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[The Genetic Basis of Cardiovascular Disease]

The Genetic Basis for Cardiac Dysrhythmias and the Long QT Syndrome

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Abstract

Cardiac muscle excitation is the result of ion fluxes through cellular membrane channels. Any alterations in channel proteins that produce abnormal ionic fluxes will change the cardiac action potential and the pattern of electrical firing within the heart. The idiopathic long QT syndrome (LQTS) is an inherited cardiac pathology localized to mutated genes encoding for myocardial, voltage-activated sodium and potassium ion channels. The expression of abnormal sodium and potassium channels results in aberrant ionic fluxes that produce a prolonged ventricular repolarization. This prolonged time to repolarization is the electrophysiologic basis for prolongation of the QT interval. Individuals with LQTS are at significant risk for developing lethal ventricular dysrhythmias due to an abnormal pattern of cardiac excitation. Identification of a genetic basis for LQTS has had significant implications for genetic counseling, the development of effective antidysrhythmic drug therapies, and nursing interventions.

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INTRODUCTION

All cells of the human body have membrane-spanning proteins, some of which are ion channels. Ions flow into or out of the cell by passing through these membrane channels.1 Any defect in a channel protein translates into disturbances
in cellular ion movements, thus altering the physiologic function of an organ. Mutated ion-channel proteins have been identified in numerous clinical pathologies, such as cystic fibrosis,2 Liddle's syndrome of heritable hypertension,3 and malignant hyperthermia.4 For all of these pathologies, the defective channel protein is encoded for by a mutated gene.

The long QT syndrome (LQTS) is an inherited cardiac ion-channel-associated disorder. The last decade of research has revealed that this syndrome represents a group of several different genetically based mutations in human myocardial voltage-activated ion channels.5,6 Mutations in these myocardial voltage-activated channels alter the normal flow of ions through the channels, resulting in ventricular repolarization alterations that predispose individuals to malignant ventricular dysrhythmias, such as Torsade de pointes.

This article will present the molecular basis of the cardiac LQTS. Because the primary derangement in LQTS is localized to genes encoding for myocardial ion-channel proteins, an understanding of ion-channel structure and function is essential. In addition, by understanding the ionic basis of the cardiac action potential and the electrocardiogram (ECG), the clinical signs and symptoms of LQTS will become clear. The abnormal molecular and electrophysiologic cellular mechanisms associated with LQTS can serve as a model for understanding other cardiac dysrhythmias potentially arising from mutated ion-channel genes.

CARDIAC ION CHANNELS

In general, there are two major groups of ion channels. One group includes channels whose activity is regulated by the binding of ligands, such as neurotransmitters and hormones. The second group consists of
channels that are voltage-activated. Voltage-activated channels are responsible for generating action potentials in neuronal cells and in skeletal and cardiac muscle cells.

The heart has primarily three types of voltage-activated ion channels:
1. sodium (Na+) channels
2. calcium (Ca2+) channels
3. potassium (K+) channels

Different genes contain information about the protein structure of each of these channels. The channel genes and chromosomal locations are presented in Table 1.

The structure of an ion channel can be a single protein or a combination of five different subunits referred to as [alpha]1, [alpha]2, [beta], [gamma], and [delta]. Each subunit is composed of one or more domains that are created from linked amino acids spanning the cell membrane as inward and outward loops. The ion-channel architecture is such that the assembly of [alpha]1 subunit domains within the membrane produces a pore through which ions can flow into or out of the cell (Fig 1). Other subunits coassembling with the [alpha]1 subunit may play a role in regulating the activity of the ion channel.

The influx or efflux of an ion is governed by the chemical and electrical gradient, that is, the difference in the chemical or electrical charge concentration between the intra-and extracellular compartments. Ions will flow passively (no energy use) toward regions where their concentration is lowest, and, because ions are charged particles, they will also move toward their opposing charge in an electrical field. Thus, the pull on an ion into or out of the cell is determined by both the chemical and electrical gradient for that
particular ion. Any condition that increases or decreases the ionic or electrical gradient will change the dominant force determining the direction in which that ion moves.

Whereas the chemical or electrical gradient determines the direction of an ion flux, the open or closed state of the channel pore will determine whether an ion can pass through the membrane channel. Na+, Ca2+, and K+ channels are voltage-activated; therefore, the membrane voltage or charge determines the open, closed, or resting state of the pore. The pore-forming subunit of the ion channel contains a region that acts as a membrane voltage sensor. Upon detecting a change in membrane charge, the channel undergoes a conformational change, resulting in a transition from a closed or resting state to the opening of the channel pore.9 This change is called channel activation. A change in membrane potential is also responsible for conformational changes in the channel that result in a transition from an open pore to a closed pore. This change is called channel inactivation.1 Some channels also exhibit time- and ion-dependent activation and inactivation. However, for simplicity, only the membrane voltage dependence for activation and inactivation of the Na+, Ca2+, and K+ channels will be presented in detail when discussing the ventricular action potential.

Ion movement through an open channel pore is referred to as electrical signaling. The movement of a charged molecule across a resistor, the cell membrane, generates a current.1 In electrophysiology, this ionic current is denoted by the symbol $I_x$, the $x$ representing the specific ion passing through the channel. Ion influx is an inward current, whereas ion efflux is an outward current. The ionic current, direction of ion movement, and
effects on the cell
membrane for each of the myocardial voltage-gated channels are
listed in Table 2. Inward currents carrying positively charged ions produce
membrane depolarization. In other words, the usually negatively charged inner cell
membrane becomes less
negative, or more positively charged. For example, the change in the resting
membrane potential from \(-80\) mV to \(-20\) mV is depolarization. Repolarization
refers to the membrane voltage returning back toward its more negatively charged
resting membrane potential. Outward currents carrying positively charged ions
are primarily responsible for repolarization. The following section will
illustrate how the ionic currents, working in concert, generate a ventricular
action potential.

VENTRICULAR ACTION POTENTIAL

The ventricular action potential represents changes in the cell
membrane voltage as a result of electrical signals or currents generated
primarily by the flow of ions through Na\(^+\), Ca\(^{2+}\), and K\(^+\) channels.\(^{11}\) The normal shape and
duration of the action potential are summarized into five phases, phase 0 through phase 4 (Fig
2).

The cardiac cell resting membrane potential is maintained at approximately \(-80\) mV
by the efflux of positively charged K\(^+\) ions through K\(^+\) channels. This efflux is
the inward rectifier current, IKl.\(^{12}\) Phase 0 is the upstroke of the action
potential and corresponds to a large influx of positively charged Na\(^+\) ions
through Na\(^+\) channels. This very large but brief influx of positive charge
results in membrane depolarization. The influx of Na\(^+\) ions (INa) is due to
channel activation as the membrane is depolarizing but is also very brief
because depolarization rapidly inactivates the Na\(^+\) channel.\(^{13}\)
Phase 1 is an early and brief period of membrane repolarization due to a transient efflux of K+ ions through K+ channels. This efflux is called the transient outward current, Ito.14

Phase 2, the plateau phase, refers to that period when the membrane is maintained at a relatively constant level of depolarization due to a balance between an influx of positively charged Ca2+ ions and an efflux of positively charged K+ ions.13 The influx of Ca2+ ions (ICa) through L-type Ca2+ channels drives the membrane potential toward a depolarized state while the K+ ion efflux through K+ channels counterbalances by pushing the membrane's charge back toward repolarization. As the plateau phase progresses with time, the Ca2+ channels begin to inactivate, and the efflux of K+ ions becomes the predominant current. This K+ efflux is termed the delayed rectifier current, IK.15

Phase 3 is the late phase of repolarization and is primarily due to the cessation of ICa and the continued efflux of K+ ions. Two K+ currents are primarily responsible for phase 3. The first current is IKr, the rapidly activating rectifying K+ current. The second current is IKs, the slowly activating rectifying K+ current.16

The last phase of the action potential, phase 4, represents the membrane voltage returning to its negatively charged resting potential. As stated earlier, the resting membrane potential is maintained by IK1.

In summary, the ventricular action potential reflects time-dependent changes in the membrane potential, primarily due to an intricately coordinated movement of Na+, Ca2+, and K+ ions through their respective channels. Alterations in one or
more of these ion currents will inevitably change the configuration of the action potential. The duration, or time span, of the action potential can be prolonged when there is a loss of balance between the inward movement of positively charged ions through Na+ and Ca2+ channels and the outward movement of positively charged ions through K+ channels (Fig 2). A larger or prolonged influx of positive charge carried by INa and ICa as the channels remain in an activated state will prolong the plateau phase and interfere with phase 3 repolarization. A decreased efflux of positive charge when K+ channels are not activated, or remain inactivated, results in prolongation of phase 3 repolarization. A characteristic finding in LQTS is a prolonged action potential duration, due to either a sustained inward Na+ current or a decreased outward K+ current. This prolonged action potential duration corresponds to a prolonged time to repolarization and is the electrophysiologic basis for the prolonged QT interval associated with inherited LQTS.

ELECTROCARDIOGRAM

In the clinical setting, the ECG is a surface recording of the electrical activity generated by the flow of ions through myocardial voltage-activated channels. The QRS complex, T wave, ST segment, and QT interval (the period from the beginning of the QRS complex to the end of the T wave) are the most pertinent aspects of the ECG recording when discussing the LQTS. Each of these four ECG parameters corresponds to particular phases of the ventricular action potential. An understanding of the ventricular action potential ionic fluxes and their correspondence with the ECG will illustrate the electrophysiologic basis of LQTS-associated ECG abnormalities.
The brief influx of Na⁺ during phase 0 of the action potential corresponds to the beginning of the QRS complex. Ventricular depolarization is recorded during the QRS complex. The T wave corresponds to ventricular repolarization. Because K⁺ currents are responsible for ventricular repolarization, the T wave of the ECG is a graphic recording primarily of IKr and IKs. The ST segment represents the plateau phase. Under normal conditions, the ST segment is isoelectric because the membrane potential during the plateau phase is kept at a constant voltage for a period of time. The QT interval captures the time required for cardiac depolarization and repolarization; therefore, the QT interval corresponds to the action potential duration. Any change in ionic currents that lengthens the action potential duration will also lengthen the QT interval. Thus, a longer QT interval would be expected if the depolarizing currents INa and ICa were prolonged or if the repolarizing currents IKr, IKs were reduced (Fig. 2).

Prolonged cellular repolarization can be inferred by measuring the QT interval on an ECG recording. Typically, the QT interval is normalized to the individual's heart rate, so that as the heart rate increases, the QT interval will shorten. The corrected QT interval (QTc) is calculated using Bazett's formula. The QT interval has been shown to be slightly longer in normal women, compared with men. This may be explained by differences in the abundance of ionic currents in male and female ventricular cells. The observation of QT interval shortening in men during and after puberty suggests androgen-mediated effects on ionic currents associated with the QT interval.

The following section will outline the specific gene mutations
and channel-associated derangements of the inherited LQTS.

LONG QT SYNDROME
Genotype

The hereditary form of LQTS is divided into two major types. The Jervell Lange-Nielsen (JLN) syndrome and the Romano-Ward syndrome are determined based on the genotype and the presence or absence of bilateral, congenital deafness.25 Jervell and Lange-Nielsen were the first to describe a LQTS-like pattern in a Norwegian family.26 Four of six children presented with a prolonged QT interval, episodes of syncope, and congenital hearing loss. Three of the children died at a young age from sudden cardiac death. Later reports by Romano and colleagues 27 and by Ward 28 described similar events in other families, though there were no instances of hearing loss. It is now accepted that JLN syndrome and the Romano-Ward syndrome belong to a group of congenital, inherited forms of LQTS. These pathologies are commonly referred to as idiopathic LQTS.

JLN syndrome is inherited in an autosomal recessive pattern with accompanying congenital deafness and is differentiated according to the mutated gene. The first type, JLN1, is associated with a mutation in the K+ channel gene KVLQT1.29 The second type, JLN2, is associated with a mutation in the KCNE1 gene, which encodes for the IsK (minK) subunit of the IKs channel.30 Romano-Ward syndrome is inherited in an autosomal dominant pattern and is now recognized as six different molecular genotypes of LQTS. These six types are identified, according to genotype, as follows: LQT1, LQT2, LQT3, LQT4, LQT5, and LQT6.

The LQT1 form is linked to a mutation in the KVLQT1 gene (chromosome 11p15.5), which encodes for a K+ channel.31,32 The current involved is IKs, an outwardly
rectifying current participating in phase 3 repolarization. The abnormal K+ channel exhibits a loss of function.32 A decrease in IKs results in a reduced efflux of K+ ions, which prolongs ventricular repolarization.31

LQT2 is associated with a mutation in the human ether-a-go-go-related gene, HERG, (chromosome 7q35-36).33 HERG was originally identified by Warmke and Granetzky,34 based on homology to the Drosophila fruitfly ether-a-go-go (eag) gene, which encodes for a Ca2+-activated K+ channel. Upon exposure to ether, this channel produces rapid movement of the fly's limbs, giving rise to the name ether-a-go-go.16 LQT2 is linked to a defective K+ channel that conducts IKr, the other major outward current participating in phase 3 repolarization. The mutated K+ channel exhibits diminished function, likely due to either a reduction in the number of working channels or a normal number of channels that have a reduced or absent function.5 As in LQT1, the reduced channel function results in prolonged repolarization. Because the normal HERG-encoded K+ channel appears to have a role in suppressing abnormal ventricular depolarization that could cause premature electrical firing, individuals with LQT2 may be more vulnerable to arrhythmogenic afterbeats and sudden cardiac death.8

The LQT3 form is linked to a mutation in the cardiac Na+ channel gene SCN5A (chromosome 3p21-24).35 The mutated Na+ channel is unable to inactivate during phase 0 rapid depolarization, resulting in repetitive opening of the channel and a sustained inward current that interferes with cellular repolarization, thereby prolonging the action potential.5

Although LQT4 is linked to chromosome 4(q25-27), a specific gene has not been identified. It is also unclear which particular cellular
structure(s) may be involved in this form of LQTS. Schott and colleagues 36 have speculated that calcium-calmodulin kinase, an intracellular enzyme that regulates the activity of some ion channels, could be a candidate gene product of this mutation.

The KCNE1 gene (chromosome 21) is mutated in LQT5.37 KCNE1 encodes for the IsK subunit of a K+ channel that conducts IKs involved in phase 3 repolarization.38-40 The LQT6 designation is applied to those families presenting with the long QT phenotype that does not link to any of the other identified genotypes.

The majority of idiopathic LQTS cases are linked to mutations in the K+ channel genes HERG and KVLQT1, with a minimal number accounted for by a mutation in the Na+ channel gene SCN5A. However, because no genotype has been specified for some symptomatic individuals, the quantitative distribution of cases according to genotype could change as new genetic loci for idiopathic LQTS are identified,41 and it may be found that other ionic channels, such as the L-type Ca2+ channel, are involved. Phenotype

The estimated incidence of inheritable LQTS is 1 in 10,000-15,000.8 Of all individuals diagnosed with inheritable LQTS, approximately one-third are identified during evaluation of an unexplained episode of syncope or sudden death prevented by medical treatment. The majority of individuals are diagnosed during familial LQTS screening initiated when another family member has experienced an unexplained syncopal or cardiac arrest episode that is attributed to LQTS.8 Untreated, symptomatic individuals with LQTS risk a 10-year mortality of approximately 50%.8 The overall incidence of sudden death has
been estimated at 10-30% for symptomatic LQTS individuals, with the risk of sudden death greatly increasing in those who have frequent episodes of syncope or are resuscitated from cardiac arrest.41

Typically, LQTS is characterized by a prolonged QT interval; T-wave alternans; and unexplained syncope, seizures, or sudden cardiac death.42 A QTc of 0.46 second or longer has been recommended as diagnostic of LQTS.8 LQTS-associated syncope appears to be due to a transient dysrhythmia, most commonly Torsade de pointes. Torsade de pointes appears on the ECG as a twisting of the QRS points around an axis (the isoelectric line).41 In the majority of cases, the dysrhythmogenia-induced syncope occurs when an individual becomes acutely aroused,42 either by an emotional or auditory stimulus, or by physical activity, such as a sporting event. Torsade de pointes can progress into ventricular fibrillation and sudden cardiac death.41

The cellular events responsible for dysrhythmogenesis during stressful states have not been clearly established. One explanation centers on the L-type Ca2+ channel. Maintaining the membrane at a more positive potential during prolonged repolarization may reactivate the L-type Ca2+ channel, predisposing the myocardium to early afterdepolarizations that provoke dysrhythmic activity.43,44 During stress, catecholamine-induced activation of cardiac beta-adrenergic receptors increases the activity of the L-type Ca2+ channel, thereby encouraging the development of early afterdepolarizations and dysrhythmogenesis. Studies in isolated ventricular myocytes from Sprague-Dawley rats have shown a larger L-type ICa in females, whereas males exhibit a larger ICa in response to
beta-adrenergic receptor stimulation. Given that the QT interval duration differs between men and women, findings of sex differences in human ventricular ICa would suggest potentially sex-associated variations in the incidence and treatment of stress-induced dysrhythmias in LQTS patients.

Although a prolonged QT interval, syncope, seizures, and sudden unexplained cardiac death are characteristic findings of idiopathic LQTS, the presentation of these signs and symptoms is extremely heterogeneous. Typically, symptoms occur during the preteen or teenage years. The onset of symptoms could occur shortly after birth or, although less likely, as late as middle age. A nonuniform clinical presentation also occurs within a specified genotype. For example, in a single family carrying the same genotype, some members will be symptomatic as others remain asymptomatic. The molecular or cellular basis for this phenotypic heterogeneity is unknown. One conjecture is that a particular genotype that encodes for mutations in various locations in the channel produces variable degrees of channel dysfunction, resulting in different degrees of QT prolongation, the presence of abnormal T waves, and variable degrees of symptom manifestation.

Disease management

At the present time, there is no gene-targeted therapy available for LQTS. Therefore, the therapeutic management of LQTS is aimed at preventing malignant dysrhythmias and their consequences. The majority of LQTS patients treated with beta-adrenergic receptor blockers show a reduction in the incidence of new episodes of syncope. Pharmacotherapeutic blockade of cardiac beta-adrenergic receptors prevents catecholamine-mediated increases in L-type Ca2+ channel
activity. However, LQTS patients frequently have an underlying sinus bradycardia that requires artificial pacing (implantable pacemaker) when beta-adrenergic blockade potentiates the bradycardia.47 An implantable defibrillator is considered for patients who continue to experience dysrhythmias in spite of beta-blockade and artificial pacing. Left cervicothoracic sympathetic ganglionectomy (denervation) is an alternative option for those who fail to respond to beta-adrenergic blockade.42 The treatment of asymptomatic individuals with a prolonged QT interval and who are closely related to symptomatic LQTS individuals is not clearly defined. Schwartz and colleagues have recommended treating asymptomatic individuals having a prolonged QT and congenital deafness, those who are newborns, and infants up to 1 year of age because all of these individuals are at greater risk for developing fatal cardiac events.48 The emotional impact of a sibling's sudden death may also warrant instituting treatment for other family members who have asymptomatic presentations.48 Because there appears to be a substantial incidence of mortality associated with first-time cardiac events in previously asymptomatic individuals, recent recommendations suggest unconditional treatment for all asymptomatic individuals.49

Individuals presenting with prolonged QT interval, syncope, seizures, or aborted cardiac arrest, none of which can be explained by metabolic or other organic causes, should be strongly advised to seek genetic testing to confirm or rule out an inheritable form of LQTS. A confirmation of inheritable LQTS should be followed up with additional genetic testing of family members, in particular, parents, siblings, and children of the individual diagnosed with LQTS. Genetic
testing of family members could identify others at risk for syncopal episodes and, most importantly, those at risk for life-threatening dysrhythmias.41,47

Patients with stress-induced dysrhythmias associated with LQTS would benefit from nursing interventions that teach patients and their significant others effective strategies for managing emotional and physical stress. This would be particularly important for pediatric and adolescent practitioners, because the majority of LQTS cases are identified in younger populations.5 The incidence of syncope, dysrhythmias, and, in some unfortunate cases, sudden death during sporting events makes the management of exertional stress of particular concern in active school-aged groups.

Identification of the specific mutated genes and the associated channel types involved in idiopathic LQTS has had a major impact on drug therapy. Pharmacologic management of idiopathic LQTS can now be targeted to the specific channels involved in each of the LQT genotypes. The use of K+ channel modifiers would be most beneficial for LQT1, whereas LQT2-associated prolonged repolarization can be corrected by K+ supplementation.50 Na+ channel blockers, such as mexilitine, have been shown to be effective in shortening the QTc in LQT3.51

Identification of the specific gene mutation in each of the LQTS genotypes has aided in a more comprehensive study of the altered channel currents. The identified mutated genes can be placed into a cell system, such as the Xenopus oocyte, where the gene-encoded protein would be expressed. Under these more controlled conditions, sophisticated electrophysiologic techniques can examine in detail the currents conducted by the expressed abnormal channels. In
particular, information can be obtained about altered conduction kinetics or channel responses to intracellular regulatory proteins, such as channel phosphorylation by kinases. These detailed channel studies could ultimately lead to more efficacious drug management of the LQTS disorder.9 Lastly, advances in cardiac gene therapy hold the promise of directly treating the specific genes mutated in the various LQTS genotypes.

Several LQTS genotypes have been characterized. In addition, other potential genetic candidates may exist for those symptomatic individuals who do not link to a known LQTS genotype.52 Potential cellular structures that could be mutated include the voltage-activated L-type Ca2+ channel, regulatory subunits associating with K+ and Na+ channels, and intracellular enzymes that modify the activity of the cardiac voltage-gated ion channels. Recently, mutations in the SCN5A gene (Na+ channel) were identified in a small group of individuals with ST segment elevations, right bundle branch block, and instances of idiopathic ventricular fibrillation,53 indicating that LQTS may be just one of many other potential ion-channel disorders originating from mutated cardiac channel genes. By understanding the genetics, molecular events, cellular substrates, and electrophysiologic phenomena involved in cardiac excitation, clinicians will be readily able to incorporate into clinical practice future developments in the genetic basis of cardiac dysrhythmias.

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Full Text Bibliographic Links


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Key words: dysrhythmias; inherited; ion; ion channels; long QT Syndrome; potassium channel; QT interval; sodium channel; syncope; Torsade de pointes; ventricular action potential
Table 1

<table>
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Sources: *Deal KK, England SK, Tamkin M. Molecular physiology of cardiac potassium channels, Physiol Rev, 76, pp. 4–67, ©1996.
Fig 1. Ion channel structure. The ion channel protein is composed of one or more subunits. The Na+ channel pore is open, allowing extracellular Na+ ion entry into the intracellular compartment. The K+ channel pore is closed, preventing extracellular K+ ion influx (A). An ion channel subunit is composed of one or more domains. Each domain is composed of linked amino acids that span the cell membrane as inward and outward loops. Several domains, represented by I, II, III, and IV, form the a-subunit of a channel (B). Source: Ackerman MJ, Clapham DE. Ion channels: Basic science and clinical disease. New Engl J Med. 1997;36:1575-1586. SFX Bibliographic Links
Table 2

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Table 2. Voltage-gated channels
Fig 2. The ventricular action potential and EKG recording. The solid line represents the normal ventricular action potential and EKG recording. Phases 0-4 of the action potential represent various ionic currents. In idiopathic LQTS, the action potential duration and QT interval are prolonged, due to prolonged repolarization of the myocardium. These prolonged parameters are depicted by the hatched lines. Source: Ackerman MJ. The long QT syndrome: Ion channel diseases of the heart. Mayo Clin Proc. 1998;73:250-269. SFX Bibliographic Links