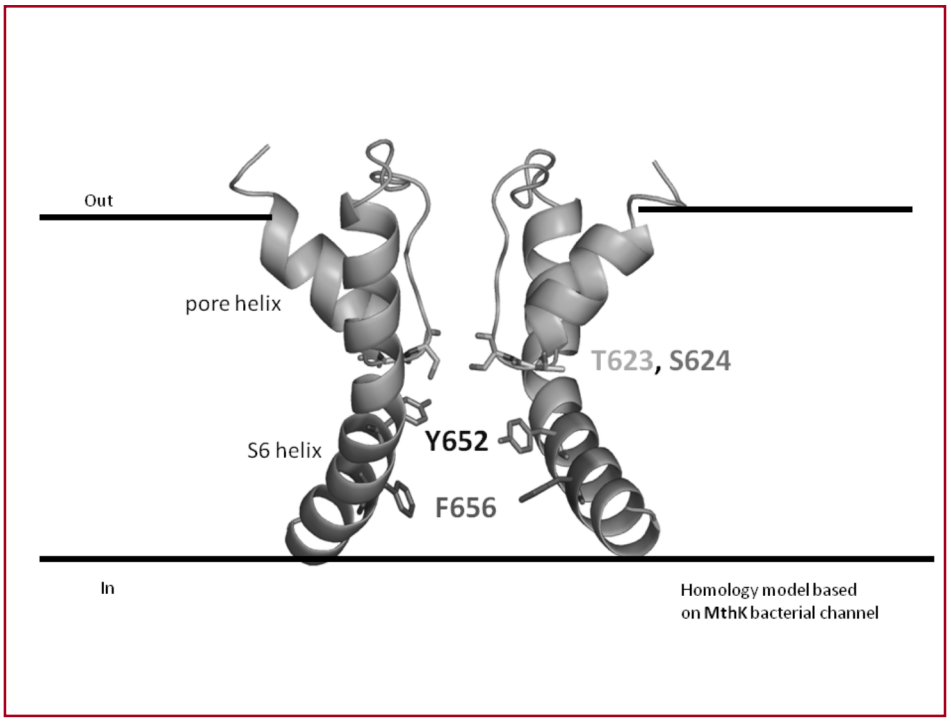

Fig 6. Structural model of drug-binding sites in the hERG channel
Two of four subunits that form the pore and inner cavity of hERG are shown. The inner helices and loops extending from the pore helices to the selectivity filter form the inner cavity and drug-binding sites of hERG. Several features may help explain the nonspecific drug-binding properties of hERG. 1) The inner cavity of hERG is long and large, that can easily trap drugs to cause channel-drug interactions. The aromatic residues (not found in other K_v channels) are critical drug-binding sites. 2) Other drug interaction sites are polar residues located close to the selectivity filter.
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are common causes. (134) Serum potassium $[K^+]o$ is a key biologic modulator of cardiac ion currents. (129) For example, hERG potassium channel requires $[K^+]o$ for its membrane stability.(135) Under low $[K^+]o$ conditions, hERG channels in the plasma membrane are internalized and degraded. For a single hERG channel, the equilibrium between K^+ bound and unbound state is $[K^+]o$ dependent. When $[K^+]o$ is decreased, the likelihood of a channel residing in K^+ unbound state increases. Thus the plasma membrane density of hERG is strictly controlled by $[K^+]o$. (135) In addition, K^+ competes with Na^+ for binding to the hERG external pore mouth. (136) Enhanced inactivation or increased inhibition by Na^+ under low $[K^+]o$ also contributes to a decreased I_{Kr}. At cellular level, reduced I_{Kr} by low $[K^+]o$ prolongs pha- se-3 action potential and facilitates EADs. (137) 3) Both external and internal K^+ modulates I_{K1} biophysic behavior. Inside of the cell, 70% of positive ions are K^+. Cohen showed that a reduction in pipette $[K^+]$ from 145 to 25 mM, decreased the rate of activation of I_{K1} at a given voltage by several-fold, and reversed the voltage dependence of recovery from deactivation, so that the deactivation rate decreased with depolarization, and caused a positive shift in the midpoint of the activation curve of I_{K1} that was several fold smaller than the associated shift of the reversal potential. (138) Reduced I_{K1} prolongs the terminal phase of cardiac action potential and facilitates DADs. (139) The ECG presentation of hypokalemia is featured by low T wave amplitude, T-U merge, enlarged U wave, and QTU prolongation. (140) Patients with severe hypokalemia are vulnerable to developing polymorphic PVCs and TdP/VF. (141) Hypoka-lemia is also an important risk factor for fatal arrhythmias in congential LQTS (33, 142) and individuals carrying functional cardiac ion channel gene SNPs.

2. Hypomagnesaemia (serum level <0.7 mmol/L) increases efflux of intracellular K^+. The cell loses K^+ which then is excreted by the kidneys, resulting in hypokalemia. Lack of magnesium inhibits the release of parathyroid hormone, which can result in hypoparathyroidism and hypocalcemia. Magnesium is an often overlooked electrolyte essential to all cells of all known living organisms. Magnesium plays an important role in enzymatic reactions and is critically involved in energy metabolism, glucose utilization, protein synthesis, fatty acid synthesis and breakdown, ATPase functions, and virtually all hormonal reactions. (143) Magnesium is also closely involved in maintaining cellular ionic balance through its association with sodium, potassium, and calcium, especially when transporting the ion across biological membranes. (144) i.e., magnesium is needed for the adequate function of the Na+/K+-ATPase pump to maintain the stability of resting potential. Lack of Mg^{2+} causes cells to depolarize easily and induce spontaneous arrhythmias. The clinical presentation of hypomagnesaemia is similar to that of hypo-kalemia, featuring QTU prolongation, TdP or even sudden death.(145, 146) About 10-20% of all hospital patients and 60-65% of patients in the intensive care unit have

hypomagnesemia. Hypomagnesemia is under diagnosed since serum magnesium levels are not routinely tested.

Myocardial stunning

1. Neurogenic stunned myocardium is a reversible syndrome defined as myocardial injury and dysfunction occurring after diverse types of acute brain injury, as a result of imbalance of the autonomic nervous system. (147) The spectrum of observed cardiac abnormalities includes electrocardiographic changes, arrhythmia, myocardial necrosis, release of B-type natriuretic peptide, and both systolic and diastolic dysfunction of the left ventricle. Cardiac abnormalities have been associated with various CNS diseases, including trauma, ischemic stroke, and intracerebral hemorrhage. Neurogenic stunned myocardium is particularly common in patients with subarachnoid he-morrhage (SAH). (148) Less common etiologies include tumors, (149) electroconvulsive therapy, seizure disorders, and CNS infections such as meningitis. ECG abnormalities are more common in patients with intracranial hemorrhage (60%-70%) or SAH (40%-70%) than those with ischemic stroke (15%-40%). The most common ECG abnormality is QT prolongation, found in 45% to 71% of patients with SAH, 64% of patients with intraparenchymal hemorrhage, and 38% of patients with ischemic stroke. (147)
2. Tako-tsubo syndrome is another form of myocardial stunning precipitated by emotional or other types of stress but without acute brain injury. (148, 150) The clinical course is similar to neurogenic stunned myocardium, featuring reversible left ventricular apical ballooning associated with dynamic QT prolongation and diffuse T wave inversion. Patients with this syndrome are mostly elder females. Clinical presentation includes chest pain, pulmonary edema, and cardiogenic shock. There is a mildly elevated serum troponin I level, (151) but angiographic evidence of clinically significant coronary disease is uncommon. Left ventricular dysfunction is usually resolved within a few weeks to a few months.

Unlike congenital and drug-induced LQTS, the dynamic changes of marked QT prolongation and diffuse T wave inversion seen in myocardial stunning may be largely due to an altered recovery sequence corresponding to the marked regional wall motion abnormalities. Such alterations may not be always associated with increased transmural dispersion of repolarization (TDR). This hypothesis may explain the fact that TdP is infrequent though it can occur and cause sudden death. Once the primary cause is removed most patients experience a benign clinical course.

Oxidation of hERG channels

Under pathologic conditions (i.e. reperfusion after acute ischemia) hERG channels are exposed to a burst of excess of reactive species including reactive oxygen and nitrogen. hERG channels can be altered by reactive species resulting in redox-dependent inactivation of α- and β-subunits channel complexes. Dysfunction of hERG channels caused by methionine oxidation is likely to occur during oxidative stress mediated by an imbalance of oxidation and elimination. hERG oxidation may be an important mechanism of acquired LQTS under oxidative stress. (152)

Other causes

A prolonged QT interval can be secondary to cardiomyopathies (hypertrophic, dilated or arrhythmogenic, etc), mitral valve prolapse, congestive heart failure, hypertension, coronary artery disease, complete heart block, (153, 154) Kawasaki syndrome, myocarditis, diabetes, anorexia nervosa, and hepatic impairment. Cardiac ion channel remodeling due to the primary condition may have resulted in a delayed repolarization. Many patients in this group also take QT prolonging drugs, with a further increased risk of sudden death.

Female gender is a risk factor for various acquired LQTS induced TdP. Female predominance in bradycardia- and electrolyte imbalance-induced LQTS has also been reported (125, 155, 156)

Genetic predisposition to acquired LQTS

Like *KCNE1* (157) and *KCNE2*, *KCNE3* is the third modifier gene in *KCNE* family expressed in cardiac myocytes and interacts with *KCNQ1* to change channel properties. Two *KCNE3* missense mutations located in the N- and C-terminal domains are linked to drug induced- and hypokalemia-induced TdP. (69, 158) Silent LQTS gene carriers (142, 159) and certain genetic modifiers such as some of the functional SNPs, (160-162) can affect the biophysical properties of cardiac ion channels, (163) resulting in a hidden condition called “reduced repolarization reserve” (164) which can be surfaced to the extent of disrupting cardiac ion channel function in the presence of QT prolonging drugs, electrolyte imbalance, ischemia or many other acquired conditions.(69, 157, 163, 165-168)

Cellular mechanism and experimental models of LQTS

Prolongation of QT interval, the time course between ventricular depolarization and repolarization, on the surface ECG is caused by lengthening the APD of ventricular myocytes. Prolongation of the QT interval can occur as a consequence of congenital defects or in response to drugs that prolong the APD via a reduction in I_{Ks}, I_{Kr}, or I_{K1}; or an increase in I_{Ca} or late I_{Na}. Though the inherited forms of the LQTS are phenotypically and genotypically diverse, they all have one thing in

common: a prolonged QT interval associated with an increased risk of arrhythmic sudden death. (21)

Work by Antzelevitch and his associates (169-171) have demonstrated that the ventricular myocardium is composed of at least three electrophysiologically and functionally distinct cell types: epicardial, mid-myocardial (M), and endocardial cells. The hallmark of the M cell is the ability of its action potential to prolong more than that of epicardium or endocardium in response to a slowing of rate. This feature of the M cell is due to weaker repolarizing current during phases 2 and 3 secondary to a smaller I_{Ks} and a larger late I_{Na} and I_{Na-Ca} compared with epicardial and endocardial cells. (172)

Under normal and most long QT conditions, the epicardial cell is the earliest to repolarize and the M cell is often the last. In an arterially perfused left ventricular wedge preparation with bipolar ECG leads placed across the transmural ventricular wall, repolarization of the epicardial action potential is coincident with the peak of the T wave and repolarization of the M cells coincides with the end of the T wave. (19) Thus, the repolarization of the M cells usually determines the QT interval. The interval between the peak and end of the T wave (Tpeak–Tend) has been suggested to provide an index of transmural dispersion of repolarization. (19) Amplification of spatial dispersion of repolarization within the ventricular myocardium has been identified as the principal arrhythmogenic substrate in both acquired and congenital LQTS. Accentuation of spatial dispersion, typically secondary to an increase of transmural, trans-septal or apico-basal dispersion of repolarization, and the development of EADs underlie the substrate and trigger for the development of TdP observed under LQTS conditions. Models of LQT1-3 and 7 have been developed using the canine arterially perfused left ventricular wedge preparations. (19, 139, 173-175) In LQT1-3 models preferential prolongation of the M cell APD can lead to an increase in the QT interval as well as an increase in transmural dispersion of repolarization, which contributes to the development of TdP. (21)Morita et al (139) demonstrated that in the LQT7 model under low $[K^+]o$ conditions the delayed late phase-3 repolarization and DADs generate U waves. Additional I_{K1} blockage by cesium chloride plus sympathetic activation by isoproterenol increased frequency of DADs. Alternating DADs at two foci resulted in bidirectional VTs.

Diagnosis of LQTS

Since treatment strategies are different, acquired and congenital forms should be differentiated. In an acquired form, the primary disease and/or the cause of QT prolongation can be identified. Drugs, hypokalemia and hypomagnesaemia-induced LQTS are often associated with dynamic QTU prolongation and T-U merge with a high tendency to the development of TdP. Acquired LQTS usually do not have the characteristic ECG patterns seen in the congenital forms. The clinical diagnosis of congenital LQTS on the other hand primarily depends on the ECG findings, family history of unexplained sudden death, blood relative(s) diagnosed with LQTS, and history of cardiac events. Electrophysiological studies are not helpful in diagnosing LQTS since TdPs are mostly non-inducible. Commercial genetic testing is fast, accurate and reliable in the United States. Considering the cost, it should be used based on appropriate indications. In 1993 Schwartz et al (2) suggested incorporating both clinical and ECG findings in probability-based diagnostic criteria for diagnosing LQTS. The maximum score is 9, and a score of 3 or more indicates a high probability of LQTS. The criteria are as follows:

ECG findings (without medications or disorders known to affect ECG features)

QT corrected for heart rate (QTc), calculated using Bazett's formula, of more than 480 milliseconds (ms) – 3 points

QTc of 460-470 ms – 2 points

QTc of 450 ms in male patients – 1 point

Torsade de pointes (mutually exclusive) – 2 points

T-wave alternans – 1 point

Notched T wave in 3 leads – 1 point

Low heart rate for age (ie, resting heart rate below the second percentile for age) – 0.5 points

Clinical history

Syncope with stress (mutually exclusive) – 2 points

Syncope without stress – 1 point

Congenital deafness – 0.5 points

Family history (The same family member cannot be counted in both categories)

Family member with definite long QT syndrome – 1 point

Unexplained sudden cardiac death (age <30 y) in an immediate family member – 0.5 points

These criteria provide a quantitative approach to the diagnosis of LQTS by allocating numerical points to clinical features, family history, and ECG findings and divide the possibility of LQTS into low, intermediate, and high probability ranges. Based on experience and available information from genotype-phenotype correlation studies, we have focused on the following aspects which can help increase the diagnostic accuracy.

Syncope

The most common cardiac event in LQTS is syncope. LQTS-related syncope is often confused with the common faint, known as vasovagal or neurocardiogenic syncope. A careful evaluation of factors surrounding syncope can help the differentiation.(176) The LQTS syncope is usually precipitous without warning. It occurs during or just after physical exertion, emotional excitement or sudden auditory arousal (such as a doorbell or alarm clock), but may occur during sleep or at rest. Conversely, in vasovagal syncope, usually there are warning symptoms, such as dizziness,

blurring or blackening vision, tingling or sweating for seconds or even minutes prior to syncope. Also, a precipitating event is usually present, commonly pain, injury, nausea, or unpleasant or stressful experience.

Recurrent syncope is also confused by epilepsy, due to a sudden surge of electrical activity in the brain that results in complete loss of consciousness. Many electroencephalography (EEG) laboratories routinely monitor the ECG during EEG recordings. This has proven useful in detecting cardiac rhythm disorders which may or may not account for the patient's symptoms but should result in referral to a cardiologist. Recent studies suggest that LQTS patients, especially LQT2, can develop epilepsy because on channel proteins are not only expressed in the heart but also in the brain. (177)

Family investigation

Unexplained syncope or premature sudden death especially in a child or young adult should raise suspicion of a channelopathy. ECG screening of family members to determine whether a QT prolongation can be found in blood relatives is very important. Since most cases of congenital LQTS are inherited, and since up to 50% of sudden death occurred as the first symptom, once a diagnosis is established in a patient, conducting a family search starting from the 1st degree blood relatives is highly recommended.(97)

ECG evaluation

1. QT interval - making a correct QT measurement is extremely important in the LQTS diagnosis. (178, 179) Sometimes the QT readings on automatic computation can be misleading especially in individuals with a complicated T wave morphology or in the presence of a prominent U wave or TU merge. (180) In general, U wave should be excluded in QT measurement. (178) Manually measuring the QT interval to validate the machine reading is necessary for LQTS diagnosis. Among many QT formulae proposed Bazett's ($QTc=QT/\sqrt{RR}$) is the most used among clinicians. When the heart rate is in the physiologic range, Bazett's formula is reliable and the easiest in clinical settings and for drug efficacy evaluation and follow-up studies. To avoid false positives averaging R-R interval of 10 seconds or a minimum 2-3 consecutive beats is recommended for QTc calculations. Although the normal upper limit is 440 ms, there is a considerable overlap of QTc in the range of 450-470 ms between normal and LQTS subjects, complicating the ECG diagnosis.(4) Women have longer QT intervals than men. (181) The cut points of QTc $\geq$ 470 ms in males and $\geq$ 480 ms in females are insensitive but highly specific in LQTS diagnosis.(4)Additional evaluation is required in subjects with a borderline QT interval.
2. T wave morphology-diagnosing LQTS should not be based upon the QT reading alone. A prolonged QT interval in LQTS is often associated with abnormal T wave morphology. (107) Recognizing the gene-specific ST-T-U morphology in common genotypes can increase diagnostic accuracy. (97, 108, 182) Sometimes it helps to predict the underlying genotype. (80, 108, 183)
3. Serial ECGs - it is helpful to those showing a bordering QT prolongation at the initial screening since QT interval and T wave morphology may vary from time to time.(97) Serial ECGs can increase the chance of capturing a typical T wave pattern and/or a diagnostic QT interval. (97, 184)

Stress testing

1. Exercise testing - For subjects with a borderline QT interval and/or atypical T wave patterns exercise testing can be of help.(30, 185, 186) In LQT1 QTc lengthening and broad-based T wave occur in the early recovery stages. In contrast, QT shortens and the T wave normalizes in the peak exercise and early recovery stages in LQT3. In LQT2 the T wave often becomes more bifid in the later stages of recovery. The QT maximum that is diagnostic can be obtained from exercise testing and the QT response to exercise can distinguish LQT1, LQT2 and LQT3 (187) in most cases. For many years the "Vincent Bicycle Protocol" and/or a treadmill with a modified Bruce protocol have been used in testing adults and children. It is a safe, reliable and easy to reproduce in LQTS diagnosis and follow-up (unpublished information by the author). Exercise testing is also helpful in beta-blocker efficacy evaluations.
2. Drug-challenge tests - Epinephrine QT stress testing is also an effective diagnostic tool to unmask concealed LQTS, particularly LQT1. Unique responses have also been observed in patients with LQT2 and LQT3, making this test useful in the diagnostic work-up of LQTS. (188, 189)

Genetic testing and functional expression

Though LQTS is mostly a single gene channelopathy, most mutations are "private" or "family-specific" and few are hot-spot mutations. (96, 190) To date, over 1,200 mutations in at least 12 genes have been identified worldwide. It is impractical, time consuming and costly to screen all known genes by a research laboratory. In a large cohort of unrelated patients referred for LQTS genetic testing, Tester, et al (99) reported that the clinical phenotype strongly correlated with the likelihood of elucidating a pathogenic mutation with the cardiac channel gene screen. Since the vast majority of LQTS patients with mutations identified are LQT1-3, and gene-specific ECG patterns are present in the majority of LQT1-3 patients that can be easily recognized by clinicians, an ECG-based genotype prediction can provide a guide for targeted gene search that has proven cost-effective in developing countries. (183) In the United States, LQTS-gene screening is available in commercial genetic laboratories but frequently not paid by

commercial insurers. Deletion and duplication should be screened in patients with negative findings of known gene sequencing. (98) Using advanced systems, commercial labs can provide genotyping results of known genes within 1-2 months. The chance of identifying a mutation is 75% among those with a clear LQTS phenotype. Overall, genetic testing is an important aspect in LQTS diagnosis. (23) In the future, genotypic determination of LQTS patients and their family members will hopefully lead to improved gene-specific prognostic determinations and therapeutic interventions.

Treatment of LQTS

The ultimate goal of LQTS treatment is to prevent cardiac arrest and sudden death. (191) In acquired forms, removing the causative agent is the key. Magnesium can suppress TdP effectively. (192) In congenital LQTS, avoiding the use of QT prolonging drugs, keeping electrolytes in balance and avoiding gene-specific situational or environmental triggers can lower the risk of cardiac events. Depending on the genotype and severity of phenotype, treatment strategy may vary. In general, medications, cardiac devices, and surgical approaches are the therapeutic choices for congenital LQTS.

β-blocker therapy

Among all the drugs β-blocker therapy is the only one that has provided significant morbidity and mortality benefits in patients who have sustained acute myocardial infarction. β-blocker therapy is most effective in preventing cardiac events in LQTS and has served as the mainstay choice for the last three decades. Yearly follow-up to justify the dose or the body weight increase is recommended for children especially teenagers. Compliance is the key to effective therapy. In a recent retrospective study by Vincent, et al (31) β-blockers were highly effective in reduced cardiac events in LQT1 patients. They suggested that β-blockers should be administered at diagnosis and ideally before the preteen years. Propranolol (48%) and nadolol (36%) were most frequently prescribed β-blockers. The mean daily dose was 2.2±1.1 mg/kg for propranolol, and 1.7±0.79 mg/kg for nadolol. In this cohort noncompliance and use of QT-prolonging drug were responsible for almost all life-threatening cardiac events. In general, the protection of β-blockers is weighted by genotype as LQT1>LQT2>LQT3. A recent computational study indicated that high dose β-blocker is likely protective in LQT3 as well. However, patients with the following conditions are not suitable for β-blocker therapy : 1) marked bradycardia especially associated with sinus node dysfunction; 2) intolerance to β-blockers; and 3) symptomatic despite β-blocker medications. Certain genetic modifiers may affect the effectiveness of β-blocker therapy. (193-197)

Potassium supplements

Potassium supplements may be helpful in people with certain forms of long QT syndrome, such as LQT2 (198-199) and Andersen-Tawil syndrome.(79) Magnesium supplement is suitable to patients with hypomagnesaemia-induced LQTS.

Implantable Cardioverter Defibrillators (ICD)

ICDs automatically sense life-threatening rhythms and deliver electrical therapy or life-saving shock directly to the heart. This therapy has clearly been shown to be the most effective in aborting arrhythmic sudden death. (191) How much the benefit outweighs potential risks in terms of morbidity and quality of life is less clear. An ICD or ICD/pacemaker combination may be used in the following cases: 1) Medications do not work or the individual has unacceptable side effects from the medications. 2) The patient's first symptom is an aborted sudden death. Pacemaker or ICD/pacer is suitable to symptomatic patients with severe bradycardia or sinus node dysfunction.

Left cardiac sympathetic denervation (LCSD)

In 1971 Moss used LCSD to treat a LQTS patient who was refractory to pharmacologic therapy. (200) The methodology has improved over time. The high thoracic left sympathectomy has been adopted, in which the lower part of the left stellate ganglion together with the first four or five left thoracic ganglia all removed. This procedure produces an adequate cardiac sympathetic denervation and is associated with a very low incidence of Horner's syndrome. LCSD is known to raise the threshold for ventricular fibrillation and reduce the arrhythmias associated with acute myocardial ischemia in animal models without reducing heart rate or impairing myocardial contractility. A significant protective effect of LCSD among high-risk patients with LQTS was shown by Schwartz et al. (201, 202) Li (203) took a less invasive approach by videoscopic denervation, which has shown the promising result. Videoscopic denervation can provide faster recovery with much less surgical trauma than the traditional LCSD. (204, 205)

Prognosis

Once diagnosed LQTS can be effectively treated and sudden death can be prevented. Not every LQTS needs an ICD especially since up to 50% of gene mutation carriers never experience cardiac events. Risk stratification of the individual patient optimizes appropriate and individualized therapy and clinical outcomes.

Conflict of Interest

None of the authors have financial or other conflict of interest to disclose

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