Clinical and Genetic Determinants of Torsade de Pointes Risk

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Torsade de pointes (TdP) is a stereotyped polymorphic ventricular tachycardia characterized by a cyclic shifting of the QRS axis (twisting around the points of the isoelectric line) preceded by a prolonged QT interval (Figure 1). It is the quintessential arrhythmia of the long-QT syndrome (LQTS), whether congenital or acquired, and results from a complex interplay among structural, metabolic, genetic, and pharmacological determinants. Epidemiological risk factors such as sex, electrolyte imbalance, ischemia, and QT-prolonging drugs are well established. In this review, we explore the epidemiology, proposed mechanisms, ECG risk factors, and genetic architecture of TdP, particularly highlighting models from recent genetic association studies of QT interval and sudden cardiac death (SCD).

Epidemiology of TdP

The incidence of TdP is difficult to estimate because it can manifest as syncope or SCD without ECG documentation of the rhythm. US vital statistics recorded from 1989 to 1998 suggest that >300,000 lives are lost to SCD annually and that the proportion of SCD among cardiac causes of death has increased.1 As many as 80% of individuals dying suddenly are found to have coronary artery disease with acute or prior myocardial infarction, whereas 10% to 20% have no evidence of structural heart disease.2 Presumptive cardiac arrhythmia is suggested in autopsy studies as the most likely cause of sudden death in many persons <35 years of age who are free of structural heart disease.3

Contributions From Postmortem Genetic Analyses

Results from postmortem analyses have added to the greater appreciation for the potential role of primary electric disorders such as TdP as an underlying cause of SCD. Chugh et al4 performed an autopsy investigation of 270 hearts from victims of SCD and found that 14 hearts (5%) were structurally normal. Postmortem molecular screening in 12 cases of unexplained SCD found that 2 of 12 cases had the same putative LQTS gene mutation with a significantly increased proportion of mutation carriers in women compared with men (44% versus 7%; P<0.008). These findings suggest that electric disorders, whether genetic or not, may represent an important contribution to SCD in general and to SCD in individuals with structurally normal hearts in particular.

QT Interval as a Noninvasive Risk Factor

The QT interval is an easily measured and noninvasive risk factor; QT interval prolongation is associated with SCD in the general population. The heart rate–corrected QT interval (QTc) has a graded influence on increasing risk of SCD even among patients without recognized LQTS gene mutations.7,8 However, in observational community-based studies, it is unclear whether the QT association with SCD is explained by TdP or whether the QTc is a nonfunctional marker of other independent SCD risk factors such as coronary disease.9–11 Additional ECG risk predictors are discussed below.12,13

Risk Associated With Female Sex

Female compared with male sex is associated with a 2- to 3-fold increased frequency of TdP, particularly after puberty.14,15 The sex differences may involve the influence of gonadal steroids on repolarization. Testosterone has been shown to shorten the action potential duration (APD) in guinea pig ventricular myocytes, likely as a result of suppression of the L-type calcium current and enhancement of the delayed-rectifier Ik1 current.16 Testosterone also diminishes dofetilide-induced proarhythmia in female rabbits.17 In guinea pigs, progesterone shortens APD mostly through inhibition of inward calcium current and enhancement of the Ik1 delayed rectifier current.18 The role of estrogen as a contributor to disproportionate risk of TdP in women remains unclear.19

Electrolyte Imbalance

Electrolyte imbalances are a common risk factor for TdP, most importantly hypokalemia. Thiazide diuretics are associated with SCD, which may be mediated by their potassium-
wasting effects. Repletion of potassium has been shown to improve repolarization in the setting of congenital or acquired QT prolongation. Aldosterone antagonists, which reduce potassium loss, were shown in the Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) to reduce the rates of SCD by 37% in patients with reduced left ventricular ejection fraction after acute myocardial infarction, although direct myocardial effects could be an alternate explanation.

Structural Heart Disease
Increased risk of TdP is associated with structural heart disease, including ischemic heart disease. In a study of patients receiving dofetilide, 32 cases of TdP were observed; NYHA class III or IV dilated cardiomyopathy was associated with TdP with an odds ratio of 3.9 (95% confidence interval, 1.1–13.1) after controlling for QTc and sex. A recent trial of dronedarone in patients with severe heart failure was stopped prematurely as a result of increased mortality caused predominantly by heart failure death but also with a trend toward increased rates of SCD.

Pharmacological Risk Factors
Proarrhythmic effects of antiarrhythmic agents with strong $I_{Kr}$ blocking effects are well recognized, particularly in the setting of risk factors as mentioned above, and have been a dominant factor in the lack of more widespread use in arrhythmia prevention. However, noncardiac medications with comparatively modest effects on repolarization have been associated with TdP. When the risk has outweighed the benefit or nonarrhythmic alternatives in class exist, several of these compounds have been pulled from the market by regulatory agencies (Table 1). QT prolongation or other markers of TdP potential (eg, potassium channel binding assays) are one of the greatest factors leading to the loss of promising therapies from the drug development pipeline. There has been an increased call for awareness of medications that prolong the QTc and/or predispose to TdP that has led to development of consensus-based lists of implicated drugs, including an online registry located at www.QTdrugs.org.

However, acquired QT prolongation is an imperfect surrogate for TdP risk. Some agents clearly prolong the QT interval but only infrequently lead to TdP. For example, amiodarone is known to display characteristics of all 4 Vaughan-Williams class antiarrhythmic effects, including the blockade of both $I_{Kr}$ and $I_{Ks}$ delayed rectifier potassium channels (class III), sodium channels (class I), L-type calcium channels (class IV), and adrenergic receptors (class II). In canine models, long-term amiodarone administration has been shown to prolong APD and QTc but to provide antiarrhythmic effects with a reduction in TdP rates. Recent rabbit models suggest a dose-related effect of amiodarone, with lower doses inhibiting $I_{Kr}$ and promoting arrhythmic activity and escalating doses preferentially blocking late sodium channel currents and thereby suppressing proarhythmia.

Ranolazine, a novel antianginal agent known to inhibit late sodium channel current and $I_{Kr}$ potassium current (thus...
prolongation is created equal. Effects, leading to the corollary that not all drug-induced QT prolongation,42 an observation supported by dog models.43 Reduced nonsustained ventricular tachycardia despite QTc prolongation,42 an observation supported by dog models.43 The recently designed Ranolazine Implantable Cardioverter-Defibrillator Trial (RAID) clinical trial is actively enrolling patients with increased risk for SCD to investigate the potential antiarrhythmic properties of ranolazine (www.clinicaltrials.gov; unique identifier: NCT01215253). The examples of amiodarone and ranolazine support a model in which modifiable risk factors interact with an underlying fixed substrate, including genetic factors, to lead to proarrhythmia. Because cardiac tissue has multiple redundant repolarization mechanisms, it would be unlikely for a single lesion to result in TdP. Rather, akin to contemporary carcinogenesis theories, the phenotype of TdP is the result of multiple hits that could include genetic predisposition—congenital LQTS, subclinical rare gene mutations, or predisposing common allelic variants as discussed later—and environmental or other nongenetic factors such as hypokalemia, \( I_{Kr} \)-blocking drugs, and ischemia.45

**Proposed Mechanisms of TdP**

The mechanisms of proarrhythmia leading to TdP are not fully understood. However, experimental evidence suggests that the occurrence of TdP is a downstream outcome of a chain of events involving a complex array of ion channel interactions that set up a substrate for arrhythmia in the setting of an appropriate trigger. Well-described theories of pathogenesis include triangulation, reverse-use dependence, short-term variability (also known as instability), dispersion of repolarization (known together as TRLaD), and early afterdepolarizations (EADs). We consider in turn these proposed mechanisms and a selection of relevant models for understanding TdP pathogenesis (Table 2).46,47

**Dispersion of Repolarization**

Whole-organism models have the disadvantage of competing effects of anesthesia required for in vivo rabbit and dog experiments,48,49 as well as that of the translation and torsion of the left ventricle in intact animals. Yan et al50 have described an experimental model involving canine left ventricular wedge preparations to better understand the action potential in an electrically coupled environment while removing the potentially confounding variable of anesthesia. In this model, a transmural wedge is resected from the anterior wall of the left ventricle, along with native branches of the left anterior descending coronary artery. Microelectrodes can then be used to record action potentials in epicardium, midmyocardium, and endocardium, as well as subendocardial Purkinje fibers. This model has established that M cells, which make up the midmyocardium, have disproportionate prolongation of APD in response to class III blocking agents such as d-sotalol were also found to preferentially prolong the APD of the M cell (Figure 2).51 Heterogeneity of APD across the layers of conductive tissue within the ventricular wall locally, called transmural dispersion of repolarization, predisposes to TdP52,53 in in vivo models. Transmural dispersion of repolarization has been demonstrated by Kozhevnikov et al54 in anesthetized dog models of the intact left ventricle with 3-dimensional mapping of activation and repolarization during dofetilide infusion. Medina-Ravell et al55 demonstrated that increased transmural dispersion of repolarization with biventricular pacing promoted TdP in a rabbit wedge model and correlated in humans with a similar biventricular pacing protocol with prolonged QT and JT intervals and polymorphic ventricular tachycardia on surface ECGs.

**Table 2. Models for Understanding Torsade de Pointes Proarrhythmia**

<table>
<thead>
<tr>
<th>Model</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Left ventricular wedge</td>
<td>Avoids anesthesia; transmural</td>
<td>Limited apical-basal; reduced global coupling</td>
</tr>
<tr>
<td>Intact animal heart</td>
<td>Preserves anatomy; spatial resolution</td>
<td>Anesthesia; less transmural</td>
</tr>
<tr>
<td>Zebrafish</td>
<td>Tissue transparency; oral perfusion; no anesthesia; high throughput</td>
<td>Not transmural; no dispersion data; distant phylogenetically from humans</td>
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<tr>
<td>ECG QT interval</td>
<td>Practical; noninvasive</td>
<td>Single measurement does not capture dynamic nature, change over time</td>
</tr>
<tr>
<td>Congenital LQTS</td>
<td>Model ion channelopathy</td>
<td>Poor generalizability to general population</td>
</tr>
<tr>
<td>Population GWASs</td>
<td>Variants are common; gene discovery; human in vivo</td>
<td>Modest effect size makes studying pathophysiology in individuals of limited value compared with LOTS</td>
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<tr>
<td>Induced pluripotent stem</td>
<td>Human in vitro</td>
<td>Poor coupling; ability to define relevant myocardial cellular subtypes</td>
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<td>cardiac cells</td>
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LQTS indicates long-QT syndrome; GWAS, genome-wide association study.
Isolated left ventricular wedge preparation models have limited resolution to detect the impact of between-region heterogeneity of repolarization. In an anesthetized canine model, Opthof et al.\(^5\) demonstrated greater apical-basal dispersion of repolarization, arguing that some heterogeneity in repolarization is spatial (whole heart) as opposed to transmural. This hypothesis has been further supported in anesthetized swine models by Xia et al.\(^5\) in which intact swine left ventricular endocardial and epicardial mapping was performed and spatial dispersion of repolarization was found to account for regional differences in time from peak to end of the T wave (discussed below).

**TRIaD Conceptual Framework**

Hondeghem\(^5\) developed an automated system called SCREENIT using an isolated intact rabbit heart (Langendorff model) to try to predict compounds that could potentiate proarrhythmia. In an anesthetized canine model, Opthof et al.\(^5\) demonstrated greater apical-basal dispersion of repolarization, arguing that some heterogeneity in repolarization is spatial (whole heart) as opposed to transmural. This hypothesis has been further supported in anesthetized swine models by Xia et al.\(^5\) in which intact swine left ventricular endocardial and epicardial mapping was performed and spatial dispersion of repolarization was found to account for regional differences in time from peak to end of the T wave (discussed below).

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**Long RR interval or pause obligates a prolonged APD. If sinus cycle length is regular, then an inevitably shortened TR interval (RR minus APD) leads to a shortened APD, which is then followed by a longer TR and a longer APD. This can become an oscillating short-long-short cycle and lead to the stereotyped pattern that can herald an episode of TdP. Instability, defined as a short-term variation in APD, is thought to contribute to proarrhythmia as demonstrated in the Langendorff model. Dispersion of repolarization, the last component of the TRIaD framework, is described above.**

**EAD: A Common Trigger**

In the setting of triangulation, instability, and dispersion of repolarization, EADs are thought to be a common trigger initiating polymorphic ventricular tachycardia. Initial evidence for EADs generated in the intact electrically coupled left ventricle was reported by Yan et al.\(^6\) in which both canine wedge preparations and rabbit isolated left ventricular preparations were challenged with exposure to dl-sotalol and azimilide (both \(I_{Kr}\) blockers) and monitored for phase 2 EADs. They found that both dl-sotalol and azimilide produced frequent phase 2 EADs but that progression to TdP-like polymorphic ventricular tachycardia required evidence of marked increase in transmural dispersion of repolarization.

**Emerging Models**

Milan et al.\(^6\) recently introduced another potential model for study of myocardial repolarization and arrhythmogenesis using zebrafish. This in vivo model poses unique practical advantages in that the zebrafish is transparent during embryogenesis, can be paralyzed and orally perfused without anesthesia, and can easily be genetically manipulated and propagated. They observed that common QT-prolonging compounds such as haloperidol and astemizole can significantly prolong the QT interval on the zebrafish surface ECG compared to non-QT-prolonging controls.
individual with known LQTS type 1. In this model, Moretti et al. used a retrovirus vector to deliver human transcription factors into dermal fibroblasts to generate induced pluripotent stem cells with a known KCNQ1 gene mutation. These induced pluripotent stem cells were then directed to differentiate into contracting embryoid bodies expressing myocardial cell markers. Microelectrode recordings were used to infer atrial-, nodal-, and ventricular-type embryoid bodies. EADs in the LQT1 embryoid bodies were induced with exposure to catecholamines but were not observed in controls. This model represents a potential opportunity for in vitro study of human genotype-phenotype relationships, and recent investigations have examined KCNH2-induced pluripotent stem cells and response to HERG-binding drugs, but several hurdles must be overcome, including identification of appropriate controls and more precise phenotyping.

ECG Predictors of TdP

The QT Interval

Electrocardiographic QT interval prolongation has been the most commonly identified ECG manifestation associated with the risk of TdP. A prolonged QT interval is a part of the diagnostic criteria for congenital LQTS; a QTc >500 milliseconds has consistently been associated with risk of syncope or SCD in patients with congenital LQTS. Several studies have reported the association of QT interval prolongation in unselected individuals with risk of SCD. For example, a Dutch population-based study of ~8000 elderly men and women >55 years of age showed a nearly 3-fold risk of SCD associated with a more modest QTc prolongation (>450 milliseconds found in 6% of male patients, >470 milliseconds in 5% of female patients). Chugh et al. also demonstrated in a population-based case-control study of patients with known coronary artery disease that, after diabetes mellitus and QT-prolonging drugs were controlled for, a prolonged baseline QTc was independently predictive of SCD (odds ratio, 5.53; 95% confidence interval, 3.20–9.57). Increased QTc dispersion has been identified in population studies as a predictor of cardiac death, but a direct association with TdP has not been well validated.

T-Wave Morphology

T-wave morphology and other parameters have been increasingly studied to find additional ECG predictors of TdP. On the basis of compelling data from animal models demonstrating the cellular basis of the T wave (Figure 2), perhaps the most studied ECG parameter is the interval between the peak and the end of the T wave (Tpeak-end). It has been suggested that, because the T wave reflects phases 2 and 3 of the monophasic action potential repolarization, Tpeak-end more accurately represents elements predisposing to TdP. Microvolt T-wave alternans (beat-to-beat alternation in the morphology and amplitude of the T wave) has been extensively studied as a marker for stratifying risk for ventricular arrhythmias but has not been validated as a predictor of TdP.

Yamaguchi et al. tested this hypothesis in vivo by studying 27 patients with documented drug-induced QT prolongation, of whom 12 developed TdP. Logistic regression analysis in this small sample found that Tpeak-end was a more reliable predictor of TdP than both QTc and QTc dispersion. This observation was further supported by Shimizu et al. in patients with ventricular hypertrophy, by Topilski et al. in patients with bradyarrhythmias and notch T waves, and by Watanabe et al. in patients with documented nonsustained ventricular tachycardia who demonstrated increased risk of both induced and noninduced ventricular tachycardia in the setting of prolonged Tpeak-end.

In vivo associations between T-wave morphology and TdP have been further supported in humans by Topilski et al. who noted that patients without known LQTS gene mutations who had notched T waves had a strong association of longer Tpeak-end with risk for TdP. This has also been supported by Bozkaya et al. who demonstrated predisposition to ventricular arrhythmias in patients with prolonged Tpeak-end, notched T waves, or U waves.

Short-Term Variability of QTc

The oscillating short-long-short sequence of variability in QTc interval, known as short-term variability, has been shown to predict TdP. Thomsen et al. performed some of the first in vivo studies in anesthetized dogs with chronic atrioventricular block and demonstrated a dose-dependent increase in d-sotalol-induced TdP that was not explained by incremental prolongation of the QTc but rather by an increase in short-term variability. A case-control pilot study by Hinterseer et al. compared 20 patients with documented TdP with 20 matched control subjects and demonstrated significantly increased baseline short-term variability assessed by surface ECG in patients in the absence of QTc prolongation.

Spectrum of Genetic Determinants of QT Interval

The allelic architecture, a function of the frequency and the effect size of all genetic variants contributing to a trait, underlying the complex phenotype of myocardial repolarization involves a spectrum of genetic variants. At one end of this spectrum are rare variants such as those underlying congenital LQTS that have strong effects on myocardial repolarization, leading to phenotypes such as QTc prolongation and a strong predisposition to syncope or SCD. These mutations are typically rare, private to individual families, and not found on screening the general population at large. They arise spontaneously in a single individual and may be inherited, although strong negative selective pressures as a result of lethality before reproduction often prevent such variants from rising in frequency within the general population. Less clinically apparent are rare variants with more moderate effects on repolarization representing variable or incomplete penetrance of heritable LQTS mutations that may have a more ambiguous inheritance pattern. Finally, common allelic variants discovered as single-nucleotide polymorphisms associated with modest effects on myocardial repolarization have been identified in unselected populations, but their relationship to TdP remains to be determined. We consider in turn these 3 classes of alleles (genetic variants).
Rare Variants With Strong Effects
Congenital LQTS is a rare familial disorder with a prevalence estimated at 1:2000 to 1:5000; genotype-phenotype relationships and clinical course have been well described. A survey of 262 unrelated LQTS patients found that the vast majority (78%) of mutations among LQTS patients were present in a single family or individual. The majority of identified mutations involve the LQT1, LQT2, or LQT3 genes. KCNQ1 (LQT1) and KCNH2 or HERG (LQT2) encode voltage-gated inward rectifying potassium channels; reduced repolarization current (loss of function of fks and Ifk, respectively) can result from mutations causing intrinsic channel or protein trafficking defects. SCN5A (LQT3) encodes the cardiac sodium channel, and the failure of these channels to close properly as a result of gain-of-function mutations can lead to action potential prolongation.

In fact, some populations with unique demographic histories may appear to violate the rule that LQTS-causing mutations are private to individual families. This has been uniquely demonstrated in Finland, where 4 distinct founder mutations make up as many as 73% of cases of LQTS. A recent screening of 6263 individuals from a population-based survey in Finland identified 27 individuals who carried 1 of the 4 founder mutations, demonstrating an increased prevalence of ~0.4% or 1 in 250.

Rare Variants With Incomplete Penetration
LQTS mutations with incomplete penetrance have been shown to lead to the variable phenotype seen in many patients with congenital LQTS. This particular subset of patients is an important group for further study because they may help us to better understand why some patients carrying an identifiable congenital LQTS gene mutation may have a normal QTc at baseline but suffer SCD in the setting of adrenergic challenge, hypokalemia, or exposure to a QT-prolonging drug.

Some of the earliest evidence of incomplete penetrance was reported by Priori et al, who studied LQTS probands and found that 33% of 46 genotyped family members thought to be clinically unaffected carried the same familial LQTS gene as the proband. A subsequent study by the same investigators genotyped 430 probands and 1115 family members and demonstrated an average penetrance of 60.9%. Thus, although LQTS is a familial disorder with autosomal dominant inheritance leading to an average 50% mutation transmission, phenotype penetrance was reduced, suggesting that several so-called unaffected patients might actually be susceptible to TdP in the setting of an appropriate exposure. Lehtonen et al evaluated 16 cases of TdP and found that 3 individuals (19%) carried 1 of the 4 Finnish founder LQTS mutations despite a normal baseline QTc, demonstrating both incomplete penetration of mutation carriers and the inconsistent resting QTc correlation with TdP risk.

Several lines of evidence support the hypothesis that environmental modifiers can be an important second hit to individuals with latent mutations. Shimuzu et al have shown that epinephrine significantly increased QT and T peak-end intervals in asymptomatic LQT1 mutation carriers with QTc <460 milliseconds. Vyas et al demonstrated that epinephrine challenge can unmask subclinical LQT1 gene carriers with a median increase in QTc of 78 milliseconds. Jeyaraj et al evaluated largely unaffected LQT2 mutation carriers with baseline QTc <450 milliseconds and demonstrated an increased T peak-end interval after exposure to erythromycin, a known HERG channel inhibitor. Yang et al studied patients with presumed drug-induced QTc prolongation and found that 10% to 15% of patients had an identifiable mutation in a known congenital LQTS coding region.

Common Variants With Modest Effects
Genome-wide association studies (GWASs) involve testing the majority of common variants that can be efficiently assayed in large sample sizes. GWASs have recently provided more insight into the heritability of complex traits such as myocardial repolarization by identifying common allelic variants that individually have a modest effect on the quantitative continuous heart rate-adjusted QT interval. These common variants could be associated with TdP and SCD by incrementally reducing repolarization reserve, an effect that could be augmented by environmental factors such as sex, ischemia, structural heart disease, hypokalemia, or QT-prolonging drug exposure. An additional advantage of a GWAS is the ability to use large population-based cohorts without ascertainment on disease.

Some of the earliest studies of single-nucleotide polymorphisms suggested that polymorphisms may be common in 1 population and rare in another yet produce a consistent repolarization phenotype. Splawski et al identified an amino acid–altering polymorphism of the cardiac sodium channel gene SNC5A S1102Y, of which the minor Y allele was identified in 13 of 23 black patients with arrhythmia and/or QT-prolongation compared with only 13 of 100 black control subjects, reflecting a significantly increased risk of arrhythmia associated with this variant. Burke et al further validated the association of Y1102 with SCD in blacks, whereas Chen et al reported this same allele Y1102 in a white family (the allele is rare in individuals of European ancestry, <1%) and noted a strong association with syncope, ventricular fibrillation, and SCD.

Common QT variants have recently been identified in several genes, some known to be involved in myocardial repolarization and some novel. Early GWASs investigating QTc prolongation identified common variants in the nitric oxide synthase 1 adaptor protein NOS1AP, a gene involved in regulating neuronal nitric oxide synthase now known to modulate cardiac repolarization. Two much larger GWAS meta-analyses were recently published. The analysis of the QTGEN consortium included 13 685 individuals of European ancestry and identified variants in 5 loci (NOS1AP, KCNQ1, KCNE1, KCNH2, SCN5A) known to be involved in myocardial repolarization and variants in 5 newly identified loci, collectively explaining ~6% of QT interval variability. The analysis of the QTSCD consortium involved 15 842 individuals and validated the identification of common variants in known LQTS genes (KCNQ1, KCNH2, SCN5A, KCNJ2), as well as variants in novel loci without known roles in cardiac electrophysiology. Table 3 lists common genetic variants associated with the QT interval.
Common Variants as a Second Hit to Individuals With LQTS Mutations

Recent studies provide evidence that common variants can also unmask latent rare familial mutations with incomplete penetrance. For example, Crotti et al. genotyped an older female proband who presented with ventricular fibrillation, acquired QTc prolongation, and diagnosed LQT2 involving a rare KCNH2 mutation that was shared by multiple relatives in her family. However, the proband also carried the minor allele of common polymorphism K897T on the nonmutant allele that involved KCNH2. Relatives with LQT2 who did not also carry the minor allele of polymorphism K897T were asymptomatic, suggesting that common variants can be modifiers of the expression of latent congenital LQTS mutations, although limited numbers of individuals with and without the polymorphism and the mutation prevent definitive conclusions. Similarly, a South African LQT1 founder population harboring a mutation in KCNQ1-A341V was studied to examine the modifying effect of common variation in NOS1AP, which encodes nitric oxide synthase 1 adaptor protein and is known to have quantitative QT effects. NOS1AP alleles associated with QT interval lengthening were significantly associated among LQT1 carriers with QTc prolongation and cardiac arrest and SCD. Subsequent studies have further validated the complex interplay of common variants found in individuals with congenital LQTS.

Common Variants and Other Repolarization Measures

There has been limited investigation into common variants and their association with other ECG measures of repolarization such as Tpeak-end and short-term variability, which are potential ECG manifestations of disordered repolarization. A study by Porthan et al. examined single-nucleotide polymorphisms (known to influence QTc) and their association with Tpeak-end as well as specific T-wave morphologies. The results of this study demonstrated a modest influence of polymorphisms on Tpeak-end but suggested little contribution of common variants to the prognostic value of T-wave morphology.

Common QT Variants and SCD or TdP

Prolongation of the QT interval is associated with SCD. It is therefore plausible that common genetic variation associated with longer QT interval will be associated with increased risk of SCD. Common variation at NOS1AP has been examined for an association with SCD because it has been the most strongly associated locus in GWASs. An analysis from the Cardiovascular Health Study and Atherosclerosis Risk in Communities found that a common allele at NOS1AP associated with longer QT interval was in fact associated with SCD in white adults. A meta-analysis of these findings with an independent study from the Netherlands further strengthened the association.

Table 3. Single-Nucleotide Polymorphisms and Nearby Genes Significantly Associated With the QT Interval

<table>
<thead>
<tr>
<th>Locus</th>
<th>SNP</th>
<th>Associated Function*</th>
<th>Allele Frequency</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associations with loci having known cardiac function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1q NOS1AP</td>
<td>rs12143842</td>
<td>Nitric oxide synthase 1</td>
<td>0.26</td>
<td>2 × 10⁻⁷⁸</td>
</tr>
<tr>
<td></td>
<td>rs12029454</td>
<td></td>
<td>0.15</td>
<td>3 × 10⁻⁴⁵</td>
</tr>
<tr>
<td></td>
<td>rs16857031</td>
<td></td>
<td>0.14</td>
<td>1 × 10⁻³⁴</td>
</tr>
<tr>
<td>11p KCNQ1</td>
<td>rs2074238</td>
<td>α Subunit, slow inward-rectifying K⁺ channel</td>
<td>0.06</td>
<td>3 × 10⁻¹⁷</td>
</tr>
<tr>
<td></td>
<td>rs12576239</td>
<td></td>
<td>0.13</td>
<td>1 × 10⁻¹⁵</td>
</tr>
<tr>
<td></td>
<td>rs12296050</td>
<td></td>
<td>0.21</td>
<td>3 × 10⁻¹⁷</td>
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<tr>
<td>7q KCNH2</td>
<td>rs4725982</td>
<td>α Subunit, rapid inward-rectifying K⁺ channel</td>
<td>0.22</td>
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</tr>
<tr>
<td></td>
<td>rs2968864</td>
<td></td>
<td>0.25</td>
<td>8 × 10⁻¹⁶</td>
</tr>
<tr>
<td>3p SCN5A</td>
<td>rs12053903</td>
<td>Na⁺ channel</td>
<td>0.34</td>
<td>1 × 10⁻¹⁴</td>
</tr>
<tr>
<td></td>
<td>rs11129795</td>
<td></td>
<td>0.24</td>
<td>5 × 10⁻¹⁴</td>
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<tr>
<td>21q KCNE1</td>
<td>rs1805128 (DS500)</td>
<td>β Subunit, slow inward-rectifying K⁺ channel</td>
<td>0.01</td>
<td>2 × 10⁻⁸</td>
</tr>
<tr>
<td>17q KCNJ2</td>
<td>rs17779747</td>
<td>Slow inward-rectifying K⁺ channel</td>
<td>0.35</td>
<td>6 × 10⁻¹²</td>
</tr>
<tr>
<td>Associations with loci having unclear relationship with repolarization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16q CNOT1</td>
<td>rs37062</td>
<td>RNA transcription</td>
<td>0.24</td>
<td>3 × 10⁻²⁵</td>
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<tr>
<td>6q c1orf204</td>
<td>rs11756438</td>
<td>Phospholamban</td>
<td>0.47</td>
<td>5 × 10⁻²²</td>
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<td>1q ATP1B1</td>
<td>rs10919071</td>
<td>β Subunit, Na/K-ATPase</td>
<td>0.87</td>
<td>1 × 10⁻¹⁵</td>
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<td>1p RNFI207</td>
<td>rs846111</td>
<td>Ring finger protein</td>
<td>0.28</td>
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<td>16p LITAF</td>
<td>rs8049607</td>
<td>Tumor necrosis factor</td>
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<td>5 × 10⁻¹⁵</td>
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<td>17q LG3</td>
<td>rs2074518</td>
<td>DNA ligase III</td>
<td>0.46</td>
<td>6 × 10⁻¹²</td>
</tr>
</tbody>
</table>

*Single-nucleotide polymorphisms (SNPs) are associated with loci that may include many genes. A nearby biological candidate is highlighted when suspected to underlie the association. Most SNPs are noncoding.
†p-values are shown from QTGEN for all SNPs except for KCNJ2 and ATP1B1 which are from the QTSCD study.

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More recently, a candidate gene study of TdP cases and controls demonstrated a TdP association of the KCNE1 missense D85N single-nucleotide polymorphism that has been associated with QT interval duration and congenital LQTS. These studies provide proof of principle that identifying common variants related to an SCD risk factor can also identify SCD and TdP variants. Ongoing work is testing other common QT interval variants for a relationship to SCD and drug-induced QT prolongation.

Conclusions
TdP remains a clinically important problem in the context of a large population burden of SCD. The QT interval continues to play a powerful role in predicting risk of SCD, although it is a crude and imperfect predictor of TdP. We have learned a great deal from genetic studies, most recently in the form of GWASs, in better appreciating the complex allelic architecture underlying channelopathies predisposing to TdP. The newer models, including zebrafish and induced pluripotent stem cells, provide exciting opportunities for improving our ability to resolve the complexity of TdP.

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Disclosures
None.

References
35. Yap YG, Cann J. Risk of torsades de pointes with non-cardiac drugs: doctors need to be aware that many drugs can cause QT prolongation. BMJ. 2000;320:1158–1159.
41. Yap YG, Cann J. Risk of torsades de pointes with non-cardiac drugs: doctors need to be aware that many drugs can cause QT prolongation. BMJ. 2000;320:1158–1159.


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