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Personalized medicine to treat arrhythmias

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Abstract

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 mechanism 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.

Keywords

genomics; pharmacogenomics; arrhythmia; long QT syndrome; atrial fibrillation

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 “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

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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 associations 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 as a consequence 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 has 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 is 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, i.e. 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 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 includes 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 atrial fibrillation and early onset have been described, and in some cases genomic

loci and individual genes have been implicated by both linkage and candidate gene approaches. Examples include mutations in genes encoding ion channels [26,27], in *NPPA* which encodes atrial natriuretic peptide [28], and somatic mutations in *GJA5* encoding an atrial-specific connexin [29]. Similarly, the GWAS paradigm has been successfully applied to identify common genomic variation associated with increased atrial fibrillation risk [30,31]. Again, new genes and pathways have resulted. By far, the strongest signal for atrial fibrillation susceptibility is a set of SNPs at chromosome 4q25, near the gene encoding the transcription factor *PITX2*.

One goal of genomic studies in atrial fibrillation is to identify patients susceptible to arrhythmia prior to development, so that prophylactic therapies to prevent the arrhythmia and its consequences might eventually be implemented. Within a family, even rare variants that appear to confer high risk may not cause the arrhythmia in all carriers, the phenomenon of incomplete penetrance. By contrast, the risk associated with common variation such as that at chromosome 4q25 is generally small, with odds ratios under 2. Several lines of evidence have now implicated combinations of variants (gene-gene interactions) as increasing risk for the development of the arrhythmia [6,32]; eventually, genetic risk scores may add importantly to our ability to identify patients in advance of the development of the arrhythmia. Another key hypothesis that genomic studies enable is the idea that genetics may be used to identify specific subsets of patients with atrial fibrillation, with the idea of selecting more effective therapies in individual patients [33].

The way in which common or rare variants generate an atrial fibrillation-prone substrate is under intensive study. Shortening of atrial action potentials and development of atrial fibrosis are commonly invoked. A cardiac specific splice variant of *PITX2* is known to modulate left-right development in early heart, and to underlie development of a sleeve of left atrial myocardium that invaginates into the pulmonary veins [34]; this is a particularly important observation since mapping studies have revealed that atrial fibrillation commonly originates from abnormal automaticity in such pulmonary sleeves. *Pitx2*-null mice display inducible atrial fibrillation and upregulation of possibly profibrillatory genes such as *Kcnq1* and *Nppa* [35]. Thus, as with studies in the congenital arrhythmia syndromes, genomic discoveries advance our understanding of the fundamental basis for atrial fibrillation, as they identify new genes, and thus point to new genetic pathways contributing to risk for the arrhythmia. Elucidating these pathways may well enable development of new biomarkers and ultimately new drugs targeting specific underlying pathophysiologic defects in individual subjects.

Other arrhythmias

Other forms of ventricular tachycardia and ventricular fibrillation commonly arise in the setting of advanced underlying heart disease, usually due to acquired lesions such as coronary artery disease but occasionally arising from cardiomyopathies (which are often, in turn, genetic). A GWAS has implicated variants at chromosome 21q21 as modulating risk for ventricular fibrillation due to acute coronary artery occlusion; the closest gene, *CXADR*, encodes a Coxsackie virus receptor and has been implicated as a modulator of cardiac conduction [36]. This signal remains to be further validated, and currently does not have any implications for individualized therapy.

Using new genomic knowledge to personalize antiarrhythmic therapy

Response to currently used antiarrhythmic therapies is notoriously variable, with some patients deriving clear cut benefit, such as reduction in episodes of paroxysmal atrial fibrillation, while other derive no benefit or even develop new arrhythmias, such as diLQTS.

Pharmacokinetic variation

Some variability in response to antiarrhythmic drug therapy, as in variability in response to many other forms of pharmacologic therapy, can be attributed to variable drug disposition [37]. For example, loss-of-function variants in *CYP2D6*, encoding a hepatic cytochrome P450 responsible for metabolism of approximately 25% of clinically used drugs, are common, and 5–10% of Caucasian and African populations carry loss-of-function variants on both *CYP2D6* alleles, “poor metabolizers”. *CYP2D6* is responsible for the bio-inactivation of a number of beta-blockers, including metoprolol and timolol, and use of these drugs in poor metabolizers (or the co-administration of potent *CYP2D6* inhibitors such as certain SSRIs or quinidine in extensive metabolizers) can result in high drug concentrations, and increased risk for bradyarrhythmias and bronchospasm. The sodium channel blocking antiarrhythmic propafenone is also metabolized by *CYP2D6*. In this case, the downstream metabolite 5-hydroxy propafenone, retains the sodium channel blocking properties of the parent drug but is devoid of its beta-blocking activity. As a result, poor metabolizers administered propafenone develop higher concentrations of the parent drug, and display greater heart rate slowing. The digitalis glycoside digoxin is excreted unchanged in the bile and kidney by P-glycoprotein, the drug efflux transporter encoded by *ABCB1*. Some reports suggest that variants in *ABCB1* are associated with higher digoxin concentrations and thus, possibly, an increased risk for drug toxicity. These examples highlight the principle that for each drug, a set of genes whose products are responsible for absorption, distribution, metabolism, and elimination can be identified and, as a consequence, variants in these pathways can be associated with variable drug concentrations and thus drug actions.

Targeting specific molecular mechanisms

Most antiarrhythmic drugs were developed long before the molecular and cellular basis of arrhythmias was well defined, and thus currently used drugs often interact with multiple potential drug targets (such as ion channels or beta receptors) and thus do not target the molecular basis for arrhythmogenesis in an individual subject. With an increase in understanding of the molecular basis of certain arrhythmias, as described above, has come the opportunity to target therapies specifically to underlying molecular derangements and thus increase efficacy.

Targeting specific molecular mechanisms – congenital arrhythmia syndromes

The familial arrhythmia syndromes provide beautiful examples of how application of this paradigm can inform mechanism-based therapy. The *KCNQ1*- and *KCNE1*-linked forms of congenital LQTS result in defective I_{Ks} and this explains the clinical observation that patients with these subtypes of the disease most often develop arrhythmias during exercise or other adrenergic stress [38]. In these patients, beta-blockers are therefore a logical mechanism-based therapy, and indeed are highly effective [39]. By contrast, mutations in the cardiac sodium channel gene *SCN5A* cause the congenital LQTS subtype 3 by destabilizing the channel's fast inactivation [40]. As a result, the channel does not remain closed during plateau of the action potential, thereby generating a persistent inward current that accounts for action potential prolongation. Preliminary data strongly support the idea that drugs which block this “late” cardiac sodium channel can be effective in LQT3 [41,42]. The situation is somewhat murky, however, because block of cardiac sodium channels can, itself, be arrhythmogenic [43,44] and because many of these patients appear to derive some benefit from beta blocker therapy. Thus, an increasing body of knowledge supports the concept that diverse molecular lesions can culminate in the long QT syndrome phenotype, and understanding the specific genetic lesion may, in turn, inform rational therapy. Within the last several years, accrual of large numbers of subjects with congenital LQTS has enabled tests of the hypothesis that specific residues or regions within the mutant channels

may confer different pathophysiologies, notably in terms of response to therapies such as beta blockade [45]. Thus, genotyping in patients with known congenital long QT syndrome is becoming standard of care as therapeutic decisions can be made on the basis of specific genotypes now, and in the future.

CPVT is caused by intracellular calcium dysregulation due to “leaky” ryanodine release channels and adrenergic stimulation exacerbates the “leak” in mouse models [7]. In patients with CPVT, arrhythmias occur consistently with exertion, and beta blockers are highly effective. In addition, studies in a mouse model surprisingly identified the sodium channel blocking drug flecainide as an effective antiarrhythmic [46]. Subsequent work has revealed that flecainide also blocks dysfunctional ryanodine release channels that underlie the clinical manifestations of this syndrome, and preliminary data strongly support the efficacy of the drug in patients [47].

Targeting specific molecular mechanisms – atrial fibrillation

Atrial fibrillation remains the commonest arrhythmia targeted by antiarrhythmic drugs, and the idea, based on the congenital long QT syndrome paradigm, that targeting drugs to specific molecular subtypes of the arrhythmia might improve efficacy is appealing. However, studies delineating such molecular mechanisms are, as outlined above, in their infancy and so it is not yet clinical standard of care to use genetic information to guide therapy in this arrhythmia. One approach is to target mechanisms in distinct functional subsets. For example, some patients develop atrial fibrillation at night or with vagal stimuli, and local application of acetylcholine or analogs to the atrium results in heterogeneous action potential shortening and atrial fibrillation with atrial stimulation. The underlying mechanism is likely shortened atrial action potential duration due to activation of I_{K-ACh} , and compounds targeting this channel are effective prevention of the arrhythmia in experimental animals.[48]

A number of reports have identified a relationship between AF susceptibility alleles at 4q25 and decreased efficacy of ablation [49,50], decreased antiarrhythmic drug therapy efficacy in AF [51], recurrent arrhythmia after elective cardioversion [52], and development of atrial fibrillation after cardiac surgery [53]. The mechanisms remain uncertain, but one possibility is that the 4q25 locus creates an AF substrate that is resistant to these forms of therapy by the time of initial clinical presentation; this could arise, for example, through enhanced atrial fibrosis occurring prior to initial presentation. If this were to be the case, then genetic testing to identify individuals at risk prior to initial presentation would be a possible therapeutic approach. Other studies have identified variants in beta adrenergic receptor genes as modulators of drugs used to slow ventricular response rates during atrial fibrillation [54]. The effects are modest, and at this point unlikely to impact clinical care.

Using mechanism-based knowledge to discover new targets

As discussed above, the identification of disease genes and underlying cellular mechanisms in the congenital arrhythmia syndromes has not only revolutionized our understanding of normal electrophysiology but has also pointed to specific “targets” for therapeutic intervention. In some cases, drugs are already available to be deployed against these mechanisms: beta blockers or blockers of the fast inward sodium current are examples. In other cases, genetic mechanisms can suggest possible avenues for future drug development in selected individuals: selective blockade of leaky ryanodine release channels in CPVT is an example [55,56]. A further understanding of the molecular mechanisms and gene-gene interactions underlying AF susceptibility will doubtless inform further drug target identification and development in atrial fibrillation.

Future directions

The notion of subsetting arrhythmias by specific underlying genetic and molecular mechanisms is a consistent theme in modern therapeutics, from cancer to hypertension to atherosclerosis. Thus, a future view of therapeutics includes the idea of genotyping individuals to establish which drugs, and perhaps which dosages, might be most effective in an individual subject. This genotyping could be accomplished at the time of initial antiarrhythmic therapy, but with the ever decreasing costs of whole genome sequencing, an alternate vision is that patients will have sequence data acquired early in life, and then deployed, as needed, during encounters with the healthcare system [57]. In this way, for example, a patient susceptible to atrial fibrillation could be identified early, or QT prolonging drugs could be avoided in individuals carrying specific risk alleles for diLQTS. Such a vision is enabled not only by advances in genomic technology but also in methods to manage very large datasets, such as whole genomes or comprehensive electronic medical records [58]. Indeed, the coupling of genetic information to electronic medical records may not only serve as a platform for delivering genomic care and thus improving outcome of drug therapy, but also as a tool for discovery of the genetic basis of susceptibility to a wide range of diseases and to variable drug responses.

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Highlights

- Most antiarrhythmic drugs were developed when arrhythmia mechanisms were poorly understood.
- Antiarrhythmic drug therapy is not predictably effective and can produce serious side effects.
- Family and population studies identify DNA variants generating the arrhythmia-prone heart.
- Mechanism-based therapy is now being realized in some genomically-defined subsets.
- Sequencing may in the future allow presymptomatic intervention in arrhythmia-prone patients.