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# Personalized medicine to treat arrhythmias

Dan M Roden

The efficacy of antiarrhythmic drug therapy is incomplete, with responses ranging from efficacy to no effect to severe adverse effects, including paradoxical drug-induced arrhythmia. Most antiarrhythmic drugs were developed at a time when the mechanisms underlying arrhythmias were not well understood. In the last decade, a range of experimental approaches have advanced our understanding of the molecular and genomic contributors to the generation of an arrhythmia-prone heart, and this information is directly informing targeted therapy with existing drugs or the development of new ones. The development of inexpensive whole genome sequencing holds the promise of identifying patients susceptible to arrhythmias in a presymptomatic phase, and thus implementing preventive therapies.

**Addresses**
Vanderbilt University School of Medicine, Nashville, USA

Corresponding author: Roden, Dan M (dan.roden@vanderbilt.edu)

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## Introduction

The idea of 'personalizing medicine' is increasingly used synonymously with the idea of applying information about genomic variation to understand disease risk, disease progression, and variable drug responses in an individual [1]. However, physicians have been 'personalizing' care of patients for millennia, taking into account readily identifiable features such as age, sex, ancestry, educational level, or personal wishes such as desirability for complex therapy at end of life; these are important aspects of personalizing care. This review will address how advances in genomic medicine are providing a new potential dimension to such personalization, specifically in arrhythmia management, and will describe avenues for future work in the field. Work identifying key genetic variants that create an arrhythmogenic substrate will be described first and the way in which this knowledge is being increasingly applied to clinical medicine will then be discussed.

## Genetic variants and arrhythmia susceptibility

The field attempts to identify genetic variants associated with arrhythmia susceptibility using either candidate or unbiased approaches in families and/or in large populations in which individuals are phenotyped as affected or unaffected for a target phenotype. Candidate approaches examine the association between specific genotypes, chosen on the basis of an understanding of underlying pathophysiology, and the phenotype. The advantage is that the specific variants make some physiologic sense; however, this approach is now well-recognized to suffer from very frequent failure of replication [2]. Unbiased approaches include linkage analysis in large kindreds and genome-wide association studies (GWAS), enabled by the identification of large numbers of common single nucleotide polymorphisms (SNPs), in populations. Major advantages are statistical rigor and identification of entirely new pathways to arrhythmia susceptibility. The family approach requires large kindreds, but recent developments in genome sequencing have opened the possibility of identifying new disease genes even in small families with a single affected individual.

### Familial arrhythmia syndromes

The idea that rare familial syndromes confer high risk for arrhythmias has been recognized since the mid-20th century. Studies of large, multi-generational kindreds with highly penetrant forms of congenital arrhythmia syndromes led, in the mid-1990s, to the identification of disease genes initially in the long QT syndromes [3,4] and subsequently in other familial arrhythmia entities. The work has not only identified disease genes for these rare syndromes, but has also elucidated the key molecular components governing normal cardiac electrophysiology. Similar approaches have implicated disease genes for multiple subtypes of other congenital arrhythmia syndromes such as catecholaminergic polymorphic ventricular tachycardia (CPVT), the Brugada syndrome, and the short QT syndrome. While these are unusual diseases, the delineation of disease genes, the development and wide deployment of genetic testing, and the increasing recognition by the general cardiology community of these unusual phenotypes have led to the recognition that the diseases are less rare than previously appreciated, and that the manifestations may be milder than those in the initially described cases and highly variable across mutation carriers even within individual families, the phenomenon of incomplete penetrance [5,6•]. As discussed below, recognition of congenital arrhythmia syndromes of this type is especially important to guide therapies since knowledge of the fundamental underlying pathophysiologic disturbance, derived directly from human genetics, often informs rational, mechanism-based therapies [7].

The congenital long QT syndromes are a collection of diseases characterized by prolongation of the QT interval on the surface electrocardiogram and their susceptibility to a morphologically distinctive ventricular tachyarrhythmia termed 'torsades de pointes'. The evidence linking specific genetic variants to the congenital long QT syndrome in specific families is variable: in some cases, there is strong evidence from genetic linkage in large families whereas in other cases, a rare variant has been described in an ion channel or modulatory protein gene that segregates with the phenotype and is therefore implicated as a disease gene. Notably, in the latter cases, formal strong genetic evidence is lacking and so the association may be spurious [8].

These genetic studies have identified increased net inward current during cardiac repolarization as the fundamental lesion in the congenital long QT syndrome. This can arise from mutations that cause loss of outward current, notably in the potassium channel genes *KCNQ1* and *KCNH2* or their subunits, or mutations that directly cause increased inward current through sodium or calcium channels during the repolarization process. Notably, the identification of these mutations has served to directly highlight and clarify the role of the encoded channels in normal cardiac physiology. Thus, for example, the channel resulting from expression of *KCNQ1* with its function modifying subunit *KCNE1* generates $I_{Ks}$, an adrenergically sensitive current that probably serves to limit action potential prolongation under conditions of sympathetic stimulation. Similarly, the channel resulting from *KCNH2* expression (termed HERG or Kv11.1) is now recognized to play a key role in driving the cardiac potential from plateau potentials toward resting potentials during late phase 3 of the action potential. Most recently, the unbiased approach of whole exome sequencing in *de novo* severe long QT syndrome cases in neonates has identified mutations in calmodulin [9•]. While the mechanisms are still being explored, the finding itself highlights the potential for new technologies in human genetics to advance our understanding of basic mechanisms.

## GWAS for ECG phenotypes

The GWAS technique has been applied to identify multiple loci in which polymorphisms contribute to variability in the QT interval and other intervals on the electrocardiogram. The strongest QT signal is surprisingly near the *NOS1AP* gene, encoding an ancillary protein for neuronal nitric oxide synthase, and not previously implicated in cardiac electrophysiology [10,11]; one report implicates the encoded protein (termed CAPON) and as a modulator of electrical signaling in heart, but confirmatory data remain lacking [12]. Interestingly, these GWAS analyses of the QT interval have also implicated common variation at the congenital long QT syndrome disease genes as a modulator of QT interval. That is, rare variants in these genes may cause the congenital long QT syndrome, while common variants contribute to variability in the QT interval in the population. Interestingly, variants in QT GWAS loci (in *KCNH2*, *NOS1AP* and *KCNQ1*) have been implicated as modulators of the clinical severity of the congenital long QT syndromes, that is, common variants appear to contribute to variable penetrance [13–16]. This is an example of how gene–gene interactions may identify clinical subsets with extreme values of human traits such as arrhythmia susceptibility.

## Drug-induced long QT syndrome

A clinical entity related to the congenital long QT syndrome is the drug-induced form of the disease (diLQTS) [17]. diLQTS not only occurs in 1–3% of patients treated with QT prolonging antiarrhythmic drugs (usually to prevent atrial fibrillation), but also occasionally and unpredictably arises during treatment with 'non-cardiovascular' drugs such as certain antibiotics, antipsychotics, and methadone; indeed, diLQTS has been a major cause of drug relabeling and withdrawal. Evidence that diLQTS shows a genomic component include the clinical similarity to the congenital LQTS and one small study that suggested that first degree relatives of individuals with diLQTS displayed exaggerated responses when challenged with the QT-prolonging antiarrhythmic quinidine [18]. A range of genetic approaches, from candidate gene to unbiased techniques, have been applied to study subjects with diLQTS. In a large candidate gene study, a variant resulting in D85N in *KCNE1* was associated with an increased risk for diLQTS, with an odds ratio of approximately 10 [19••]. In another study, variants in *NOS1AP* were found to be associated with an increased risk for amiodarone-related diLQTS [20]. A GWAS that examined 216 cases of diLQTS in Caucasians and 771 ancestry-matched controls found no common variant that increased risk [21]. This finding, in turn, suggests that rare variants or as yet uncertain (and perhaps non-genetic) factors modulate risk. Small studies using next generation sequencing have suggested an increased burden of rare variants in congenital long QT syndrome disease genes among patients with diLQTS [22,23].

## Atrial fibrillation

The commonest arrhythmia seen in clinical practice is atrial fibrillation, which increases risk for stroke, congestive heart failure, and death. There is considerable variation in the way in which patients with atrial fibrillation present, from the relatively young, apparently healthy individual devoid of traditional risk factors (which include diabetes and hypertension) to the elderly patient with evidence of underlying structural heart disease and multiple other risk factors. A history of atrial fibrillation among first-degree relatives is another risk factor, implying a genetic component to risk [24,25]. Indeed, families with apparently Mendelian forms of