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Arrhythmia pharmacogenomics: methodological considerations

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Arrhythmias are common clinical problems. Atrial fibrillation (AF) affects 2–5 million Americans, is a common cause of cardiovascular morbidity including hospitalization, heart failure, and stroke, and is associated with increased mortality [1]. Sudden cardiac death (SCD) due to very rapid ventricular arrhythmias (ventricular tachycardia, VT, and ventricular fibrillation, VF) is the commonest cause of death among American adults, accounting for 250,000–500,000 cases annually, 10–20% of all adult death [2]. This review will outline the challenges and opportunities presented in applying contemporary genetic analyses to understanding variability in drug response in this area. Relevant clinical features are first discussed, followed by a description of challenges in the field and current status.

Atrial fibrillation

Most patients with AF have concomitant structural abnormalities of the heart such as left ventricular hypertrophy. In a minority, AF occurs in the absence of such abnormalities, and is termed “lone AF”. A family history of AF is common in affected individuals, and is even more common in those with lone AF [3,4]. Other studies associate indices of oxidant stress [5] or renin-angiotensin activation [6–8] with the arrhythmia. One setting in which AF is especially common is in patients who have undergone cardiac surgery, where the incidence can be as high as 25% in the week after the procedure. In this setting, inflammatory pathways have been implicated [9,10].

Clinical presentations in AF are highly heterogeneous. AF results in loss of coordinated atrial activity, and irregular and often rapid ventricular response rates due to conduction of atrial fibrillatory activity through the atrioventricular node. Therapies are thus designed to prevent the arrhythmia and maintain normal atrial activity (“rhythm control”) or to slow conduction through the AV node, thereby slowing the ventricular response rate (“rate control”). It is intuitively obvious that a strategy to prevent the arrhythmia and maintain normal cardiac electrical activity should be superior to one designed to ignore the arrhythmia but treat its symptoms; nevertheless, randomized trials comparing rhythm control to rate control have shown, if anything, slight superiority of the rate control strategy [11]. One reasonable explanation for this apparent paradox is that the drugs used for rhythm control are not uniformly effective, and do carry serious cardiac and non-cardiac risks of their own.

In patients who are highly symptomatic with the arrhythmia, a rate control strategy is often ineffective. In such individuals non-pharmacologic, catheter-based ablative therapies are now being developed to identify specific regions within the atria – notably extensions of the left atrial myocardium into pulmonary veins – that drive fibrillatory activity. These approaches are meeting with increasing, although currently incomplete, success [12,13].

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The highly variable clinical presentations, including variable and unpredictable responses to drugs and other therapies, uncertain etiologies, variable associations with concomitant heart disease, and familial aggregation, notably in lone AF, all point to a potential role for genetic variants in the etiology of the arrhythmia as well as in the variable response to drugs. Candidate pathways for modulating such variability include the ion channels and associated proteins that determine electrical activity, genes associated with structural heart disease, inflammatory or oxidant stress pathways, and developmental pathways determining atrial architecture.

Patients with AF are at increased risk for thrombus formation and thromboembolism. AF is common in patients with stroke, and thromboembolism is the presumed mechanism. Randomized clinical trials have shown that therapy with the vitamin K antagonist anticoagulant warfarin can reduce stroke incidence 60–80% with an acceptable risk of bleeding [14]. Warfarin is a cumbersome drug to use, since it requires intensive monitoring of its pharmacologic endpoint (extent of anticoagulant assessed as the “International Normalized Ratio,” or INR) and doses vary widely among individuals. At least 50% of this dose variability is now attributed to genetic variants in the coding region of *CYP2C9* (which bio-inactivates the drug) and in the promoter region of *VKORC1* (encoding the pharmacologic target) [15, 16]. A large randomized multi-center trial will start in the spring of 2009 to examine the contribution of pre-prescription genotyping to improving warfarin therapy [17].

Sudden cardiac death

In most cases of SCD, there is underlying coronary artery disease. VF may occur during an acute myocardial infarction [18]; as well, myocardial infarction may lead to myocardial scarring and increased susceptibility to VF weeks, months, and years later [19]. Efforts to prevent SCD have been directed almost exclusively at the latter group, in whom the extent and severity of underlying structural heart disease predicts increasing risk, thereby allowing evaluation of preventive therapies. By contrast, predicting who will develop VF during an acute myocardial infarction, and deploying preventive antiarrhythmic therapies, has proven much more problematic; the best antiarrhythmic in this setting is an effort to reduce myocardial ischemia (e.g. mechanical or pharmacological thrombolysis). Pharmacologic therapies have been relatively unsuccessful in reducing SCD in such patients (and occasionally increase risk [20]). Accordingly, placement of implantable cardioverter-defibrillator devices (ICDs) is the approach of choice for patients judged to be at high risk for SCD due to underlying heart disease [21].

In addition to those patients with advanced coronary or other heart disease, there is a smaller group of patients, often younger, who are at high risk because of inherited heart diseases, such as hypertrophic cardiomyopathy or the congenital long QT syndromes (LQTS) [2]. Linkage analysis in large kindreds has led to identification of disease genes, with the subsequent recognition that mutations in multiple genes can culminate in very similar phenotypes, and penetrance can be highly variable [22]. Thus, advances in identifying genetic causes of these diseases in probands with obvious phenotypes (like electrocardiographic abnormalities, left ventricular hypertrophy, or SCD) has led to the identification of family members who are mutation carriers and yet who may have very little clinical phenotype. In patients with certain subtypes of LQTS, treatment with beta-blockers, a relatively benign pharmacologic therapy, appears to be effective in reducing SCD risk [23]. Otherwise, in patients who have “monogenic” arrhythmia syndromes, ICDs are the only preventive therapy deployed. Given the intrusive nature of this treatment, and the relatively young age of many affected mutation carriers, efforts are underway to understand modifiers of the arrhythmia phenotype (accounting for SCD in some individuals and no clinical phenotype in others) and to thereby stratify a risk for SCD.

A number of studies discussed below implicate a family history of SCD as a risk factor for SCD. Therefore, risk may include a genetic component, and identifying that component could direct improved prophylactic therapies. Candidate pathways for modulating such risk include those pathways implicated in the rarer monogenic diseases (contractile proteins, cell-cell adhesion proteins, ion channel proteins). As well, experiments in animals suggest that release of membrane lipids during ischemia may be especially arrhythmogenic [24]; thus, another candidate pathway for mediating SCD risk is variability in the acute electrophysiological response to a coronary thrombus. Identification of risk pathways for SCD could lead to development of new antiarrhythmic drugs.

The long QT syndrome and the problem of drug-induced torsades de pointes

The cardiac cycle is characterized by cardiac depolarization, contraction, and then a recovery process mediated by return of the action potential to its baseline state, repolarization. The congenital LQTS [23] is characterized by a prolonged repolarization phase, and a morphologically distinctive polymorphic ventricular tachycardia, termed torsades de pointes (TdP); TdP is the cause of death in most cases of the congenital LQTS. Therapy with certain antiarrhythmic and other drugs can also prolong the QT interval, and has been associated with TdP [25]. The incidence of this drug-induced long QT syndrome (diLQTS) is as high as 5% with certain antiarrhythmic drugs, and it can also occur during therapy with drugs not used in therapy of cardiovascular disease. These include some antipsychotics, antibiotics, and antihistamines; however, this is not a class effect and the risk for each drug must be evaluated individually. Clinical risk factors for the drug-induced arrhythmia include underlying slow heart rates, hypokalemia, female gender, recent conversion from AF, and structural heart disease such as left ventricular hypertrophy [25]. However, predicting the arrhythmia in an individual still is not possible.

One common form of the congenital LQTS arises from loss of function mutations in *KCNH2* (also termed *HERG*), whose expression results in a potassium current important in cardiac repolarization, I_{Kr} . Virtually all drugs that cause diLQTS are I_{Kr} blockers, and this has led to routine pre-clinical screening for *KCNH2* block by new drugs in development. However, the relationship between potency of I_{Kr} block and downstream risk of TdP remains uncertain [25]. As described below, efforts are underway to identify genomic contributors to diLQTS risk.

Challenges in arrhythmia genetics and pharmacogenetics

With this background, the opportunities and challenges in applying contemporary genomic approaches to clinical arrhythmia problems can be enunciated.

Case ascertainment

Challenges include making a precise diagnosis, understanding the clinical subtype if necessary, and identifying clinical covariates. For example, Figure 1 illustrates three patients referred for evaluation of TdP. The top rhythm shows typical features of diLQTS: very clear QT prolongation and a pause in cardiac rhythm prior to the development of the arrhythmia. The second shows no QT prolongation, and was observed in a patient with acute myocardial ischemia, another setting in which polymorphic ventricular tachycardia (but without QT prolongation) can be seen; this arrhythmia is clinically and mechanistically distinct from diLQTS. The third appears to be a polymorphic ventricular tachycardia, but is actually a recording artifact superimposed on a regular rhythm indicated by the arrows. Including either of the latter cases in a series of TdP to investigate underlying genetic causes would be an obvious experimental mistake.

Clinical covariates

A second challenge in the broad area is identifying clinical covariates. For example, in virtually all case series of diLQTS, there is a two-threefold higher increase in prevalence in women [26]. The mechanisms for this gender-specific risk are not well understood, but failing to correct for gender would also be an experimental mistake.

Definition of endpoints, and the use of surrogate endpoints

The most appropriate endpoint for any study of arrhythmias is either symptoms or a cardiovascular event such as syncope or death. However, these may be difficult to quantify (in the case of symptoms) or relatively uncommon (in the case of “hard” endpoints). Thus, surrogate endpoints linked to the final phenotypes have been deployed in this field. For example, in studies of diLQTS risk, it is common use the extent of drug related prolongation of the QT interval as a marker of risk, rather than the arrhythmia itself. The fibrillatory rate during AF [27] may be a reflection of differing underlying atrial electrophysiologic derangements, and thus may be a surrogate for understanding AF genetics. The surrogate approach has the virtue that larger numbers of subjects, with a readily acquired and quantified endpoint for pharmacologic therapy, can be accrued. On the other hand, the relationship between the surrogate and the true endpoint, like SCD, diLQTS or AF may be non-linear or occasionally non-existent. In the 1980s, suppression of isolated premature ventricular contractions (PVCs) was taken as a surrogate for reducing SCD risk until the Cardiac Arrhythmia Suppression Trial showed increased SCD rates in patients receiving drugs that potentially suppressed PVCs [20].

Identifying candidate genes for arrhythmia phenotypes

The simplest approach is one which considers obvious candidate genes, such as those known to encode ion channels, their ancillary subunits, elements of physiologic systems that modulate cardiac electrical activity (adrenergic, oxidant, inflammatory signaling), or genes whose protein products modulate electrical activity in other ways (e.g. calcium control genes).

Unbiased approaches are also being used to identify loci associated with increased arrhythmia prevalence as described below. A variation on this approach is to use variability in electrocardiographic parameters, which are readily recorded in large numbers of subjects, as surrogates for arrhythmia susceptibility. A genome-wide association study (GWAS) analyzing variability in the distribution of QT interval durations in normal subjects identified a locus on chromosome 1 near a gene encoding an ancillary subunit of the neuronal nitric oxide synthase gene (*NOS1AP*) [28]. The encoded protein, termed CAPON, is expressed in heart and modulates cardiac ion channel function through mechanisms that remain to be determined [29].

Another interesting unbiased approach to identifying genes modulating diLQTS risk has been high-throughput screening in sensitized embryonic zebrafish. Heart rate is readily recorded in these animals, and exposure to I_{K_r} blockers results in predictable heart rate slowing [30]. Screening large numbers of mutagenized zebrafish for excessive heart rate slowing to low dose blockers, or resistance to heart slowing with high dose blockers, identified multiple new genes modulating this drug response phenotype, including elements of the *heg-san-vtn* pathway [31].

Accumulating case series

AF is a common arrhythmia and does not usually cause death. Thus, accruing very large numbers of well-characterized patients is feasible, and has been important starting point for clinical and genetic studies. Further, AF is sufficiently prevalent within a population that large

population-based studies, such as Framingham or the Rotterdam Heart study [32], can, over time accrue sufficiently large numbers of patients with incident AF to enable studies of clinical and genetic predictors of the arrhythmia.

By contrast, SCD represents a greater challenge in case ascertainment. One approach is to examine SCD in large population based studies, such as Framingham, the Rotterdam Heart Study [33], the Atherosclerosis Risk In Communities (ARIC) Study, or the Cardiovascular Health Study (CHS) [34]. These efforts undertake extensive phenotyping of patients at entry and during followup, and thus may provide new information on clinical and genetic risk predictors of the event. The Paris prospective study recruited 7,000 middle aged men in the late 1960s, followed them for a quarter century, and identified family history as a risk factor for SCD [35]. Another approach is to accrue SCD cases as they occur (through emergency medical services or coronary care units) and to analyze the problem in case-control fashion. Two studies have taken this approach and both suggest family history is a risk factor for SCD. One, in Seattle, studied cases identified by emergency services with out of hospital SCD [36]. The second, in the Netherlands, identified a cohort of 330 patients developing within 90 minutes of the onset of their first acute myocardial infarction [37]. The control subjects were 372 developing their first myocardial infarction, but not displaying VF. The most powerful predictor of SCD was a family history of SCD, with an odds ratio of 2.72 (95% CI 1.84 to 4.03).

For much rarer events – such as diLQTS – such large population based studies are not suitable. Here, databases accrued during drug development (by industry) or by networks of investigators brought together for specific case and control identification and curation represent alternate approaches. The Trans-Atlantic Network of Excellence in “Preventing SCD” represents such an example (<http://www.allianceagainstscd.org/definition.php>). Investigators in this network have accrued over 200 cases of diLQTS, and controls exposed to culprit drugs and not developing marked QT prolongation. These cohorts represent an important starting point for studies evaluating clinical as well as genetic risk factors for the arrhythmia [38].

Electronic medical records (EMR) linked to large collections of DNA may represent another mechanism for accruing cases and controls for clinical or genetic studies of risk. At Vanderbilt, we have created such a DNA resource, termed BioVU, that links de-identified medical records to DNA samples obtained during routine clinical care [39]. Rapid accrual of large numbers of cases, and very extensive phenotypic information contained in electronic medical records represent advantages of this approach. For common, readily ascertained phenotypes, such as AF and accompanying heart disease, using such an EMR approach seems feasible [40], although its utility for more complex phenotypes, such as diLQTS, remains to be evaluated. As of February 2009, the Vanderbilt resource includes 1.7 million deidentified electronic records, and over 50,000 are associated with DNA samples. The widespread use of electronic medical records may allow generation of much larger collections of genetic studies. In addition, integrating DNA research with the electronic medical records is a first step to incorporating DNA markers of risk of disease or of variable drug responses into clinical practice.

Current status of AF genetics and pharmacogenetics

There are considerable data that support the idea that AF includes a genetic component. To date, linkage analyses in large kindreds have identified four distinct genetic loci for the arrhythmia [41–44]. At one of these, a mutation has been identified in *NUP155*, encoding a nuclear pore protein not previously implicated in the arrhythmia [45], opening a new pathway to understanding arrhythmia susceptibility and perhaps new drug development.

In addition, smaller kindreds have been analyzed by screening coding regions of candidate genes for non-synonymous variation. Using the latter approach, mutations in ion channel genes

have been associated with AF [46–51]. In these cases, the strength of the evidence relies on the fact that mutations in plausible candidate genes were identified and that they associate with the arrhythmia across families, although a formal lod score is usually absent. In addition, a common *in vitro* electrophysiologic finding is increased outward current, a change predicted to shorten atrial action potentials which in experimental animals predisposes to AF. Increased outward current is seen with “gain of function” mutations in potassium channel genes, loss of function in cardiac calcium channel genes [52], and with mutations in the atrial natriuretic peptide gene (*NPPA*) which have also been reported in familial AF [53].

A loss of function mutation in an atrial potassium channel gene, *KCNA5*, has been described in one kindred with familial AF [54]. The predicted effect of this mutation is to prolong atrial action potential, indicating there are multiple electrophysiologic derangements in mutant potassium channels that can predispose to AF. Applying this information to affected patients will therefore require an understanding of the basic pathophysiology: in patients with “gain of function” mutation, potassium channel blockers would be logical therapy, whereas drugs to increase potassium current would be more appropriate in patients with loss of function mutations.

Variation in genes controlling the magnitude of the cardiac sodium current has also been associated with AF. AF is a common feature in the Brugada syndrome [55], a relatively rare monogenic disorder characterized by structurally normal heart, a distinctive electrocardiographic phenotype (J-point elevation in the right precordial leads that is either constant or can be provoked by sodium channel blocker therapy), and a high incidence of SCD due to VF [56,57]. Loss of function mutations in the cardiac sodium channel gene *SCN5A* are identified in 25% of patients with Brugada syndrome, and mutations in other genes (whose function is to modify cardiac sodium current) have been reported albeit much less commonly [56,58,59].

Mutations in genes encoding two sodium channels ancillary subunits, *SCN1B* and *SCN2B*, have been reported in patients with AF [60]. Interestingly, the affected patients showed ECG abnormalities reminiscent of the Brugada syndrome, although SCD did not occur. Indeed, a Finnish study reported a remarkably high prevalence of this ECG pattern (approximately 10%) in patients with lone AF [61], suggesting that abnormal sodium channel signaling could be responsible for a substantial proportion of cases of AF. Further support for this idea has come from a study in which resequencing the *SCN5A* coding region in 375 patients with AF yielded previously reported mutations (long QT syndrome, Brugada syndrome) in 3.2% and novel mutations in 2.7% [62]. Further exploration of the role of variation in the sodium channel gene and its modulators in AF seems warranted since drugs with sodium channel blocking properties (such as flecainide) are widely used in the therapy of AF. The use of such drugs in patients in whom the fundamental electrophysiologic lesion arises from loss of sodium current is not only predicted to be ineffective, but may in fact, increase SCD risk [20,63].

Case series of patients with AF have reported that common ion channel polymorphisms (e.g. S38G in *KCNE1* [64], H558R in *SCN5A* [65]) increase AF risk, but these have been small and not reproduced. A small study reported an association between lower fibrillatory rate and the 38GG *KCNE1* genotype (n=13; 392±36 vs 443±49 fpm, p=.006) but no association with the *SCN5A* H558R polymorphism. Thus, these data suggest that the *KCNE1* S38G genotype exerts functional effects on atrial electrophysiology [27].

A genome-wide approach, initially in Iceland and extended to European and Asian populations, identified polymorphisms on chromosome 4 (at 4q25), that confer an increased risk of AF with an odds ratio of ~1.4/allele [66], and this finding has now been independently replicated [32]. The variants are located in an intergenic region, and the closest gene is *PITX2*, which encodes

a cardiac transcription factor important for left-right differentiation and for the development of atrial myocardium that invaginates the pulmonary veins [67]. 4q25 risk alleles seem prevalent regardless of the subtype of atrial fibrillation; the risk has been identified in subsets with AF after cardiac surgery [68], and appears to apply regardless of age or presence or absence of left ventricular hypertrophy [32,66]. These findings suggest the possibility is that variation in PITX2 function lays down an “AF-prone” substrate as early as embryonic development, and that AF occurs later in life in susceptible individuals when as-yet-poorly understood triggers occur. Variant 4q25 alleles also associate with cases of stroke in which usual etiologies are absent (termed “cryptogenic stroke”), suggesting undiagnosed AF may play a prominent role in these patients [69].

Studies examining variability in drug response during AF have been hampered by variable endpoints used to gauge drug efficacy, the empiric and non-randomized nature in which drugs are selected for individual patients, and lack of very large cohorts of patients with well-characterized drug responses. Because renin-angiotensin activation has been implicated in AF, one study examined the role of the common angiotensin converting enzyme insertion/deletion (I/D) polymorphism in drug response. The D allele is associated with higher angiotensin II levels, and in 229 patients the D allele blunted response to antiarrhythmic drug therapy: subjects with DD/ID genotypes (71%) were more likely to have recurrent AF during therapy ($P<0.005$). Other studies using a candidate gene approach have implicated common variants in the interleukin-6 gene [70,71] in AF after surgery.

Current status of SCD genetics and pharmacogenetics

The major problem with identifying genetic contributors to SCD risk is patient ascertainment, since large scale accrual of samples from patients suffering SCD is a cumbersome undertaking. Thus, only a handful of studies have been conducted to examine the role of genetic risk markers for SCD, and these have examined candidate genes, e.g. those in which mutations cause the congenital monogenic syndromes or that encode pathways strongly modulating cardiovascular electrophysiology, such as the adrenergic system. In general, these studies have involved small numbers of cases of SCD, and have not been replicated [72]. A number of reports indicate that that monogenic arrhythmia syndromes can present as the Sudden Infant Death Syndrome (SIDS) [73–75].

The non-synonymous SCN5A variant resulting in S1103Y – identified almost exclusively in African-Americans – generates a dysfunctional channel and has been associated with increased susceptibility to a range of arrhythmia phenotypes, including SCD, diLQTS, and SIDS [76–79]. Other studies have also examined variation in SCN5A in SCD, but the results have been conflicting [80,81]. Single studies have reported associations between SCD and common variants in genes for the beta-2 adrenergic receptor [82], alpha-2 [83] adrenergic receptor, and hepatic lipase [84].

As described above, single nucleotide polymorphisms in *NOS1AP* have been identified as modulators of the normal QT interval. Two studies have examined the association between *NOS1AP* SNPs and SCD. In the Rotterdam Heart Study, involving 5374 subjects age >55 , there was a strong association between *NOS1AP* SNPs and QT duration, but no relationship to SCD (which occurred in 233 subjects) [33]. By contrast, in 14,737 European-American subjects in ARIC and CHS (with SCD in 334), *NOS1AP* alleles were identified that conferred a relative risk of 1.3 (95% CI: 1.10–1.56, $P=0.002$), using an additive model [34]; interestingly, not all the *NOS1AP* SNPs associated with SCD predicted QT prolongation. No associations were identified in 4394 African-American subjects (with 164 cases of SCD). Prolongation of the QT interval has been implicated as a risk factor for SCD in general [85,86], so this association

has biologic plausibility; it also possible that NOS1AP modulates SCD risk through other pathways. GWAS approaches will likely be reported soon in these and similar large cohorts.

diLQTS

Studies of genetic contributors to diLQTS risk have focused on logical candidate genes and are limited, in general, by small study size. As with many other rare adverse drug effects, accrual of very large numbers of affected patients and controls presents immense logistical challenges and generally requires participation from multiple centers. As discussed above, case ascertainment can be a particular problem in diLQTS.

Summary

The study of arrhythmia pharmacogenetics presents an interesting set of challenges and opportunities. Arrhythmias are common, extract a large toll in public health terms, and response to drug therapy is variable among individuals. Studies to identify mechanisms underlying variability in arrhythmia phenotypes, and thus point to subset-specific drug or other therapeutic strategies, are underway using both candidate gene and genome-wide association approaches.

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Figure 1.

Cardiac rhythm recordings in 3 patients referred for evaluation of torsades de pointes. The top recording shows typical features of diLQTS: very clear QT prolongation (arrow) and a pause in cardiac rhythm (star) prior to the development of the arrhythmia. The second shows no QT prolongation, and was observed in a patient with acute myocardial ischemia, another setting in which polymorphic ventricular tachycardia (but without QT prolongation) can be seen; this arrhythmia is clinically and mechanistically distinct from diLQTS. The third appears to be a polymorphic ventricular tachycardia, but is actually a recording artifact superimposed on a regular rhythm (indicated by the arrows).