Genetic Basis of Ventricular Arrhythmias

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Abstract Sudden cardiac death (SCD) is a leading cause of total and cardiovascular mortality, and ventricular fibrillation is the underlying arrhythmia in the majority of cases. In the young, where the incidence of SCD is low, a great proportion of SCDs occur in the context of inherited disorders such as cardiomyopathy or primary electrical disease, where a monogenic hereditary component is a strong determinant of risk. Marked advancement has been made over the past 15 years in the understanding of the genetic basis of the primary electrical disorders, and this has had an enormous impact on the management of these patients. At older ages, the great majority of SCDs occur in the context of acute myocardial ischemia and infarction. Although epidemiologic studies have shown that heritable factors also determine risk in these cases, inheritance is likely complex and multifactorial, and progress in understanding the genetic and molecular mechanisms that determine susceptibility to these arrhythmias, affecting a greater proportion of the population, has been very limited. We review the most recent insights gained into the genetic basis of both the monogenic and the more complex ventricular arrhythmias.

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Introduction

Sudden cardiac death (SCD) accounts for 15% to 20% of all natural deaths in adults in the United States and Western Europe, and up to 50% of all cardiovascular deaths [1]. Ventricular fibrillation is the most common underlying cause [2]. Ventricular arrhythmias present with various symptoms including palpitations, chest pain, or syncope and may occur in various pathologic settings such as cardiomyopathies, congenital heart disease, inflammatory myocardial disease, as well as in the structurally normal heart. SCD is rare among young individuals. In individuals younger than 40 years of age, incidence of sudden death is approximately 1.3 to 8.5 per 100,000 person-years, and the vast majority of cases are considered to be SCD [3, 4]. In this age group, a great proportion of SCDs occur in the context of potentially inherited disease such as cardiomyopathy and primary electrical disease [5, 6], and a strong monogenic hereditary component is thought to determine risk of sudden death in most cases [7, 8]. In contrast, at older ages, the great majority of SCDs occur in the context of acute myocardial ischemia/infarction [9]. Epidemiologic studies have shown that heritable factors also determine risk in these cases [10–12].

We review recent insights gained into the genetics of ventricular arrhythmias. We provide a brief update on novel genes uncovered for the monogenic primary electrical disorders and highlight results of recent genome-wide association studies that have uncovered novel genetic loci that may contribute to risk of SCD in the general population.

Monogenic Primary Arrhythmia Syndromes

Molecular genetic research into the monogenic arrhythmia syndromes over the past 15 years has had an enormous impact on the management of patients with these disorders [13]. They are now known to be caused primarily by mutations in genes encoding ion channel subunits or their regulatory components. The increased understanding of the genetic basis of these disorders has provided great insight into many aspects of these disease entities, including their pathophysiology, and prognosis, and optimal treatment options for the specific molecular genetic subtypes. Perhaps the most significant impact has been on the management of patients with the congenital long QT syndrome (LQTS). This disorder is among the most prevalent of the monogenic arrhythmia syndromes and has facilitated large studies looking into genotype–phenotype relationships. Such studies have uncovered triggers specific to the different genetic subtypes, providing opportunities for lifestyle adjustments and an explanation as to why β-blockers might not be equally effective in all genetic subtypes (i.e., they are most effective in LQTS1 subtype and of high to moderate effectiveness in the LQTS2 subtype, in accordance with the adrenergic triggers in these subtypes, and of uncertain effectiveness in LQTS3 [14, 15]. Knowledge of the genetic subtype may therefore be critical to the cardiologist in assessing optimal treatment strategies.

The availability of a genetic test has also provided an opportunity for presymptomatic diagnosis of patients with these disorders. Active cascade screening within families is generally advised after the identification of an affected proband because it leads to timely presymptomatic treatment of relatives also carrying the mutation, which may be life-saving, whereas relatives not carrying the genetic defect can be reassured [16•]. However, genetic testing is not always straightforward, and a proper interpretation of the genetic test result is critical considering the implications of mutation identification. The occurrence of a mutation within a likely gene does not automatically imply genetic causation. Analysis for co-segregation with the disorder in an extended pedigree is often helpful in establishing causality of an identified mutation, but such pedigrees are not always available. Distinguishing pathogenic mutations from innocuous and clinically silent gene variants remains a major challenge in many instances. Mutation type (e.g., nonsense vs. missense), mutation location in channel sub-domain (e.g., pore vs. transmembrane vs. linker), and ethnic-specific background rates have been shown to be critical factors in predicting the pathogenicity of novel mutations [17•]. For instance, in LQTS, a novel mutation (an unclassified variant) identified in the transmembrane regions of the *SCN5A*-encoded sodium channel is much more likely to be pathogenic than when located in an interdomain linker [17•]. Thus, genetic tests must be viewed as probabilistic tests to be interpreted along with other diagnostic tests.

In the research setting, the identification of novel genes underlying the monogenic rhythm disorders may be rather challenging. Ideally for such studies, one has access to genetic material from multiple clinically affected individuals within an extended pedigree with the possibility of establishing genetic linkage to a particular chromosomal segment followed by the sequencing of candidate genes for identification of the causal defect. However, availability of an extended pedigree is rarely the case for these disorders in particular because individuals within a pedigree might have already died suddenly of arrhythmia before DNA collection is possible. Furthermore, as is the case for most Mendelian monogenic disorders, these disorders display reduced penetrance (not all mutation carriers have clinical signs of the disorder) and variable clinical expression [18, 19], which further complicates the process of gene identification. One group of rhythm disorders for which it is exceptionally difficult to track the genetic substrate is idiopathic ventricular fibrillation (VF), defined as spontaneous VF in the absence of identifiable structural or electrical heart disease [20]. The diagnosis of this disorder, which accounts for as many as 10% of sudden deaths, mainly in the young, cannot be made on the basis of electrocardiogram (ECG) abnormalities but can only be made after the occurrence of (aborted) SCD. Many affected patients die young, thus leaving only small numbers of patients and material available for analysis. Using an alternative approach, searching for shared ancestral haplotypes (chromosomal segments) among three distantly related pedigrees with the disorder originating from one region in the Netherlands, our group recently implicated the *DPP6* gene in this disorder [21••]. *DPP6* encodes dipeptidyl-peptidase 6, a putative subunit of the transient outward current potassium-channel complex (I_{To}) [22]. Although, expression of *DPP6* was increased in cardiac biopsies of carriers of the risk haplotype [21••], more research is required to establish the pathophysiologic mechanism of *DPP6*-related idiopathic VF and how such a genetic defect is silent on ECG. Genetic testing is crucial in these patients because it is the only means of identifying those at risk of developing potentially fatal arrhythmia allowing for timely presymptomatic implantation of an implantable cardioverter defibrillator.

A disorder that has attracted much attention in recent months is the Early Repolarization Syndrome. For a long time, early repolarization, consisting of an elevation of the QRS-ST junction (J point), QRS notching or slurring (J wave), and a tall symmetric T wave, was considered to be a benign feature [23]. Three case-controls studies however recently demonstrated that a pattern of early repolarization in the inferior and/or lateral leads was more frequent in patients with idiopathic VF compared with controls [24••, 25••, 26]. A

community-based study in Finland also showed that an early repolarization pattern in the inferior leads of the ECG is associated with an increased risk of death from cardiac causes during very long-term follow-up in middle-aged individuals [27]. So far, only one mutation in the *KCNJ8* gene, encoding a subunit of the K_{ATP} channel, has been reported for the disorder in a single patient [28]. It is expected that unraveling the genetic basis of this newly recognized disease entity will aid in the understanding of the mechanism for this ECG pattern and related arrhythmia.

Arrhythmias with a More Complex Inheritance Pattern

In recent years, interest in the genetics of cardiac arrhythmias has shifted to include the search for those genetic factors influencing risk of SCD in the general adult population. In adults, the overwhelming majority (~80%) of SCDs is caused by the sequela of coronary artery disease, namely myocardial ischemia or acute myocardial infarction (MI) [9, 29], where SCD is the first clinically identified expression of heart disease in up to one half of cases [30].

In the late 1990s, two important studies advanced the concept that even in these more common arrhythmias, a genetic component also contributes to risk. In a population-based case-control study, a family history of MI or SCD, after correction for all common risk factors, was positively associated with the risk of SCD [10]. In the Paris Prospective Study, selectively performed in men, among whom 118 cases of sudden death occurred, parental sudden death was found to be an independent risk factor for sudden death [11]. A study from our group investigated this concept further in the Arrhythmia Genetics in the Netherlands Study (AGNES), conducted specifically in patients with a first acute MI [12]. In this study we demonstrated that familial sudden death occurred significantly more frequently among patients with a first MI complicated by VF (cases) compared with patients presenting with a first MI but without VF (controls) [12]. However, in contrast to the significant advances made in the understanding of the genetics of the monogenic arrhythmia syndromes, progress in understanding the genetic and molecular mechanisms that determine susceptibility to these common arrhythmias, affecting a much greater proportion of the population, has been limited [31–33]. An important reason for this slow progress is the fact that most victims die outside of the hospital, making it extremely difficult to include patients with appropriately consented DNA samples for genetic studies.

In an effort to identify common genetic variation within the genome contributing to risk of VF during acute MI, our group recently conducted a genomewide association study for VF in the AGNES population [34••]. By comparing the frequency of common single nucleotide polymorphisms (SNPs) spread throughout the 22 autosomes between MI patients with VF (cases) and MI patients without VF (controls) from the AGNES study, we identified a region on chromosome 21 in the vicinity of the *CXADR* gene associated with susceptibility to VF. *CXADR* encodes the coxsackievirus and adenovirus receptor (CAR) protein, which has a long-recognized role as viral receptor in the pathogenesis of viral myocarditis and its sequela of dilated cardiomyopathy [35, 36]. Interestingly, the frequency of active coxsackie B virus infection has been reported to be high in a group of MI patients who died suddenly [37]. Two studies have reported a physiologic role for the receptor in localization of connexin 45 at the intercalated disks of the cardiomyocytes in the atrioventricular node, and a role in conduction of the cardiac impulse within this cardiac compartment [38•, 39•]. Thus, *CXADR* can be considered a very relevant candidate gene for the association detected at this locus.

As a complementary approach to establishing direct bridges between genetic variation and arrhythmia susceptibility, researchers in the field have also undertaken a strategy whereby SNPs are first analyzed for effects on heart rate and other ECG indices of conduction and repolarization. This approach stems from knowledge that these ECG measures constitute heritable traits [40, 41] and that their extremes (too long or too short) influence risk of arrhythmia, both in the general population [42, 43] as well in specific disease groups [44], which makes ECG indices potentially relevant intermediate phenotypes. The most extensively studied ECG parameter studied until now in this way has been the QT interval, reflecting ventricular repolarization. These studies have uncovered numerous genetic loci and SNPs modulating this measure (Table 1), the most significant of which have consistently been SNPs in and around the *NOS1AP* gene, encoding the nitric oxide synthase 1 (neuronal) adaptor protein [45, 46•, 47•]. Although the exact mechanism for the effect of SNPs in *NOS1AP* on ventricular repolarization is still unknown, one must realize that this gene was previously unlinked to cardiac electrophysiology, underscoring the power of the genome-wide association approach to highlight unknown pathways that could represent an important means to ultimately unravel mechanisms of disease and development of new therapies.

Crotti et al. [48•] and Tomás et al. [49•] went on to test whether SNPs in *NOS1AP* could modulate disease expression (QTc and arrhythmia) in the congenital LQTS, where pronounced inter-individual variability in QTc-prolongation and occurrence of arrhythmia exists [19]. The first study investigated South African families segregating a founder mutation in *KCNQ1* (all affected individuals were carriers of the A341V mutation in *KCNQ1*) and demonstrated that carriers of risk alleles at *NOS1AP* SNP sites had longer QTc and an increased risk of cardiac arrest and SCD. Carrying out

Table 1 Candidate genes identified in genome-wide association studies for heart rate and ECG indices of conduction (PR, QRS) and repolarization (QTc)

QT interval	PR interval	QRS interval	Heart rate
ATP1B1 [47•]	ARHGAP24 [51•, 53•]	CAV1 [51•]	MYH6 [51•]
GINS3 [46•]	CAV1/CAV2 [51•, 53•]	CDKN1N [51•]	
KCNE1 [46•]	MEIS1 [53•]	DKK1 [51•]	
KCNH2 [46•, 47•]	MYH6 [51•]	SCN10A [52•]	
KCNJ2 [47•]	NKX2-5 [53•]	TBX5 [51•]	
KCNQ1 [46•, 47•]	SCN10A [51•, 52•, 53•]		
LIG3-RFFL [46•]	SCN5A [53•]		
LITAF [46•, 47•]	SOX5 [53•]		
NDRG4 [46•, 47•]	TBX5-TBX3 [51•, 53•]		
NOS1AP [45, 46•, 47•]	WNT1L [53•]		
PLN [46•, 47•]			
RNF207 [46•, 47•]			
SCN5A [46•, 47•]			

Only candidate genes at loci displaying association at genome-wide significance ($P<5\times10^{-8}$) are listed

ECG electrocardiogram

such studies in the setting of families with a founder mutation is attractive because it circumvents the inter-individual variability in disease manifestations that could otherwise arise as a consequence of the different primary genetic defects among study participants. In the second study, Tomás et al. [49•], who carried out association studies of NOS1AP SNPs in a large LQT patient cohort (901 patients from 520 families) with mutations in different genes, subsequently demonstrated that the effects of SNPs in NOS1AP are also detectable in a more diverse LQT patient cohort. These authors proposed that genotyping NOS1AP SNPs could in the future become useful in refining risk stratification in this disorder. However, the situation remains rather complex. One NOS1AP SNP (rs10494366) associated with risk of cardiac events in the LQTS study by Tomás et al. [49•] was not associated with risk of SCD in community-based populations [50]. Furthermore, in the latter study, another SNP (rs12567209), which was not correlated with QT interval, was still associated with SCD, suggesting that there may be multiple functional elements within the NOS1AP region, some of which may modulate risk of arrhythmia independently from the repolarization process. Research is still required to resolve the underlying issue.

Following successful identification of several loci impacting the QT interval, investigators also turned their attention to other ECG parameters, namely heart rate [51•], the PR-interval (a measure of the time required for the electrical impulse to travel from the sinus node, through the atria and atrioventricular node to the Purkinje fibers) [51•, 52•, 53•], and QRS duration (a measure of the time required for depolarization of the ventricles) [51•]. These studies presented compelling evidence that SNPs in the SCN5A and SCN10A genes modulate cardiac conduction. This finding is not surprising with respect to SNPs in SCN5A, which encodes the major sodium channel in the heart (Nav1.5). Sodium ion influx through this channel mediates the rapid

upstroke of the cardiac action potential and is therefore a critical mediator of cardiac conduction, and mutations in SCN5A cause cardiac conduction disease [54]. On the other hand, the implication of the SCN10A gene (located within <100 kb-pairs of SCN5A on chromosome 3) as a modulator of cardiac conduction was a very novel finding. Note that SCN10A variant presented to be independent of SCN5A variant. SCN10A encodes the sodium channel Nav1.8, expressed primarily in the peripheral sensory nervous system and to a lesser extent in the heart. It has been hypothesized that amino acid–altering SNPs in SCN10A might be responsible for the observed effect on cardiac conduction [52•, 53•]. The exact mechanism however is still unknown. The A-allele at SNP rs6795970, which is associated with slower conduction in the general population, appeared protective against risk of VF in the setting of acute MI in the AGNES study [52•].

These genome-wide association studies have also uncovered SNPs in or near genes encoding transcription factors involved in cardiac development, including NKX2-5 which encodes the cardiac-specific homeobox transcription factor Nkx2.5. Mutations in this gene were previously linked to atrial septal defect with conduction defects, tetralogy of Fallot, and high-degree atrioventricular block [55]. Another locus identified as impacting on conduction is in the region of the TBX3 and TBX5 genes, which encode T-box–containing transcription factors important for cardiac conduction system formation in the developing heart [56, 57]. Mutations in TBX5 cause Holt-Oram syndrome, which includes atrial and ventricular septal defects, conduction disease, and occasionally atrial fibrillation [58], whereas mutations in TBX3 cause ulnar-mammary syndrome, with limb, mammary, tooth, genital, and cardiac abnormalities [59]. Furthermore, as for genomewide association studies for QT interval, genomewide association studies for heart rate and conduction indices have also uncovered genes
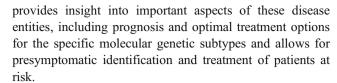
previously unlinked to cardiac electrical function (e.g., the association of *ARHGAP24*, which encodes a Rho-GTPase-activating protein, with PR, and the association of *MYH6*, encoding the alpha heavy chain subunit of cardiac myosin., with heart rate and PR), thereby potentially illuminating novel pathways.

The wealth of information being generated by genome-wide association studies is likely to trigger researchers around the world into following new avenues for research into novel pathways that could be involved in cardiac electrical function. However, one should realize that much work still needs to be done before we fully understand the exact molecular mechanisms whereby the identified genetic loci contribute to inter-individual variability in the related trait and ultimately to whether they also impact on risk of arrhythmia. Perhaps the most crucial of these issues relates to the fact that although these studies have uncovered regions on chromosomes that are linked to the traits of interest, some of which harbor highly plausible candidate genes, in basically all instances mentioned above, unequivocal evidence for genes mediating the observed effects is lacking, let alone knowledge of which functional genetic variants underlie these effects.

Another fact that needs mentioning is that the variants identified as modulators of ECG parameters, as expected in complex genetic traits, are associated with very small effect sizes. For instance, effect sizes for alleles impacting on QTc range from 1 to 3 ms per allele [46•, 47•]. Even in aggregate, the identified genetic variants still explain only a very small percentage of the variance in these traits. In a meta-analysis by Pfeufer et al. [47•] including 16,678 individuals, association signals from 10 loci found to be associated with QTc-interval (at genome-wide statistical significance) in aggregate explained only 3.3% of the variance in QTc. In another meta-analysis performed by Newton-Cheh et al. [46•], comprising 13,685 individuals, in aggregate, 5.4% to 6.5% of the variation in QT interval was explained by 14 independent variants at 10 loci. Larger and larger association studies, including more study subjects, will be required to provide unequivocal evidence for novel genetic associations and complementary strategies to uncover the genetic underpinnings of these complex traits are obviously necessary. For instance, it is generally hypothesized that other genetic variants, such as rare variants not detected in genome-wide association studies that likely have stronger influences on these ECG indices, may be present.

Conclusions

The identification of the genetic defects underlying the monogenic arrhythmia syndromes is important because it provides insight into important aspects of these disease entities, including prognosis and optimal treatment options for the specific molecular genetic subtypes and allows for presymptomatic identification and treatment of patients at risk.

Recent genome-wide association studies have generated remarkable insight into chromosomal regions and genes that impact on cardiac electrical activity. Such strategies have now started to be applied to the identification of genes impacting on arrhythmia risk in the general population. These studies are likely to provide insight into pathways determining risk of arrhythmia in the general population.

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