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Pharmacogenetic Considerations in Diseases of Cardiac Ion Channels

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ABSTRACT
Phenotypic variation within a species arises from differences in genetic makeup between individuals. This inherent diversity empowers the species as a whole to explore and expand into new environmental niches and also to survive new stressors within an ever-changing environment. Paradoxically, one class of stressors currently challenging the human population is therapeutic drugs: medications designed to combat disease are often associated with a host of nonspecific side effects. Following earlier studies of the involvement of some cardiac ion currents in unwanted drug interactions, recent reports have identified not only the ion channel subunits involved but also a range of mutations and single nucleotide polymorphisms in ion channel genes that predispose to both drug-induced and familial cardiac arrhythmia. The tendency for individuals harboring specific, often common, gene variants to succumb to life-threatening cardiac arrhythmia, and the contribution of other factors such as drug interaction to disease etiology in these cases, are discussed here together with potential pharmacogenetic strategies for arrhythmia circumvention and therapy.

The tendency for genes to mutate is the key to evolution and the existence of distinct species of living organisms. Although some gene mutations arise and are selected against because of their adverse effects on the ability of an individual to survive and compete, other variants are not harmful, are not selected against, and thus either predominate or coexist as common sequence variants in the general population (Darwin, 1859; Mendel, 1901). In contrast to conventional evolutionary pressures, the rapidity with which humans can alter their lifestyle and surroundings produces abrupt incompatibilities between the human genome and its environment, exemplified by the response of human populations to therapeutic drugs. Individual responses to drug treatment vary due to a variety of extrinsic and intrinsic factors, ranging from gross differences between patients that determine how a drug is absorbed or eliminated based on weight, age, metabolism and clearance, to more insidious ones that are not as accessible to conventional measures of drug disposition. Increasingly, the specific gene variants underlying this variability are being identified, leading to a growing consensus that accounting for these variants will result in safer, more effective drugs. The field of pharmacogenetics, therefore, aims to provide insight into how genetic determinants may underlie a subject’s response to therapeutic drugs. In the study of cardiovascular diseases, a growing body of pharmacogenetic data suggests that mutations and more common single nucleotide polymorphisms in genes that encode cardiac ion channels can determine why certain patients respond better than others do to antiarrhythmic treatment. Furthermore, these gene variants can hold the key to understanding why individuals who are asymptomatic for cardiac disease will be exposed to risk for long QT syndrome, ventricular fibrillation, syncope, or sudden death when taking medication for unrelated causes.

Cardiac Ion Currents and Arrhythmia
The electrical activity required for cardiac contraction requires the precise, concerted action of cardiac ion channels. The depolarizing upstroke of the action potential is carried by

ABBREVIATIONS: ECG, electrocardiogram; MiRP, MinK-related peptide; JLNS, Jervell and Lange-Nielsen syndrome; AF, atrial fibrillation; K, channel, voltage-gated potassium channel; Na, channel, voltage-gated sodium channel; SNP, single nucleotide polymorphism.
the movement of positively charged sodium ions through voltage-gated sodium-selective channels into the cardiac myocyte cytoplasm. This depolarization initiates calcium influx and calcium release from intracellular stores, facilitating muscular contraction. Subsequently, delayed rectifier outward potassium currents govern the timing, rate, and completion of cellular repolarization (Fig. 1A). On surface electrocardiograms (ECGs) the length of the QT interval (Fig. 1B), which is measured from the onset of the QRS complex to the end of the T wave, is indicative of the time between ventricular depolarization and repolarization. The length of the interval can be influenced by several factors, including gender, age and the presence of structural heart disease. An abnormally long “corrected” QT interval (QTc, the QT interval corrected for heart rate) is indicative of a delay in ventricular repolarization. Delayed or disordered myocardial repolarization can lead to rhythm disturbances from increased automaticity or reentry circus rhythm. This electrical instability may cause ventricular tachyarrhythmias that deplete the contractile capacity, reducing cardiac output to degrees that cause syncope and sudden death (Fig. 1C). Unfortunately, there is no clear and universally accepted definition of long QT syndrome. A diagnostic schema has been proposed for clinical long QT syndrome, based on major and minor features, including QTc intervals ≥450 ms in men and ≥460 ms in women, abnormal T-wave morphology, and symptoms or family history suggesting malignant ventricular arrhythmias (Schwartz et al., 1993). This definition, however, predated genotyping for long QT syndrome and is limited by the low penetrance of QT prolongation, which has been reported in some populations of abnormal gene carriers, as well as presence of mild QT prolongation in some “normal” subjects (Priori et al., 1999).

Genetic analyses have shown that long QT syndrome most often arises from malfunction of ion channel subunits. The majority of known long QT syndrome cases are precipitated by either an insufficient outflow of potassium ions through potassium channels or an excess inflow of sodium ions through sodium channels (Splawski et al., 2000). In either case, repolarization of the myocardium is delayed, which may give rise to early after depolarizations. Early after depolarizations, should they reach sufficient amplitude, are capable of triggering an action potential. If there are regional differences in refactororiness, reentry may occur producing a distinct form of polymorphic ventricular tachycardia called torsades de pointes—observed as a twisting of the QRS axis around the isoelectric line on an ECG. Occurrence of torsades de pointes predisposes to life-threatening ventricular fibrillation (Fig. 1D), syncope, and sudden cardiac arrest.

Long QT syndrome can be divided into two broad categories: inherited and acquired. Inherited long QT syndrome, classified LQT1 to 7 according to the underlying gene defect (Table 1), is most often associated with mutations in genes encoding voltage-gated ion channel subunits. Acquired long QT syndrome occurs when one or more stimuli, such as drugs that block certain cardiac ion channels, precipitate a prolonged QT interval. Recent studies show that even in so-called “acquired” long QT syndrome cases there may be an underlying genetic predisposition, discussed later in detail. Other forms of inherited arrhythmia without a prolonged QT interval can also arise from ion channel gene mutations, such as catecholaminergic ventricular tachycardia, associated with mutation of the RyR2 calcium channel gene (Priori et al., 2000). By the same token, genes other than those encoding ion channels can cause long QT syndrome—exemplified by the linkage of LQT4 to mutations in ankyrin B (Mohler et al., 2003) (Table 1).

Six ion channel genes have been associated with human long QT syndrome: the voltage-gated sodium (Na+) channel α subunit SCN5A (Wang et al., 1995), voltage-gated potassium (K+) channel α subunits KvLQT1 (KCNQ1) (Wang et al., 1996) and HERG (KCNH2) (Curran et al., 1995), and K+ channel β subunits MinK (KCNJ1) (Splawski et al., 1997) and MiRP1 (KCNNE2) (Abbott et al., 1999). Mutations in KCNJ2, which encodes the Kir2.1 inward rectifier potassium channel, cause Andersen’s Syndrome—associated with long QT syndrome in combination with periodic paralysis and
**TABLE 1**
Cardiac ion channel genes, inherited diseases, and risk-associated SNPs
Summary of genes harboring mutations associated with inherited arrhythmia and common SNPs associated with increased risk of arrhythmia. A gene variant is classified as a common SNP rather than a mutation here if its estimated incidence is greater than 1% in the population studied. SNPs are listed as the amino acid number and its two known variants, with the risk-associated variant on the right. LQT(1–7) is the common nomenclature used to describe long QT syndromes based on genetic classification.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosomal Location</th>
<th>Protein</th>
<th>Associated Inherited Disease</th>
<th>SNPs and Frequency in Population</th>
<th>Cellular Effects of SNP</th>
<th>Putative SNP-Associated Risk</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ1</td>
<td>11p15.5</td>
<td>K, LQT1</td>
<td>LQT1 (JLNS or RWS); AF</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>Wang et al., 1996; Neyroud et al., 1997; Chen et al., 2003</td>
</tr>
<tr>
<td>KCNH2</td>
<td>7q35-36</td>
<td>HERG</td>
<td>LQT2</td>
<td>KCN97T; 16-25% in Finns, Germans</td>
<td>Mixed effects</td>
<td>Gender-biased predispation to atypical QT interval</td>
<td>Sangunnetti et al., 1995; Pietila et al., 2002; Bezzina et al., 2003; Wang et al., 1995; Chen et al., 1998; Splawski et al., 2002</td>
</tr>
<tr>
<td>SCN5A</td>
<td>3p21-24</td>
<td>Cardiac sodium channel</td>
<td>LQT3, IVF, e.g., Brugada syndrome</td>
<td>S110Y; 13.2% in African-Americans</td>
<td>Gain of function</td>
<td>Predisposition to acquired arrhythmia</td>
<td>Pietila et al., 2002; Bezzina et al., 2003; Wang et al., 1995; Chen et al., 1998; Splawski et al., 2002</td>
</tr>
<tr>
<td>AnkB</td>
<td>4q25-27</td>
<td>Ankri-mB</td>
<td>LQT4</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>Mohler et al., 2003</td>
</tr>
<tr>
<td>KCNE2</td>
<td>21q22</td>
<td>MRP1</td>
<td>LQT5 (JLNS or RWS)</td>
<td>D83N; 7% in U.S.; S38G, 63–80% in Chinese</td>
<td>N.D.</td>
<td>N.D. Statistical association: D83N and aLQTS; S38G and AF</td>
<td>Wang et al., 2002; Lai et al., 2002</td>
</tr>
<tr>
<td>KCNJ2</td>
<td>1q23-34</td>
<td>Kir2.1</td>
<td>LQT7 (Andersen’s syndrome)</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>Abbott et al., 1999; Sesti et al., 2000; Ishard et al., 2002</td>
</tr>
<tr>
<td>RYR2</td>
<td>1q42-43</td>
<td>Ryanodine Receptor</td>
<td>CVT</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>Priori et al., 2000</td>
</tr>
</tbody>
</table>

aLQTS, acquired long QT syndrome; CVT, catecholaminergic ventricular tachycardia; IVF, idiopathic ventricular fibrillation; N.D., not described.
both JLNS and Romano-Ward syndrome, which greatly reduces \( I_{Ks} \) current density in a dominant-negative fashion by a combination of reduced unitary conductance, impaired activation, and accelerated deactivation (Splawski et al., 1997; Sesti and Goldstein, 1998). Of note, the D76N variant of MinK also greatly impairs MinK/HERG currents (McDonald et al., 1997), highlighting an emerging principle that \( KCNE \) mutations may cause arrhythmia by promiscuous disruption of multiple cardiac currents (Abbott and Goldstein, 2002). Recent studies also demonstrated linkage of a rare gain-of-function \( KCNQ1 \) mutation, S140G, with familial atrial fibrillation (AF) (Chen et al., 2003) and showed that the more common SNP of MinK, 38G (as opposed to 38S), is enriched in AF patients versus controls, especially in the homozygous form (AF, 59.3%; control, 42.6%) (Lai et al., 2002).

HERG and MiRP1 Mutations Associate with Inherited Long QT Syndrome

HERG \( \alpha \) subunits underlie the cardiac \( I_{Kr} \) current, crucial for ventricular repolarization in many species including man (Sanguinetti et al., 1995). Biophysical studies on HERG have revealed a peculiar attribute for a protein with classical \( K_{v} \) channel topology, that of inward rectification. \(^1\) Although HERG channels open rapidly in response to membrane depolarization, they very rapidly inactivate at more positive potentials. Upon membrane repolarization, however, HERG channels rapidly recover from inactivation and pass large currents before they close (deactivate) — thus displaying an inwardly rectifying current/voltage relationship. Despite this, at physiological membrane potentials and potassium concentrations, HERG channels pass only outward current, and their peculiar properties ensure that they are poised to supply a significant repolarizing force near the end of the cardiac action potential.

A range of biophysical, pharmacological and genetic data suggests that HERG may employ \( KCNE \) subunits to generate \( I_{Kr} \) in some cardiac cells. HERG currents are up-regulated by coassembly with MinK in heterologous experiments, and MinK/HERG complexes are detectable in equine heart (McDonald et al., 1997; Finley et al., 2002). Furthermore, MiRP1 (\( KCNE2 \)) coassembles with HERG, forming mixed complexes with reduced unitary conductance, faster deactivation and altered sensitivity to some pharmacological agents compared with homomeric HERG channels (Abbott et al., 1999). This together with increasing genetic evidence (see below) suggests that MiRP1 may form \( I_{Kr} \) complexes with HERG in some regions of human heart. It will be important to establish the true molecular identity of \( I_{Kr} \), given that association with \( KCNE \) subunits can alter HERG pharmacology and that drug blockade of \( I_{Kr} \) is the primary cause of acquired arrhythmia in humans.

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\(^1\) Most inwardly rectifying \( K_{v} \) channels are formed by coassembly of four principal subunits each with only two transmembrane domains and a membrane-embedded pore region; they possess no intrinsic voltage sensor and are inwardly rectifying because of blockade at depolarized voltages by intracellular moieties such as \( \text{Mg}^{2+} \) ions or polyamines.
Mutations in both HERG and MiRP1 are associated with inherited arrhythmia in humans (Curran et al., 1995; Abbott et al., 1999; Isbrandt et al., 2002). HERG mutations are most prevalent within the intracellular domains, particularly—in contrast to KCNQ1—in the N-terminal region, although hot spots also exist in and around the pore region and in the putative cyclic nucleotide-binding domain (SPLAWSKI et al., 2000). The three reported MiRP1 mutations associated with inherited long QT syndrome—M54T, I57T, and V65M—are all within the putative transmembrane domain and are associated with various loss-of-function effects on MiRP1/HERG channel gating and conductance (Abbott et al., 1999; Isbrandt et al., 2002).

HERG and MiRP1 Are Key Molecular Determinants in Acquired Long QT Syndrome

It is far more common for long QT syndrome to be acquired rather than inherited (Roden, 2001). In these instances, cardiac abnormalities are not manifested until some extrinsic factor, such as medication or metabolic abnormality, precipitates an aberrant cardiac rhythm. Acquired QT syndrome has been an intractable clinical problem because it occurs so unpredictably; however, two lines of research are now providing hope that it does not need to remain so: identification of the IKr current as a key mediator of arrhythmogenic drug activity, and the growing consensus that cardiac abnormalities are not manifested until some extrinsic stressor reduces the "repolarization reserve", i.e., the capacity of available ion currents to repolarize the myocardium, to such an extent that timely repolarization cannot occur beat-to-beat (Roden, 2001). Probably the most common clinical presentation of this is drug-induced torsades de pointes, in which a patient who may or may not have additional risk factors develops dysrhythmia after taking a medication. Among cardiac ion currents, inhibition of IKr in particular is implicated in cases of acquired long QT syndrome, and there is a clear mechanistic basis for this. If one examines the list of factors that can contribute to acquired long QT syndrome, including medication, hypokalemia, female gender, slow heart rate and inherited prolongation of the QT interval, some clear links to IKr are evident, which are discussed below.

Why Is HERG So Often Implicated in Drug-Induced Torsades de Pointes? HERG and IKr are highly sensitive to block by a broad spectrum of drugs: antidepressants (amitriptyline, imipramine), antipsychotics (chlorpromazine, haloperidol), antihistamines (teradine, astemizole), anti-anginal agents (bepridil), and antibiotics (sulfamethoxazole, clarithromycin, erythromycin) (Abbott et al., 1999; Kass and Cabo, 2000; Mitcheson et al., 2000; Sesti et al., 2000; Roden, 2001). Class IA and class III antiarrhythmic drugs may themselves cause long QT syndrome; a drug concentration that slightly prolongs the action potential plateau and is antiarrhythmic for some patients may be sufficient to induce LQT and act as a proarrhythmic in others (Kass and Cabo, 2000). A mechanism has been put forward for the molecular basis of the unusual avidity of HERG for a wide range of pharmacological agents (Mitcheson et al., 2000). First, unlike most other Kv channels, HERG lacks two specific proline residues that normally produce a kink that limits the volume of the inner cavity of the channel. Therefore, the larger HERG cavity volume may allow relatively large drugs to enter and prevent the channel from conducting potassium. Second, HERG has two aromatic residues that face the inner cavity of the channel; results of alanine-scanning mutagenesis have led to the conclusion that these residues facilitate the interaction of HERG with aromatic groups on drugs in the inner cavity by a π-stacking interaction, again favoring drug binding and channel blockade. Third, the unusual gating of HERG channels may also increase the chances of drugs being trapped within the inner cavity. Thus, unwanted clinical side effects from a wide spectrum of medications are mediated through blockade of IKr, largely because of the unusual properties of the HERG pore-forming α-subunit.

Ion Channel Gene Variants That Predispose to IKr-Associated Drug-Induced Torsades de Pointes. The peculiar structural and functional attributes of HERG most likely underlie its drug susceptibility, but this does not explain why some individuals are affected and not others. Recent studies have identified a genetic basis for variable tolerance to channel-blocking drugs: sequence variants in ion channel genes. Genetic analyses of cohorts of patients exhibiting drug-induced arrhythmia show that 10 to 15% of them harbor ion channel gene mutations or SNPs, a significant enrichment compared with the control population (Yang et al., 2002). In contrast to inherited long QT syndrome, the most frequent mutations found so far in acquired torsades de pointes populations are within KCNE genes and mostly in MiRP1 (KCNE2) (Abbott et al., 1999; Sesti et al., 2000; Yang et al., 2002). Gene variants associated with acquired arrhythmia can be considered as one of three categories, which we describe here as indirect, direct, and compound. Indirect mutations are those that impair IKr at baseline, do not affect drug sensitivity, but are associated with arrhythmia after drug administration because of superimposition of inherited impairment and coincidental drug blockade of IKr, e.g., A116V-MiRP1 with quinidine (Sesti et al., 2000). Direct mutations are perhaps the most insidious variants—those that do not affect IKr predrug but increase sensitivity to drug blockade (Priori et al., 1999). These cause no detectable phenotype before drug administration, either as QT prolongation on the patient’s ECG or by in vitro analysis in absence of drug. An example is the T8A-MiRP1 SNP, present in 1.6% of the U.S. population, which was identified in a patient who developed prolonged QTc after taking the commonly prescribed antibiotic combination of sulfamethoxazole and trimethoprim. T8A-MiRP1 increases 4-fold the sensitivity of MiRP1/HERG channels to blockade by sulfamethoxazole, without altering affinity for trimethoprim (Sesti et al., 2000). The existence of “silent” drug-susceptible SNPs such as this argues for preprescription genotyping when feasible, although other factors such as differences in drug metabolism and adrenergic stimulation, or SNPs in other subunits, probably play a role in the disease etiology of T8A-associated long QT syndrome. Otherwise, many more individuals would have succumbed to T8A-related arrhythmias, given the common occurrence of this variant and the widespread use of sulfamethoxazole. Alternatively, it may be necessary for an individual to be T8A/T8A homozygous before significant drug sensitivity is observed, a genotype predicted to occur in only 0.026% of the U.S. population. Compound mutations are...
those that both impair channel function at baseline, and also increase sensitivity to \( \text{IKr} \) blockade—an example is Q9E-MiRP1, which was discovered in a female after clarithromycin treatment precipitated torsades de pointes. Q9E impairs channel gating and also increases sensitivity to clarithromycin blockade (Abbott et al., 1999). In a recent study, two \( \alpha \) subunit mutations, one in HERG and one in KCNQ1, were found in acquired arrhythmia patients but not in controls; both mutations reduced current density at baseline but differences in drug sensitivity were not discussed. Furthermore in a preliminary study, a MinK SNP (D85N) that alters IKs kinetics was found to be enriched in acquired arrhythmia patients (7%) versus controls (2–4%) (Yang et al., 2002).

Other Factors That Contribute to \( \text{IKr} \)-Associated Acquired Arrhythmia. There are at least two other risk factors for acquired arrhythmia that can be mechanistically linked to \( \text{IKr} \): gender and hypokalemia (Rodên, 2001). Women are more vulnerable to torsades de pointes caused by \( \text{IKr} \)-blocking drugs than men (Makkar et al., 1993), although two recent, apparently contradictory, studies are illustrative of the further complexity of this gender-based susceptibility. A HERG SNP, K897T, is relatively common (16–25%, depending on ethnicity and/or study group size). In a study of middle-aged Finns, K897T was associated with significantly increased QTc in women but not men (Pietila et al., 2002). In contrast, in a study of German Caucasians, K897T was associated with shortened QTc, and more significantly in women than men (Bezzina et al., 2003). The reports suggest that other genetic and/or environmental factors contribute to \( \text{IKr} \) phenotype, highlighting the potential complexity of pharmacogenetic prediction of factors predisposing to cardiac arrhythmia.

Another predisposing factor for acquired arrhythmia is hypokalemia. In several studies of patients with torsades de pointes, hypokalemia was considered a contributory factor in the context of missense mutations in either HERG (S818L and V822M) (Berthet et al., 1999) or MiRP1 (Q9E) (Abbott et al., 1999). This has been attributed to several properties of HERG (Rodên, 2001); the most well characterized of these being that contrary to what one would expect, outward HERG current is decreased by reduction of extracellular potassium near physiological levels despite an increase in electrochemical gradient (Sanguinetti et al., 1995). Therefore hypokalemic patients receiving \( \text{IKr} \) blockers such as quinidine and dofetilide are at increased risk for acquired long QT syndrome (Berthet et al., 1999) because of an already reduced repolarization reserve (Rodên, 2001). Increasing serum potassium in patients suffering from hypokalemia-induced torsades de pointes shortens the QT interval and attenuates abnormalities in myocardial repolarization.

Lethal Mutations and Subtle SNPs in the SCN5A Gene

Voltage-gated sodium channel genes encode large plasma membrane proteins organized into four covalently linked, similar repeating units each resembling superficially \( \kappa \), \( \alpha \) subunits (Fig. 2C). The SCN5A cardiac \( \text{Na}^{+} \) channel is primarily responsible for the depolarizing Phase 0 of the cardiac action potential (Fig. 1A). Arrhythmia-associated SCN5A mutations are most often gain-of-function mutations, causing increased net inward current flux of \( \text{Na}^{+} \) ions through SCN5A channels and preventing timely repolarization. The most common mechanism for sodium channel gain-of-function is a destabilization of the inactivated state, causing either delayed inactivation or an increase in plateau current. Aside from long QT syndrome, other familial cardiac arrhythmias are known although the underlying gene defect is not always understood. One well understood example is the Brugada syndrome, a form of idiopathic ventricular fibrillation again caused by SCN5A mutations (Chen et al., 1998). This disorder manifests as J-point and ST segment elevation in the right precordial leads of the ECG, without significant prolongation of the QT interval. Patients with the Brugada syndrome may be susceptible to ventricular arrhythmias after treatment with drugs that block \( \text{IKr} \), specifically class I antiarrhythmic agents such as flecainide, which is used to accentuate the ECG abnormalities of suspected Brugada patients to aid diagnosis (Gasparini et al., 2003). SCN5A mutations are capable of producing a wide range of clinical symptoms; whereas LQT and Brugada syndrome sufferers experience life-threatening arrhythmias, other SCN5A mutations can cause cardiac-conduction disease, light-headedness, or syncope.

In 2002, Splawski and colleagues reported a S1102Y SNP in the SCN5A gene that is associated with increased risk of cardiac arrhythmia. At the cellular level, the S1102Y SNP increases the rate of activation of the sodium channel, as well as allowing greater peak amplitude and a larger sustained current than the wild-type protein (Splawski et al., 2002). The proband was a 36-year-old African-American woman with idiopathic dilated cardiomyopathy and hypokalemia who developed long QT syndrome while on the antiarrhythmic drug amiodarone. When the frequency of Y1102 was analyzed in the general U.S. population using control samples, it was found to be substantially more prevalent in West African, Caribbean, and African-American populations. Though most carriers will not develop arrhythmia, the Y1102 SNP appears to increase the likelihood of arrhythmia when superimposed upon other risk factors. Thus, as with MiRP1, SCN5A sequence variability represents a tangible molecular basis for predisposition to acquired arrhythmia (see Table 1).

Gene-Guided Therapies

Several proposed experimental strategies for therapy are emerging based on current knowledge of the molecular basis of cardiac ion channel disorders. A subset of long QT syndrome-associated mutations, most commonly in HERG, reduces \( \text{IKr} \) by defective HERG trafficking. HERG blockers such as E-4031 can actually increase \( \text{IKr} \) current density in these cases by acting as “pharmacological chaperones” that stabilize HERG, reducing misfolding and retention, and more recent studies have identified agents such as fexofenadine that rescue HERG mutants without channel block (Rajamani et al., 2002). Fexofenadine (terfenadine carboxylate), a metabolite of terfenadine, is a H1 receptor antagonist currently used to treat allergies, but it also binds to HERG channels with only weak channel block, unlike terfenadine, which was withdrawn from sales because of high-affinity HERG block. A pharmacological approach has also been used to rescue long QT syndrome-associated mutant \( \text{IKr} \) channels, using stilbenes and fenamates that bind to \( \text{IKr} \) channels and restore the allosteric interplay between MinK and KCNQ1 necessary
for correct channel function (Abitbol et al., 1999). Application of these therapies to patients will require genotyping to identify mutants that would benefit from specific rescue strategies.

Another gene-guided approach is gene therapy; although this has been hampered by practical difficulties in safe and specific delivery, experimental reports describe the possible future applicability of this to human ion channel disorders. Ectopic expression of MiRP2, which forms a constitutively open potassium channel with KCNQ1, enhances repolarization in guinea pigs and thereby reduces the QT interval (Mazhari et al., 2002). The use of Q9E-MiRP1 has also been explored as a potential therapy for reentrant atrial cardiac arrhythmias (Burton et al., 2003). Blockade of Q9E-MiRP1/HERG channels with clarithromycin gives repolarization-delaying effects similar to those of class III antiarrhythmics (Abbott et al., 1999). Thus it is proposed that ectopic expression of Q9E-MiRP1 in affected atrial tissue combined with application of low doses of clarithromycin could delay atrial repolarization enough to block reentrant atrial arrhythmias without affecting less-sensitive wild-type I_{Kr} channels in the ventricle, therefore avoiding the unwanted side effect of ventricular long QT syndrome.

A third strategy, and one that is already being tested in cases of inherited arrhythmia, is the use of the genetic lesion to guide the choice of antiarrhythmic drug. An example is the indication of flecainide treatment for patients carrying the SCN5A-AKPQ mutation that causes abnormal, repetitive openings of the cardiac sodium channel and thus a delay in repolarization. Flecainide, a potent open sodium channel blocker, reduced the average QTc interval in five male ΔKPQ patients by almost 100 ms, consistent with blockade of the abnormal reopenings that occur during the plateau phase in SCN5A-ΔKPQ sodium channels (Windle et al., 2001).

A further potential strategy that exploits knowledge of the molecular etiology of drug-channel interactions in arrhythmia, and one that may prove the most beneficial to public health overall, is that of avoidance of specific drug-gene variant interactions by tailoring drugs and drug prescriptions based on gene mutations or common SNPs harbored by individuals requiring arrhythmia therapy. This approach relies upon patient genotyping and the existence of a database of known adverse drug-gene interactions. At present, widespread spread genotyping is hampered by practical considerations; a nonbiased approach to genetic profiling requires the sequencing of tens of thousands of allelic variants per individual, too costly and time-consuming with present technologies. How- ever, the sequencing of hundreds of thousands of SNPs in 2 years; by late 2001, 1.4 million SNPs were released into the public domain, and this number continues to grow. Ready availability of genetic information is already beginning to aid diagnoses and guide treatment options for patients with cardiac arrhythmias and may lead to bespoke drugs designed by pharmaceutical companies to best suit patients with more common SNPs. Thus, whereas therapeutic drugs expose the inherent vulnerability of many individuals to emergent stressors, research into the mechanisms behind adverse drug-pharmacogenomic interactions will ultimately lead to a gene-guided design of compounds that are not only safer but also more effective because of our increased understanding of drug-protein interactions.

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Mohler PJ, Schott JJ, Gramolini AO, Dilly KW, Gustimosin S, duBuell WH, Song LS, Haurogne K, Ryndt F, Ali ME, et al. (2003) Ankyrin-B mutation causes type 4 disease onset. Recently, an SNP Consortium was launched to produce a public resource of SNPs in the human genome (http://snps.cshl.org). Originally, the goal was to discover 300,000 SNPs in 2 years; by late 2001, 1.4 million SNPs were released into the public domain, and this number continues to grow. Ready availability of genetic information is already beginning to aid diagnoses and guide treatment options for patients with cardiac arrhythmias and may lead to bespoke drugs designed by pharmaceutical companies to best suit patients with more common SNPs. Thus, whereas therapeutic drugs expose the inherent vulnerability of many individuals to emergent stressors, research into the mechanisms behind adverse drug-pharmacogenomic interactions will ultimately lead to a gene-guided design of compounds that are not only safer but also more effective because of our increased understanding of drug-protein interactions.
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