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Pharmacogenetics of potassium channel blockers

Dan M. Roden, M.D.

Vanderbilt University School of Medicine, Nashville

Drugs vary in their effects for many reasons such as incomplete compliance, the underlying disease being treated, clinical covariates such as age and sex, and interaction with other drugs being prescribed. Work over the past several decades, and accelerating in the last ten years, has identified an increasingly large set of DNA variants that can modulate drug actions. Thus, a contemporary view includes a consideration of pharmacogenetic factors as a source of variability in drug action in human subjects.¹

This review will focus on genetic factors modulating the effects of potassium channel blockers whose major clinical action is to prolong cardiac repolarization. In the case of potassium channel blocking antiarrhythmic drugs, this effect on repolarization, and its surface ECG correlate, QT interval prolongation, is the desired therapeutic effect which is associated with arrhythmia suppression. In other cases, drugs that inhibit cardiac repolarization are used therapeutically for other clinical conditions such as psychiatric or infectious diseases. In this setting, QT interval prolongation is an “off target” effect. A major reason for the interest in QT pharmacogenomics is the problem that marked QT prolongation can generate the morphologically distinctive polymorphic ventricular tachycardia “torsades de pointes”, the “drug-induced long QT syndrome” (diLQTS).

Potassium channels are ubiquitous across many cell types, and a wide range of drugs have been developed to inhibit their function. For example, sulfonylureas interact with ATP-inhibited potassium channels in the pancreas to produce therapeutic effects in diabetes,² while the broad spectrum potassium channel blocker 4-aminopyridine has been used therapeutically for multiple sclerosis.³ These drugs do not produce major effects on the QT interval on the surface electrocardiogram and will not be discussed further here.

Some potassium channel blocking antiarrhythmics produce little or no other cardiac ion channel electrophysiologic effect and are termed “pure” potassium channel blockers. Sotalol, dofetilide, and possibly ibutilide fall into this category although sotalol’s effects are also mediated by beta-blockade and early reports suggested ibutilide may also enhance late sodium current,⁴ an issue discussed further below. Other potassium channel blocking antiarrhythmics have additional cardiac electrophysiologic effects, such as block of sodium

Correspondence: Dan M. Roden, M.D., Professor of Medicine, Pharmacology, and Biomedical Informatics, Director, Oates Institute for Experimental Therapeutics, Assistant Vice-Chancellor for Personalized Medicine, 1285 MRB IV, Nashville, TN 37232-0575, Telephone: 615-322-0067, Fax: 615-343-4522, ; Email: dan.roden@vanderbilt.edu

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or calcium channels: amiodarone, dronedarone, and quinidine fall into this category. Accordingly, predicting the whole-heart effects of these drugs is especially complex, reflecting the fact that some effects prolong QT while others may shorten it. In addition, flecainide and propafenone, generally classified as relatively “pure” sodium channel blockers, also display potassium channel blocking effects and can prolong QT intervals in humans.

A wealth of data supports the idea that the major mechanism whereby potassium channel blocking drugs, whether “pure” or “mixed”, prolong the QT interval by inhibiting a major repolarizing potassium current in heart, I_{Kr} .⁵⁻⁷ Thus, a discussion of variability in the clinical actions of I_{Kr} blockers focuses on variability, whether genetic or other, in factors that modulate the interactions of drugs with the Kv11.1 channel (encoded by *KCNH2*, formerly termed “HERG”) responsible for I_{Kr} and its resultant effect on QT interval prolongation. These include delivery of the drug to the channel, the number of channels present, and the number of other repolarizing and depolarizing channels present. Further, as discussed toward the end of this review, recent work has identified alternate mechanisms whereby even “pure” potassium channel blockers may modulate cardiac repolarization. Thus, even a simple interaction of a drug with a singular molecular target such as the Kv11.1 channel, can introduce important complexities in analysis of variability of drug actions.

Two fundamental processes can lead to variability in drug action. The first is *pharmacokinetic* variability due to variability in drug concentrations at the target site(s) of action. The second source of variability is *pharmacodynamic*; here, drug concentrations at the site of action are constant and yet there is variability in drug action at the cellular, tissue, whole organ, or whole organism level.¹

Pharmacokinetic mechanisms

Pharmacokinetic effects are generally analyzed in terms of four fundamental processes that determine such drug concentrations: absorption, distribution, metabolism, and elimination. Non-genetic factors such as co-administration of inhibiting drugs or dysfunction of excretory organs can perturb these processes. For example, sotalol and dofetilide are not metabolized but are excreted largely unchanged by the kidneys. The drug transporter responsible for this excretion has not been definitively identified, but as a general rule, subjects with decreased renal function must have the drug doses reduced or the drug stopped to avoid very high drug concentrations, excessive QT interval prolongation and torsades de pointes. Genetic factors may also play a role. For example, among “non-cardiovascular” potassium channel blockers, the antipsychotic thioridazine is metabolized by the enzyme *CYP2D6*, and poor metabolizers (5–10% of Caucasian and African subjects), who lack active enzyme, will develop higher than usual drug concentrations at ordinary drug doses and some data suggest that this is associated with an increased risk of torsades de pointes.⁸ Similarly, poor metabolizers for *CYP2B6* may be at increased risk for methadone-induced torsades de pointes.⁹

It is thought that drugs blocking the Kv11.1 channel must access the drug binding site from the interior of the cell so it is possible that variability in intracellular drug concentrations,

due to variable drug uptake or efflux, could account for variability in drug action. *In vitro* experiments have demonstrated that manipulating the function of drug uptake or efflux transport molecules can produce such variability in Kv11.1 block,^{10,11} but DNA variants that generate this effect in human subjects have not yet been reported.

Pharmacodynamics

Multiple biologic mechanisms may underlie pharmacodynamic variability. These include variability in expression or function of the target molecules with which drugs interact to achieve their effects and/or variability in the broad biologic context – including genetic alterations contributing to the disease being studied – in which drugs act. In the case of potassium channel blockers, variability in effects might be due to variability in the number of Kv11.1 channels in the membrane, or to genetic or other mechanisms (such as phosphorylation or interaction with modulating proteins) that interfere with channel function or with drug access to or binding to its target sites of actions. In addition, net drug action in a cell may be modulated by the number or function of other channels that also contribute to repolarization. For example, reduction in I_{Ks} , a second major cardiac repolarizing potassium current, may render the heart more dependent on robust I_{Kr} function to accomplish normal repolarization. In this situation, then, administration of an I_{Kr} blocker may unmask this dependency by producing exaggerated QT prolongation and torsades.

This is one example of the general phenomena of “repolarization reserve”.^{12–14} It is postulated that normal cardiac repolarization is accomplished by multiple partially redundant processes such as I_{Ks} and I_{Kr} . A reduction in function in one of these processes may be subclinical at baseline (because other mechanisms are still present to accomplish normal repolarization), but revealed, by exaggerated QT prolongation and torsades de pointes, by I_{Kr} block.

Heart disease itself may modulate the number or function of channels and thus lead to altered drug actions; it is likely that clinical risk factors for torsades, such as congenital long QT syndromes, heart failure, left ventricular hypertrophy, female gender, or after cardioversion of atrial fibrillation, act in this fashion.⁷ There are many other settings in which marked lability in QT duration or morphology have been consistently reported: these include stress cardiomyopathy,¹⁵ post pacing or bundle branch block (“memory”) changes,^{16,17} diabetes,^{18–20} and subarachnoid hemorrhage.²¹ The fundamental mechanisms leading to these QT changes are not well understood and in fact whether they increase torsades risk is uncertain, but changes in critical signaling pathways that regulate channel synthesis or function seem likely.

Methodologic considerations in studying the genomics of drug-induced QT interval prolongation

Two general approaches have been used in this area of science. One is to study the extent to which drug exposure prolongs the QT interval across a population and to relate variability in this metric to genetic variants. A second approach is to study subjects who develop exaggerated QT prolongation (QTc >480 or 500 ms or some other cutoff) and/or torsades de

pointes and compare them to a large sample drawn from a representative population or a sample of subjects exposed to the same drugs without developing marked QT prolongation.

The specific genetic analysis in these settings is often constrained by sample size. For relatively small samples, it is unrealistic to look for associations across large numbers of genetic variants and so an investigator often chooses a small number of relatively common variants in logically chosen “candidate genes” compares their frequency across a population or in cases and controls. Candidate genes for modulating variability in the effects of I_{Kr} blockers include pharmacokinetic and pharmacodynamic genes: the latter include *KCNH2* itself, genes encoding other repolarizing potassium channels in heart, genes encoding depolarizing sodium or calcium channels in heart, genes controlling sodium-calcium or sodium-potassium fluxes, and genes identified as modulators of baseline QT by unbiased approaches discussed below.

The candidate gene approach has the advantage that it makes physiologic sense, but experience has shown that candidate gene associations are very often not replicated when larger numbers of study subjects are accrued.²² Accumulation of very large sets of study subjects can enable unbiased approaches, such as the genome-wide association study (GWAS), to identify new associations between genetic loci and human traits.²³ For example, in a very large GWAS analysis of QT variability, the top association was with single nucleotide polymorphisms (SNPs) near *NOS1AP*, which encodes a subunit for neuronal nitric oxide synthase.²⁴ The mechanism of the association has not been definitively established but *NOS1AP* has been reported to modulate sodium, potassium, and calcium channel function.^{25,26} The advantage of this approach that entirely new modulators of human traits may be identified, as in the case of *NOS1AP* and the QT. However, while these associations are highly statistically significant, each SNP contributes a very small amount to the trait under study. For example, the association between *NOS1AP* variants and QT has a P value of 10^{-213} , but the effect size is ~3 msec/allele.

For a relatively rare adverse drug effect, such as torsades de pointes, it is often not possible to generate very large numbers of affected subjects (by definition) so unbiased approaches may be limited by small sample sizes. As in any contemporary genetic analysis, correction for potential confounders such as ancestry, gender, extent or type of underlying heart disease, or even specific drug exposure, is generally required.

What is the evidence that drug-induced long QT syndrome is a genetic problem?

The occasional patient who develops marked QT interval prolongation and torsades de pointes presents a problem for the clinician because the reaction is “idiosyncratic”, i.e., unanticipated in that patient. Shortly after the initial cloning of major congenital long QT syndrome disease genes came a series of case reports that rare disease-associated variants in these genes were occasionally found in patients with drug-induced arrhythmias, i.e. subclinical congenital long QT syndrome appears to be a risk factor for the drug-induced form.^{27,28} This observation is entirely in keeping with the reduced repolarization reserve concept outlined above and points to genetic predisposition as a contributor to the

“idiosyncratic” nature of diLQTS. Another observation supporting the idea that individuals vary in specific susceptibility was from Kääb and colleagues who studied 22 subjects with drug-induced torsades de pointes. After clinical stabilization and return of the QT interval to normal, these subjects were rechallenged in a coronary care unit with intravenous sotalol, and marked QT interval prolongation was again observed, and not seen in a group of control subjects.²⁹

Pharmacogenomic studies in the drug-induced long QT syndrome

The development of complex models of multiple physiologically-based ion channel behaviors to predict the cellular consequences of a range of pathophysiologic interventions (changes in rate, potassium, drug exposure, etc.). The original Luo-Rudy model was used to show that reduction in I_{Kr} not only produced action potential prolongation (as expected), but also generated early afterdepolarizations which the model could then attribute to reactivation of L-type calcium channels,³⁰ as also predicted from experimental data.³¹ Similarly, slight reduction in I_{Ks} produces very minimal action potential prolongation, but markedly exaggerates the effects of an I_{Kr} blocker.³² This is an example of reduced repolarization reserve.

Pharmacogenetic studies of diLQTS have used both candidate gene and genome-wide approaches (Table 1). One set of studies in this area has examined the frequency of subclinical congenital long QT syndrome mutations in patients with the drug-induced form of the arrhythmia. One study sought sequence variants in *KCNE2*, a potassium channel subunit modulating Kv11.1 function, in 98 subjects with diLQTS and found three rare variants and one polymorphism (T8A),³³ now recognized to occur in 0.3% of the population.³⁴ The rare variants were associated with decreased potassium current even prior to drug, while potassium channels reconstituted by co-expression of Kv11.1 and the T8A variant *KCNE2* displayed normal potassium current at baseline but exaggerated block by sulfamethoxazole, the drug that produced diLQTS in the affected patient. Surveys of other potassium and sodium channel congenital long QT syndrome disease genes have suggested that 5–40% of subjects with diLQTS may have subclinical versions of the congenital syndrome.^{35–38}

With accumulation of larger sets of cases and controls, surveys of larger numbers of candidate polymorphisms were enabled. One such study examined 1424 single nucleotide polymorphisms (SNPs) in 18 candidate genes in 176 patients with documented torsades de pointes during treatment with a QT prolonging drug, 207 patients exposed to QT prolonging drugs with minimal QT prolongation, and 837 population controls.³⁹ A single SNP in *KCNE1*, encoding a potassium channel modulating subunit, was present in 8.6% of diLQTS cases and 1.8–2.9% of controls, giving an odds ratio of 9.0; the direction of the signal was replicated in a second set.³⁹

In an analysis of 167 SNPs across the *NOS1AP* locus in 58 subjects with diLQTS and 87 controls (all Caucasian), one variant, rs10800397, was associated with diLQTS risk, particularly in subjects with amiodarone-induced torsades de pointes.⁴⁰ A GWAS analysis of 216 cases and 771 ancestry matched controls failed to identify any signal at genome-wide

significance.⁴¹ Whether this result reflects low case numbers, a large contribution by non-genetic factors, or other experimental variables, is not known. As might be expected from a GWAS involving relatively small numbers of cases, the study was underpowered and could identify only variants occurring with a minor allele frequency >10% and conferring an odds ratio >2.7.

One other possibility is that torsades de pointes risk is modulated by multiple rare variants across multiple ion channel or other genes. Accordingly, in an exome sequencing experiment involving 65 patients with diLQTS and 148 drug-exposed ancestry-matched controls, rare variants were sought across all genes, and across subsets of genes associated with arrhythmias,⁴² with replication in 551 subjects in the exome sequencing project.⁴³ There were significant associations between variants in *KCNE1* and *ACN9* in the diLQTS cases. The *KCNE1* signal replicates the candidate gene study described above; *ACN9* is a gene involving gluconeogenesis and its relationship to cardiac arrhythmias remains to be determined. When a specifically predefined set of seven congenital long QT syndrome genes encoding potassium channels or their modulatory subunits were examined, rare variants were commoner among subjects (37%) compared to controls (21%, $P=0.009$). These data further support the idea that subclinical congenital long QT syndrome disease genes do predispose to diLQTS, but are not found in a majority of subjects.

Another approach is to examine variants associated with variability in the extent to which drug exposure prolongs QT interval. While this method does not explicitly consider patients with torsades de pointes, it does allow larger numbers of subjects to be enrolled. In one study, a GWAS analysis of 404 European-American subjects all exposed to sotalol and ascertained via an electronic medical record identified associations at near genome-wide significance in *NRG3*, a gene known to be involved in cardiac development.⁴⁴ Interestingly, a previous GWAS had identified variants in *NRG3* as contributing to diLQTS risk after exposure to the antipsychotic drug iloperidone.⁴⁵ A candidate analysis of change in QT during antipsychotic therapy implicated *NOS1AP*, previously associated with baseline QTc, and *NUBPL*, associated with iloperidone change in QTc.⁴⁶ A GWAS of the same dataset also implicated variants in the drug transporter *SLC22A23* in variable quetiapine effects.⁴⁶

Animal models have also been used to identify genes modulating QT interval prolongation by drugs. Zebrafish in which the orthologue of *KCNH2* has been knocked out displayed marked action potential prolongation, while heterozygotes display only minimal action potential prolongation but do demonstrate exaggerated action potential prolongation on exposure to dofetilide.⁴⁷ This experiment suggests that zebrafish action potentials can be used to search for new genes involved in QT prolongation by drugs. Dofetilide exposure in zebrafish with random mutations across the genome identified lines with exaggerated QT prolongation that was transmissible across generations,⁴⁷ and subsequent analyses implicated variants in *GINS3* as one potential modulator of QT prolongation in this model. Interestingly, GWAS has identified the *GINS3* locus as a modulator of baseline QT interval in human subjects.²⁴ The function of this gene and its associated biologic pathway(s) remain to be determined but the series of studies illustrates the way in which human population data can be combined with model organism data to discover new pathways in QT regulation and other biologic processes.

Current state of the art

For some adverse drug reactions, single variants, often in the HLA-B locus (for immunologically-mediated reactions) contribute strongly,^{48,49} or indeed completely define, risk. In the case of diLQTS, on the other hand, the datasets outlined above support the idea that rare variants in multiple pathways, including ion channels and perhaps other electrical signaling pathways whose function has not yet well defined (e.g. *GINS3* or *NRG3*) play a role. However another possibility is that the adverse drug reaction is determined not simply by germline genomic variation interacting with drug exposure, but also by environmental influences, specifically signaling pathways modulated by underlying heart disease or other known diLQTS risk factors.

One potential example is variability in gene expression or function conferred by microRNAs. Xiao and colleagues⁵⁰ reported that prolonged exposure to dofetilide in canine cardiomyocytes resulted in an unexpected shortening of action potential duration. Subsequent investigation attributed this change to a decrease in two microRNAs and a consequent increase in the other repolarizing current, I_{Ks} .

Lu and colleagues noted that the tyrosine kinase inhibitor nilotinib, which is associated with QT prolongation in human subjects, does not acutely block I_{Kr} .⁵¹ However, with chronic exposure, action potentials in canine cardiomyocytes were prolonged and this change was attributed to both downregulation of important repolarizing potassium currents (I_{Kr} and I_{Ks}) as well as increases in the late sodium current. Our group then went on to show that hours of exposure to “pure” I_{Kr} blockers, such as dofetilide, strikingly increased late sodium current and produced arrhythmogenic afterdepolarizations in mouse myocytes; acute dofetilide exposure produced no change in action potential in mouse cardiomyocytes as expected since I_{Kr} plays no role in repolarization in these cells.⁵² Intracellular perfusion with PIP3 – the downstream effector of PI3-Kinase (PI3K) signaling – reversed the effect, implicating inhibited PI3K signaling as a major proximate mechanism underlying the increasing late sodium current. Other reports indicate that increased late sodium current (reversible by pipette PIP3) may also underlie increased action potential duration in diabetes.¹⁹ Further, mice in which the α -isoform of PI3K (which we have shown mediates the change in late sodium current⁵³) display increased susceptibility to atrial fibrillation.⁵⁴ These findings suggest a molecular basis for the link between structural heart disease and diLQTS susceptibility.

Another well-recognized risk factor is hypokalemia. We have shown that decreased extracellular potassium strikingly increases the I_{Kr} -blocking potency of dofetilide or quinidine.⁵⁵ The underlying mechanism likely represents a potassium-induced shift in the balance between open and inactivated states of the channel during depolarization⁵⁶ or to increased block by extracellular sodium when extracellular potassium is decreased.⁵⁷ Another report suggest that hypokalemia generated arrhythmias by inhibiting Na-K-ATPase and activating CaM Kinase, thereby enhancing late sodium current, prolonging repolarization, and generating arrhythmias; dofetilide potentiated this effect.⁵⁸

Another interesting model system which is now being introduced into this area is the development of technologies to derive cardiomyocytes from human subjects via induced pluripotent stem cells (iPSCs). In cells derived from patients with congenital long QT syndrome, action potentials are longer than those seen in subjects without mutations, and the cells display marked action potential prolongation and arrhythmogenic afterdepolarizations on exposure to very low concentrations of I_{Kr} -blocking drugs.⁵⁹ Another approach to translating the effects of drugs on individual ion channels to effect in the whole heart is systematic exploration of the ECG effects of a drugs known to be “pure” or “mixed” potassium channel blockers; initial studies suggest that Kv11.1 block produces consist changes in T wave morphology regardless of whether other pharmacologic properties are superimposed.⁶⁰ Recent proposals from the pharmaceutical industry and the Food and Drug Administration suggest that these new approaches, including the use of iPSC-derived cardiomyocytes, systematic ECG analyses, and *in silico* modeling, may complement or supplement current approaches to evaluating the potential that a new drug entity might cause diLQTS.⁶¹

Conclusion

The QT interval on the surface electrocardiogram serves as an interesting model of a multicomponent integrated readout of many different biologic systems, including ion channels, modulatory subunits, the signaling systems that modulate their activity, and the mechanisms that regulate the expression of their responsible genes. A highly integrated system like this behaves in a relatively consistent way in normal human subjects, and indeed in subjects harboring congenital long QT syndrome disease mutations, the vast majority of heart beats do not trigger fatal cardiac arrhythmias. The problem of drug exposure causing exaggerated QT interval prolongation and torsades de pointes has evolved from a historical curiosity as an “idiosyncratic” drug action to a set of genomic and model system experiments that highlight the multicomponent nature of cardiac repolarization and the way in which simple perturbations can, in some subjects, yield exaggerated responses. Future directions will involve cellular approaches coupled to evolving technologies that can interrogate not just cells but multicellular systems up to and including the whole heart, and provide an increasingly sophisticated view of mechanisms in this previously “idiosyncratic” drug reaction.

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Key Points

- The QT interval on the surface electrocardiogram serves as an interesting model of a multicomponent integrated readout of many different biologic systems, including ion channels, modulatory subunits, the signaling systems that modulate their activity, and the mechanisms that regulate the expression of their responsible genes.
- A highly integrated system like this behaves in a relatively consistent way in normal human subjects, and indeed in subjects harboring congenital long QT syndrome disease mutations, the vast majority of heart beats do not trigger fatal cardiac arrhythmias.
- The problem of drug exposure causing exaggerated QT interval prolongation and torsades de pointes has evolved from a historical curiosity as an “idiosyncratic” drug action to a set of genomic and model system experiments that highlight the multicomponent nature of cardiac repolarization and the way in which simple perturbations can, in some subjects, yield exaggerated responses.
- Future directions will involve cellular approaches coupled to evolving technologies that can interrogate not just cells but multicellular systems up to and including the whole heart, and provide an increasingly sophisticated view of mechanisms in this previously “idiosyncratic” drug reaction.

Table 1

Identifying possible risk variants predisposing to drug-induced long QT syndrome

Approach	Outcome	References
Sequencing congenital LQTS disease genes in diLQTS cases	Rare variants (possible subclinical congenital LQTS) in ~5–30%	33, 35, 38
Examine associations with large numbers of SNPs in candidate genes	<i>KCNE1</i> D85N identified as a risk allele (1.8–29% in controls; 8.6% in cases; odds ratio 9–12)	39
	<i>NOS1AP</i> variant as modulator of amiodarone-induced diLQTS	40
	<i>NOS1AP</i> and <i>NUBPL</i> variants as potential modulators of QT prolongation by antipsychotics	46
Genome-wide association study (GWAS) of QT prolongation by drugs	GWAS of QT prolongation Variant in <i>NRG3</i> as potential modulator of iloperidone effect	45
	Variant in <i>SLC22A23</i> as potential modulator of quetiapine effect	46
	Variant near <i>NRG3</i> as potential modulator of sotalol effect	44
Genome-wide association study (GWAS) of diLQTS	No variants at genome-wide significance in 216 diLQTS cases and 771 controls	41
Exome sequencing	Variants in <i>KCNE1</i> and <i>ACN9</i> reach significance. Slightly more rare variants in K ⁺ channel genes in cases (37%) versus controls (21%)	42
Identifying mutant zebrafish lines with exaggerated or blunted responses to dofetilide challenge	Variants in <i>GINS3</i> (implicated in control of baseline QT ²⁴) as potential diLQTS risk.	47

LQTS: long QT syndrome; diLQTS: drug-induce LQTS

Data from Refs 33, 35, 42, 44, 47.