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Determinants of incomplete penetrance and variable expressivity in heritable cardiac arrhythmia syndromes

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Abstract

Mutations in genes encoding ion channel pore-forming α -subunits and accessory β -subunits as well as intracellular calcium-handling proteins that collectively maintain the electromechanical function of the human heart serve as the underlying pathogenic substrate for a spectrum of sudden cardiac death (SCD)-predisposing heritable cardiac arrhythmia syndromes, including long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT). Similar to many Mendelian disorders, the cardiac “channelopathies” exhibit incomplete penetrance, variable expressivity, and phenotypic overlap, whereby genotype-positive individuals within the same genetic lineage assume vastly different clinical courses as objectively assessed by phenotypic features such as electrocardiographic abnormalities and number/type of cardiac events. In this Review, we summarize the current understanding of the global architecture of complex electrocardiographic traits such as the QT interval, focusing on the role of common genetic variants in the modulation of ECG parameters in health and the environmental and genetic determinants of incomplete penetrance and variable expressivity in the heritable cardiac arrhythmia syndromes most likely to be encountered in clinical practice.

INTRODUCTION

Over the past decade, the discovery that mutations in genes encoding cardiac ion channel α - and β -subunits serve as the primary genetic substrate for a spectrum of sudden cardiac death (SCD)-predisposing inherited cardiac “channelopathies”[1, 2], including long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT), has impacted profoundly how these genetic disorders are diagnosed, risk stratified, and managed clinically. While the availability of genetic testing provides an important opportunity to identify and deliver prophylactic

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treatment to genotype-positive individuals at-risk for potentially fatal cardiac arrhythmias, it has also exposed the glaring fact that the cardiac channelopathies, like many monogenic disorders, exhibit incomplete penetrance and variable expressivity whereby family members who harbor the same disease-causative mutation often assume vastly different clinical courses.

By definition, disease penetrance represents the probability that individuals who harbor the same disease-causative mutation manifest the objective clinical/phenotypic features associated with that disorder (Figure 1a and b).[3] In contrast, variable expressivity is defined as the type and severity of clinical/phenotypic features observed across all genotype-positive individuals who harbor the same disease-causative mutation (Figure 1c).[4] In the case of the cardiac channelopathies, the “expressivity” spectrum of genotype-positive individuals ranges from overt electrocardiographic abnormalities (e.g. QT interval prolongation in LQTS or ST-segment elevation and inverted T-waves in leads V₁–V₃ in BrS) and arrhythmia-triggered cardiac events [e.g. syncope, seizure, out-of-hospital cardiac arrest (OHCA), or sudden cardiac death (SCD)] to the absence of any discernible features on electrocardiogram (ECG) and a lifelong asymptomatic state. The fact that the electrocardiographic and arrhythmic manifestations of these disorders do not occur in all individuals with the same genotype (incomplete penetrance) and that the type and severity of presenting symptoms varies between genotype-positive individuals (variable expressivity) suggests that additional genetic and environmental determinants influence the phenotypic manifestations of a given disease-causative mutation in the context of a particular host.

In this review, we describe the current understanding of the genetic architecture underlying complex electrocardiographic traits such as the QT interval, common genetic variants linked to the modulation of ECG parameters in the general population, and lastly the genetic determinants underlying incomplete penetrance and variable expressivity in heritable arrhythmia syndromes, with a primary focus on congenital LQTS.

Electromechanical activity of the heart in health and disease

In healthy individuals, the spontaneous depolarization of specialized “pacemaker” cells within the sinoatrial node of the right atrium initiates cardiac electrical activity. Initial depolarizing electrical impulses are conducted rapidly to adjacent atrial cardiomyocytes by intracellular gap junctions, where they trigger the excitation and contraction of the atria that manifests as a P wave on surface ECG. Next, these excitatory impulses are propagated via the atrioventricular node and Purkinje fibers to the apex of the heart and then into the right and left ventricles. The depolarization of ventricular cardiomyocytes and subsequent contraction of the ventricles are represented by the QRS complex, whereas the repolarization of the ventricles is represented by the T wave on surface ECG (Figure 2a).

At the cellular level, the rhythmic opening and closing of depolarizing inward (Na⁺ and Ca²⁺) and repolarizing outward (K⁺) ion channels within individual cardiomyocytes underlies the normal generation and propagation of action potentials required to produce the electrical impulses that maintain the electromechanical pump function of the human heart. As such, mutations in the genes that encode the pore-forming α - and accessory β -subunits of Na⁺, Ca²⁺ or K⁺ channels expressed in the heart can give rise to a spectrum of inherited cardiac “channelopathies” that are associated with distinct electrocardiographic patterns reflective of the underlying perturbation(s) of the cardiac action potential (Figure 2b). Here, we briefly review the pathophysiology of LQTS, SQTs, BrS and CPVT, which collectively represent the most commonly encountered heritable cardiac channelopathies in clinical practice.

In LQTS, genetic defects in cardiac ion channel function that impart either a gain-of-function to inward depolarizing Na^+ and Ca^{2+} currents (I_{Na} and $I_{\text{Ca,L}}$) or a loss-of-function to outward repolarizing K^+ currents (I_{Kr} , I_{Ks} , and I_{K1}) prolongs ventricular cardiac action potential duration (Figure 2c), which manifests as QT interval prolongation on ECG ($\text{QTc} > 470$ ms for males and > 480 ms for females as 99th percentile values in otherwise healthy adults, Figure 2b).[2, 5] The resulting increase in cardiomyocyte refractoriness, enhancement of the $\text{Na}^+/\text{Ca}^{2+}$ -exchange (NCX) current, and abnormal spontaneous reactivation of the L-type Ca^{2+} channel can trigger early afterdepolarizations (EADs) that can give rise to *torsades de pointes*, the characteristic and sudden death-predisposing form of polymorphic ventricular fibrillation observed in LQTS.[2, 6]

In direct contrast to LQTS, SQTs arises from genetic defects that impart either a loss-of-function to the $I_{\text{Ca,L}}$ inward depolarizing Ca^{2+} current or a gain-of-function to the outward repolarizing K^+ currents (I_{Kr} , I_{Ks} , and I_{K1}). The resulting acceleration of cardiac repolarization abbreviates the cardiac action potential (Figure 2c), shortens the QT interval (< 330 for males and < 340 for females, Figure 2b), and is hypothesized to provide a substrate for sudden death-predisposing re-entrant atrial and ventricular arrhythmias via the formation of a strong transmural dispersion of repolarization between the epicardial and endocardial layers of the heart.[5, 7]

BrS and a spectrum of related disorders termed “J-wave syndromes” arise, in part, from genetic defects that confer a loss-of-function to inward depolarizing Na^+ and Ca^{2+} currents (I_{Na} and $I_{\text{Ca,L}}$) or in rare circumstances gain-of-function to outward repolarizing K^+ currents (I_{to} and I_{KATP}) active during phase 1 of the cardiac action potential. Similar to SQTs, the resulting predominant, unopposed I_{to} current in the right ventricular epicardium is hypothesized to cause the heterogenous loss of the action potential dome (Figure 2c), ST-segment elevation with inverted T-waves in the right precordial leads (V_1 – V_3 , Figure 2b), and the initiation of polymorphic ventricular tachycardia or fibrillation via phase 2 re-entry.[2, 8]

While LQTS, SQTs, and BrS represent genetic disorders that arise from defects in the genes encoding transmembrane ion channel function, CPVT represents a disorder arising from defects in the genes that encode intracellular calcium-handling proteins responsible for maintaining the crucial link between electrical and mechanical activation in the heart known as excitation-contraction coupling. Autosomal dominant gain-of-function mutations in the *RYR2*-encoded ryanodine receptor 2 (RyR2, CPVT1) or autosomal recessive loss-of-function mutations in the *CASQ2*-encoded calsequestrin 2 (CPVT2) results in the abnormal, non-action potential triggered Ca^{2+} release from the sarcoplasmic reticulum (SR) often termed “spontaneous calcium release” (SCR).[9, 10] Compensatory activation of the NCX current in response to SCRs gives rise to delayed afterdepolarizations (DADs), inappropriate activation of the I_{Na} current, generation of extrasystolic beats, and the initiation of potentially lethal polymorphic ventricular tachycardia, particularly in settings associated with increased β -adrenergic activity such as physical and emotional stress.[11]

The genetic and electrophysiological basis of these cardiac channelopathies are summarized in Figure 3 and reviewed in detail elsewhere.[2, 12, 13]

Penetrance, expressivity, and overlapping phenotypes in heritable cardiac arrhythmia syndromes

In 1992, nearly four years before *KCNQ1* (LQT1) was identified officially as the culprit gene residing within the chromosome 11p15.5 genetic locus that was closely linked with LQTS in several families, Vincent et al observed that there was a significant overlap between the heart rate-corrected QT intervals (QTc) in carriers (range 410 to 590 msec;

mean 490 msec) and non-carriers (range 380 to 470 msec; mean 420 msec) of the 11p genetic marker.[14] Coupled with the fact that 63% percent of 11p genetic marker carriers had a history of syncope and 5% a history of OHCA, these findings provided the earliest evidence that incomplete penetrance and variable expressivity would become clinical hallmarks of congenital LQTS.[14] While subsequent studies reported that LQTS disease penetrance ranges from 25% [3] to 100% [15] in individual LQTS families, the mean penetrance across multiple LQTS subtypes in a population-based study was shown to be ~40% [16] indicating that incomplete penetrance in LQTS represents the norm rather than the exception. Furthermore, even in families that harbor highly penetrant mutations such as the KCNQ1-A341V South African founder mutation where 88% of genotype-positive individuals display QT prolongation and 79% have experienced an arrhythmia-triggered cardiac event, there is a high degree of phenotypic variability illustrating that very few LQTS-causative mutations completely escape the phenomena of incomplete penetrance and variable expressivity.[17]

LQTS is certainly not the only inherited cardiac channelopathy subjected to the genetic phenomena of incomplete penetrance and variable expressivity. In a 2000 study, Priori et al estimated that the overall disease penetrance across several small BrS families harboring mutations in the *SCN5A* gene (BrS1) was 16% (range 12.5% to 50%).[18] On the other end of the spectrum, CPVT has an estimated overall penetrance of 78% [19] suggesting that the degree of incomplete penetrance and variable expressivity is highly variable between cardiac channelopathies [20].

In addition to displaying incomplete penetrance and variable expressivity, some individuals with disease-causative mutations in the *SCN5A*-encoded Nav1.5 sodium channel display phenotypic “overlap” or “pleiotropy”, whereby a spectrum of heritable cardiac channelopathy phenotypes co-exist within the same multigenerational pedigree. To date, several *SCN5A* mutations, including delK1500-SCN5A [21], delKPQ1505-1507 [22], E1784K-SCN5A [23], and 1795insD-SCN5A [24] have been associated with a spectrum of arrhythmia phenotypes that includes LQTS (LQT3), BrS (BrS1), cardiac conduction disturbances (CCD), sick sinus syndrome (SSS), or in some cases a combination of these phenotypes. While *in vitro* functional studies suggest that *SCN5A* mutations associated with phenotypic overlap commonly share biophysical features including a hyperpolarizing shift of inactivation and an enhanced tonic block by class IC antiarrhythmics such as flecainide, it is likely that additional environmental and genetic determinants influence the precise phenotypic expression of *SCN5A* mutations associated with multiple biophysical defects (e.g. those mutations that are not “pure” loss- or gain-of-function).[12, 25]

While the genetic determinants underlying the incomplete penetrance, variable expressivity, and phenotypic overlap observed in the cardiac channelopathies remains poorly understood, several important demographic and environmental modifiers of ECG phenotype and arrhythmia risk have been elucidated. Gender is a well-known modifier of both ECG phenotype and risk of SCD in LQTS [26, 27] and BrS [28]. These sex-specific differences may be linked to the differential effect of sex hormones on cardiac ion channel current densities and functional cardiac repolarization reserve (Table 1). Age-related changes in the heart, particularly depolarization abnormalities (e.g. conduction slowing) in BrS, also appear to modulate clinical phenotype.[29] Lastly, exogenous factors including electrolyte imbalances such as hypokalemia [30] and the presence of QT-prolonging drugs can unmask concealed LQTS [31, 32], whereas hyperthermia/fever [33] and the presence of Na⁺ blocking drugs can unmask the electrocardiographic and arrhythmic manifestations of BrS. The established environmental modifiers of electrocardiographic traits in health and disease-severity in the cardiac channelopathies are summarized in Table 1.

Genetic architecture of electrocardiographic traits

As mentioned previously, even in the general population quantitative electrocardiographic traits such as the QT interval are highly variable as evidenced by the observation that while nearly 40% of patients with genetically confirmed LQTS have non-diagnostic QT intervals, 5–10% of ostensibly healthy individuals have a QTc exceeding the electrocardiographic guideline designation of “prolonged QTc” (> 450 ms in men and > 460 ms in women) or “short QTc” (< 350 ms for males and < 360 ms for females, Figure 4).[34, 35] While approximately 30–40% of QT interval variability appears to be heritable[36–38], the genetic architecture of QT interval duration appears to be quite complex and determined by both the frequency and effect size of a spectrum of genetic variants present within a given individual.[39]

On the severe end of this spectrum are extremely rare “private” mutations, generally $< 0.1\%$ minor allele frequency (MAF), in the genes that encode cardiac ion channel α and β subunits that severely perturb myocardial repolarization and typically result in what are classically considered to be rare monogenic diseases such as LQTS and SQTs that are associated with the phenotypic extremes of QT interval duration and an increased risk of SCD compared to the general population (Figure 5). As a result of the strong negative pressure exerted against these variants secondary to the reduction in fecundity associated with SCD, these variants are rarely maintained in successive generations and generally fail to reach detectable levels in the general population.[40, 41]

On the opposite end of this spectrum are common, generally $> 5\%$ MAF, genetic variants present in the general population identified through large scale genome-wide association studies (GWAS) that weakly enhance/perturb myocardial repolarization, minimally impact QT interval duration, and have an uncertain impact on risk of SCD in isolation. In theory, the accumulation of multiple common variants in a single individual that either weakly reduce or weakly enhance myocardial repolarization could coalesce to produce polygenic LQTS or SQTs associated with the same extreme QT abnormalities and risk of SCD as monogenic disease (Figure 5). However, at present there is no concrete evidence in the literature to support the notion of polygenic inheritance in the cardiac channelopathies.

Lastly, in the middle of this spectrum are rare (generally $> 0.1\%$ but $< 5\%$ MAF) variants that moderately perturb myocardial repolarization and encompass both LQTS/SQTs mutations with incomplete penetrance/variable expressivity (lower frequency end of the spectrum) as well as strong genetic modifiers of QT interval duration (upper frequency end of the spectrum) that may result in borderline QT abnormalities, but often fail to produce the objective manifestation(s) of disease when in isolation (Figure 5).[39] Low penetrance/expressivity rare variants such as these may partly explain why recent analyses of population-scale exome sequencing data from the NHLBI exome sequencing project (ESP) revealed that 1:31 individuals harbor a previously LQTS-associated variant in one of the established LQTS-susceptibility genes.[42] Given the discrepancy between the LQTS genotype prevalence (1:31) observed in the NHLBI ESP and the estimated LQTS disease prevalence (1:2000 to 1:5000), it is clear that variants and mutations that reside within this portion of the spectrum follow an ambiguous inheritance pattern and may often require a second genetic or environmental “hit” (e.g. second low prevalence moderately deleterious variant or QT-prolonging drug) to produce the overt QT abnormalities typically associated with monogenic disease.[3]

Common polymorphisms modulating QT interval in health

The discovery that QT prolongation/shortening is associated with increased cardiovascular morbidity and mortality in apparently healthy individuals[43–45] has sparked a concerted

effort in recent years to elucidate the genetic determinants that modulate QT interval duration and SCD risk in the general population. Here, we briefly review the candidate and GWAS that have provided a great deal of insight into the heritable component of QT interval variation.

Most early studies focused on the association between a small number of common candidate genetic variants in the ion channel genes responsible for congenital LQTS and QT interval variability in larger population-based cohorts of healthy individuals. These efforts resulted in the identification of common non-synonymous genetic variants such as *KCNH2*-K897T[46–51], *KCNE1*-D85N[48], *SCN5A*-H558R[48, 52], and *SCN5A*-S1103Y[53–55] and non-coding variants in *KCNQ1*[48, 49], *KCNH2*[49, 50], and *KCNE1*[49] associated with QT interval duration and or SCD risk in otherwise healthy individuals. Unfortunately, discordant observations suggest that some of these early findings may be population-specific as exemplified by *KCNH2*-K897T, which was shown to prolong the QT interval in Finnish cohorts[46, 51] but shorten the QT interval in North American[50] and Western European cohorts[47–49].

GWAS have provided even greater insight into the genetic determinants of QT interval variability in health by allowing researchers to assay the vast majority of common variants in the human genome, rather than small pre-selected subsets. The power of this approach was quickly realized when early GWAS revealed a strong and replicable association between common variants in the *NOS1AP*-encoded nitric oxide synthetase 1 adaptor protein (also called CAPON), a gene not previously linked to cardiac electrophysiology, and QT interval duration in several distinct population-based cohorts.[56, 57] Building on these findings, two large GWAS meta-analyses of at least 13,000 individuals were published in 2009 by the QTGEN and QTSCD consortia, respectively that identified common variants in 6 established genetic loci (*NOS1AP*, *KCNQ1*, *KCNE1*, *KCNH2*, *SCN5A*, and *KCNJ2*) as well as several novel genetic loci that collectively explained ~6% of heritable QT interval variability.[58, 59] The common variants associated with QT interval variability in health identified through candidate gene studies and GWAS are summarized in Table 2.

Genetic determinants of incomplete penetrance and variable expressivity in heritable cardiac arrhythmia syndromes

At present, most studies looking to elucidate the genetic determinants of incomplete penetrance and variable expressivity in the cardiac channelopathies have focused on the co-inheritance of functional SNPs that influence the arrhythmia risk associated with a given disease-causative mutation by either enhancing or repressing the electrophysiological defect conveyed by that mutation. In most instances, these are amino acid-altering SNPs that reside on the opposite allele of the gene harboring the primary disease-causative mutation or in a completely separate channelopathy-susceptibility gene altogether. As briefly touched on above, it has been hypothesized that familial LQTS-causative mutations associated with low penetrance fail to completely abolish repolarization reserve resulting in concealed disease. However, when an individual inherits a low penetrance mutation with a functional polymorphism that further reduces repolarization reserve, the presence of this “second hit” unmasks the otherwise concealed LQTS phenotype.

Several pertinent examples of this “second hit” concept have been described in the literature. First, an estimated 4% to 8% of LQTS probands harbor a second independent disease-causative mutation.[60, 61] Thus, the presence of compound heterozygosity or digenic heterozygosity may explain some of the extreme variable expressivity observed in multigenerational LQTS pedigrees. Secondly, Crotti et al demonstrated, in a multigenerational LQT2 pedigree with the low penetrant *KCNH2*-A1116V mutation, that manifest disease was only observed in individuals who also inherited the minor allele of the

common KCNH2-K897T polymorphism. Lastly, as first described by Westenskow et al[61] and later by Lahtinen et al[17], penetrance and expressivity in *KCNQ1* (LQT1) mutation-positive subjects is modified by the common KCNE1-D85N polymorphism. Recently, KCNE1-D85N functionally perturbs both I_{Ks} and I_{Kr} [62] and functions as a risk factor for drug-induced LQTS in the general population.[63] Thus, it appears that common amino acid-altering genetic variation associated with QT interval variability in the general population may also serve as genetic modifiers of LQTS disease severity regardless of whether the second hit occurs within or outside the gene harboring the primary disease-causative mutation.

In addition to common genetic variation within established LQTS-susceptibility genes, several studies have also implicated common genetic variants in genes that modulate cardiac ion channel function through either post-translational or transcriptional effects as genetic determinants of LQTS disease severity. First, polymorphisms in the $\alpha 2$ and $\beta 1$ adrenergic receptor genes that result in the loss of $\alpha 2$ autoinhibitory feedback/increased presynaptic epinephrine release (ADRA2C-del322-325)[64] or enhanced $\beta 1$ activity secondary to improved coupling to adenylyl cyclase (ADRB1-G389R)[65] modify disease expressivity in LQT1 via enhanced baroreceptor/autonomic responsiveness.[66, 67]

In contrast to the adrenergic receptor polymorphisms where the increased risk of life-threatening arrhythmias appears to be largely independent of QT interval duration, common *NOS1AP* variants (rs4657139 and rs16847548), previously associated with QT interval duration in the general population, modestly influence QT interval duration, occurrence of symptoms, and risk of cardiac arrest/sudden death in the large South African KCNQ1-A341V LQT1 kindred.[68] While the precise mechanisms of these *NOS1AP* variants remains unknown, a second study by Tomas et al provided further evidence that the alleles tagged by these variants are risk-conferring genetic modifiers of QT interval (average QTc prolongation of 7 and 8 ms per variant) and incidence of cardiac events in a prospective registry of 901 LQTS patients.[69]

Emerging role of non-coding variants in the allele-specific modification of heritable arrhythmia syndrome disease severity

Despite a concerted effort over the past decade, it is clear that a significant proportion of the variability in disease penetrance and expressivity observed within many multigenerational cardiac channelopathy pedigrees cannot be explained by established environmental and genetic determinants alone. As such, it stands to reason that yet undiscovered elements within an individual's genetic background underlie these genetic phenomena in the cardiac channelopathies. Here, we review several recent studies that provide initial evidence that non-coding genetic variants within key regions responsible for regulating the expression of established channelopathy-susceptibility genes may function as allele-specific genetic determinants of incomplete penetrance, variable expressivity, and/or phenotypic overlap in the cardiac channelopathies.

Previous studies have hypothesized that genetic variation within the 3' untranslated region (3' UTR), the canonical region of mRNA transcripts that contain *cis*-regulatory binding sites for small non-coding microRNAs (miRs) that inhibit gene expression post-transcriptionally, contributes to individual variation in disease severity.[70] To date, a number of studies have demonstrated that naturally occurring miR binding site polymorphisms (miR-SNPs) can either cause or modulate a spectrum of disease phenotypes including solid organ cancers[71–73], asthma[74], α -thalassemia[75], hereditary thrombophilia[76], and Friedrich ataxia[77]. However, the vast majority of these studies were unable to demonstrate clear allele-specific effects as the causal miR-SNPs were either involved in the progression of

complex disease processes, implicated as the primary disease-causative mutation, or located outside the gene believed to harbor the primary genetic driver of disease pathogenesis.

In early 2012, a study by our group demonstrated that minor alleles of miR-SNPs rs2519184 (A), rs8234 (G), and rs10798 (G) in the 3' UTR of *KCNQ1*-encoded Kv7.1 tetrameric K⁺ channel serve as potent allele-specific modifiers of both QTc and symptomatology (e.g. syncope, seizures, or OHCA) in type 1 LQTS (LQT1).[78] In a combined cohort of 168 American and Dutch LQT1 patients, the inheritance of a "suppressive" minor 3'UTR haplotype (e.g. A-G-G or G-G-G) on the healthy *KCNQ1* allele accentuated the severity of the LQT1 phenotype, whereas the inheritance of the same A-G-G or G-G-G 3'UTR haplotype on the mutant *KCNQ1* allele attenuated the severity of the LQT1 disease phenotype (Figure 6a).[78]

Taken collectively with *in vitro* evidence from dual-luciferase reporter assays carried out on immortalized rat neonatal cardiomyocytes, these findings suggest that the minor alleles of rs2519184 (A), rs8234 (G), and rs10798 (G) exert their allele-specific modifying effect by reducing the expression of the transcript on which they reside, thereby altering the stoichiometric ratio of normal and mutant α -subunits available to co-assemble into functional Kv7.1 channels (Figure 6b).[78] As such, when the minor alleles of these SNPs reside on the normal allele (i.e. *in trans*), expression of the healthy *KCNQ1* allele is suppressed and the LQT1 phenotype is accentuated and *vice versa* (i.e. attenuated) when these SNPs reside on the 3' UTR of the mutant *KCNQ1* allele (i.e. *in cis*, Figure 6b). Not only does the modifying effect associated with the minor alleles of SNPs in the 3'UTR of *KCNQ1* far exceed that of any previously identified LQTS genetic modifier, but this discovery may also represent a potential paradigm shift in our understanding of the genetic basis of Mendelian disorders as one of the most important genetic determinants of disease severity in LQT1 appears to be the 3'UTR haplotype on the *KCNQ1* allele inherited from the **unaffected** parent.

The modifying role of non-coding SNPs in established channelopathy-susceptibility genes is not limited to the aforementioned *KCNQ1* 3' UTR SNPs. In another recent study, Park et al demonstrated that within a multigenerational BrS/overlapping phenotype pedigree harboring the truncating Q646RfsX5-*SCN5A* mutation, those individuals, who also harbored a 2-SNP minor haplotype (rs41310749 and rs41310239) in the *SCN5A* promoter on both the mutant and normal *SCN5A* alleles (i.e. homozygous for the minor alleles), had a severe arrhythmia phenotype (defined as suffering from syncope, OHCA, or SCD) in comparison to the mild arrhythmia phenotype (defined as no cardiac events) displayed by those Q646RfsX5-positive individuals who only inherited the 2-SNP haplotype on their mutant *SCN5A* allele. [79] Interestingly, in comparison to the wild-type 2-SNP *SCN5A* promoter haplotype, previous *in vitro* studies conducted in a variety of cell types displayed a trend towards reduced promoter activity associated with the minor 2-SNP *SCN5A* promoter haplotype.[80] As such, Park et al hypothesized that the modest reduction in both mutant and normal *SCN5A* expression associated with the minor 2-SNP promoter haplotype functioned in an additive manner to aggravate the underlying arrhythmia phenotype associated with the Q646RfsX5 loss-of-function mutation.[79]

Unfortunately, it is still too early to accurately assess the clinical applicability of these recent discoveries to the risk-stratification and clinical management of *KCNQ1*- and *SCN5A*-positive individuals. Additional studies are needed to unravel the precise molecular basis of the observed modifying effects [e.g. specific microRNA(s) or transcription factor(s) involved] and to ensure that the observed modifying effects are not mutation- and/or population-specific.

Concluding remarks

Advances at the bench and bedside have unearthed a number of important environmental and genetic determinants responsible for the marked variability in electrographic traits and risk of arrhythmia-associated symptoms observed in health and disease. However, our enhanced understanding of the genetic determinants of incomplete penetrance and variable expressivity in the heritable cardiac arrhythmia syndromes has yet to translate into truly meaningful advances at the bedside. While we now understand how certain genetic determinants within an individual's genetic background may function to enhance or suppress the phenotype associated with a given genotype, the advent of exome and genome sequencing is beginning to teach us that these discoveries likely represent single pieces of a very complex puzzle as a large number of ostensibly healthy individuals sequenced through population-scale exome/genome projects (e.g. 1000 genomes and the NHLBI exome sequencing project) harbor functionally relevant genetic variation in the molecular constituents of the cardiac sodium, calcium, and/or potassium ion channel macromolecular complexes.

Thus, it is difficult to attribute the marked incomplete penetrance and variable expressivity observed in Mendelian/monogenic disorders such as the cardiac channelopathies solely to the interaction between a specific disease-causative mutation and a single candidate genetic modifier. Rather, these genetic phenomena likely arise from the complex interplay between the plethora of genetic variation present within an individual's genome and acquired "environmental" factors that collectively modify the function/expression of cardiac ion channels and thereby alter the electrophysiological properties of the heart. As the cost of genome sequencing continues to decrease, a primary challenge will be to look beyond the isolated contribution of single candidate variants and instead focus on developing comprehensive approaches that integrate data from next-generation sequencing, functional studies, and systems biology in a global fashion. The systematic exploration of the genetic variation that comprises the complete genetic architecture of the cardiac channelopathies promises to finally yield meaningful personalized approaches to the diagnosis, risk-stratification and clinical management of patients with these potentially lethal, yet highly treatable genetic disorders.

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Abbreviations

3'UTR	3' untranslated region
BrS	Brugada syndrome
Ca²⁺	calcium
CCD	cardiac conduction disturbance
CPVT	catecholaminergic polymorphic ventricular tachycardia
ECG	electrocardiogram
GWAS	genome-wide association study
K⁺	potassium
LQTS	long QT syndrome

MAF	minor allele frequency
miR	microRNA
miR-SNPs	microRNA binding site single nucleotide polymorphisms
Na⁺	sodium
NCX	Na ⁺ , Ca ²⁺ exchange current
OHCA	out-of-hospital cardiac arrest
QTc	heart rate-corrected QT
SCD	sudden cardiac death
SCR	spontaneous Ca ²⁺ release
SNP	single nucleotide polymorphism
SQTS	short QT syndrome
SSS	sick sinus syndrome
SNP	single nucleotide polymorphism

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Figure 1.

Penetrance and expressivity in a generic heritable cardiac arrhythmia syndrome. **a** | Representative multigenerational pedigree displaying complete penetrance (100%) for the electrocardiographic and arrhythmic hallmarks of the disease. **b** | Representative multigenerational pedigree displaying incomplete penetrance (33%) for the electrocardiographic and arrhythmic hallmarks of the disease. **c** | Representative multigenerational pedigree displaying incomplete penetrance (66%) and variable expressivity as some individuals display the electrocardiographic hallmarks of the disease without symptomatology.

Figure 2.

Electrical activity of the heart in health and disease. **a** | Schematic representation of the normal cardiac conduction system and the correlation between the action potentials of cardiomyocytes in distinct areas of the heart and the surface electrocardiogram. **b** | Schematic representation of a normal ECG (black) and typical ECGs for patients with LQTS (left, red), SQTS (middle, red), and BrS (right, red). **c** | Tracings of normal ventricular action potentials (black) and tracings that display epicardial action-potential prolongation in LQTS (left, red), action-potential abbreviation in SQTS (middle, red), and the transmural gradient between the epicardial action potential (right, solid red line) and endocardial action-potential (right, dotted red line) that results in the inscription of the J-wave in BrS. BrS, Brugada syndrome; ECG, electrocardiogram; LQT, long QT syndrome; SQT, short-QT syndrome. Reproduced in part from Wilde, A. A. & Bezzina, C. R. Genetics of cardiac arrhythmias. *Heart* 91(10), 1352–1358 © 2005, with permission from BMJ Publishing Group Ltd.

Figure 3.

Current-centric classification of heritable cardiac arrhythmia syndromes. The clinical phenotypes resulting from the abnormal ventricular cardiac action potential depolarization (orange) or repolarization (purple) are grouped according to the specific current perturbed by an underlying genetic defect. Blue circles represent loss-of-function mutations to the specified current, whereas green circles represent a gain-of-function. Solid lines indicate those disorders that are autosomal dominant, whereas dashed lines indicate those disorders that are autosomal recessive. Abbreviations: BrS, Brugada syndrome; LQT, long QT syndrome; I_{CaL} , L-type calcium current; I_{K1} , inwardly rectifying current; I_{KATP} , ATP-sensitive potassium current; I_{Kr} , rapid component of the delayed rectifier potassium current; I_{Ks} , slow-component of the delayed rectifier potassium current; I_{to} , transient outward potassium current; I_{Na} , cardiac sodium current; SQT, short-QT syndrome.

Figure 4.

QTc distribution in health and disease. The distribution of QTc values in health was derived from nearly 80,000 healthy adult males and females.[81] The distribution of QTc values in LQTS were derived from all patients with genetically proven LQTS evaluated in the Mayo Clinic Long QT Syndrome Clinic and the distribution of QTc values in SQTS from cases identified in a recent meta-analysis[82]. Permission obtained from Wolters Kluwer Health © Taggart, N.W. et al. Diagnostic miscues in congenital long QT syndrome. *Circulation* 115(20), 2613–2620 (2007).

Figure 5.

Genetic architecture underlying the complex phenotypes associated with perturbed myocardial repolarization/depolarization. A spectrum of genetic variation underlies the genetic architecture of myocardial repolarization/depolarization abnormalities. At the severe (red) end of the spectrum are extremely rare (<1% minor allele frequency) mutations that strongly perturb the cardiac action potential and typically result in monogenic disorders such as LQTS and BrS. In the middle of the spectrum (yellow) are rare variants that moderately perturb the cardiac action potential, but often require a second hit (e.g. genetic modifier, QT-prolonging drug, etc.) to myocardial repolarization/depolarization to produce the electrocardiographic or arrhythmic manifestations associated with monogenic disease. Lastly, at the benign (green) end of the spectrum are common (>5% minor allele frequency) variants that weakly perturb the cardiac action potential and only contribute to the electrocardiographic and arrhythmic manifestations of disease in rare circumstances when multiple hits (genetic and environmental) to myocardial repolarization/depolarization are present.

Figure 6.

The allele-specific effects and hypothesized mechanism of LQT1 disease-modifying SNPs in the 3'UTR of *KCNQ1*. **a** | Summarized allele-specific effects of SNPs rs2519184, rs8234, and rs10798 on the heart-rate corrected QT interval (dark gray bars) and occurrence of symptoms (light gray line) in the combined Mayo Clinic and Academic Medical Center LQT1 cohort. **b** | Hypothesized microRNA-mediated mechanism whereby the minor alleles (dark gray boxes) of SNPs in the 3'UTR of *KCNQ1* alter the stoichiometric assembly of wild-type (white circles) and mutant (dark circles) Kv7.1 α-subunits derived from mutant (black) and normal (white) *KCNQ1* alleles, respectively. Numbers above genotype denote group sizes. ** $p < 0.05$ for average QTc and % cardiac events in comparison to the wild-type 3'UTR haplotype (NGAA/MGAA), * $p < 0.05$ for average QTc compared to the wild-type 3'UTR haplotype (NGAA/MGAA), N, normal *KCNQ1* allele, M, mutant *KCNQ1* allele. Reproduced from Amin, A.S., Giudicessi, J.R., and Tijssen, A.J., et al. Variants in the 3' untranslated region of the *KCNQ1*-encoded Kv7.1 potassium channel modify disease severity in patients with type 1 long QT syndrome in an allele-specific manner. *Eur Heart J* 33(6), 714–723 © 2012 with permission from Oxford University Press.

Table 1

Demographic and exogenous modifiers of ECG phenotype and SCD risk

	AP effect	ECG effect	SCD risk
Gender/Sex Hormones			
Estrogen	↑ $I_{Ca,L}$	QT prolongation	↓ BrS and ↑ LQTS
Progesterone	↓ $I_{Ca,L}$	QT shortening	↓ LQTS
Testosterone	↓ $I_{Ca,L}$ and ↑ I_{Ks}	QT shortening	↑ BrS and ↓ LQTS
Exogenous			
Hyperthermia/fever	↓ I_{Na} and ↑ I_{Kr}	ST-segment elevation and QT prolongation *	↑ BrS and ↓ LQTS *
Hypokalemia	Hyperpolarization and paradoxical ↓ I_{Kr}	QT prolongation	↑ LQTS
Na ⁺ channel blockers	↓ I_{Na} (predominantly)	ST-segment elevation	↑ BrS
QT-prolonging drugs	↓ I_{Kr} (predominantly)	QT prolongation	↑ LQTS

* Fever-induced QT prolongation/ventricular arrhythmias have only been described in type 2 LQTS. Abbreviations: AP, action potential; BrS, Brugada syndrome; ECG, electrocardiogram; $I_{Ca,L}$, L-type Ca^{2+} current; I_{Ks} , slow component of the delayed rectifier K^{+} current; I_{Kr} , rapid component of the delayed rectifier K^{+} current.

Table 2

Common variants in established and novel genetic loci associated with QT interval variability in health

Locus	SNP ID	MAF	Amino Acid Change*	Function	QT Effect	Reference
Established loci						
1q <i>NOS1AP</i>	rs12143842	0.26	None	Nitric oxide synthetase 1 adaptor	↑ QT interval	55, 56
	rs12029454	0.15	None		↑ QT interval	55
	rs16857031	0.14	None		↑ QT interval	55
	rs4657139	0.41	None		↑ QT interval	53, 54
11p <i>KCNQ1</i>	rs2074238	0.06	None	α-subunit, I _{Ks} channel	↓ QT interval	55, 56
	rs12576239	0.13	None		↑ QT interval	55, 56
	rs12296050	0.21	None		↑ QT interval	56
7q <i>KCNH2</i>	rs4725982	0.22	None	α-subunit, I _{Kr} channel	↑ QT interval	55, 56
	rs2968864	0.25	None		↓ QT interval	55, 56
	rs1805123	0.24	K897T		Discordant	43–48
3p <i>SCN5A</i>	rs12053903	0.34	None	α-subunit, I _{Na} channel	↓ QT interval	55, 56
	rs11129795	0.24	None		↓ QT interval	56
	rs1805124	0.18	H558R		↑ QT interval	45, 49
21q <i>KCNE1</i>	rs1805128	0.01	D85N	MinK β-subunit	↑ QT interval	55, 56, 45
17q <i>KCNJ2</i>	rs17779747	0.35	None	α-subunit, K _v 2.1 channel	↓ QT interval	56
Novel loci						
16q <i>CNOT1</i>	rs246196	0.24	None	RNA transcription	↓ QT interval	55, 56
6q <i>c6orf204</i>	rs11756438	0.47	None	Phospholamban	↑ QT interval	55, 56
1q <i>ATP1B1</i>	rs10919071	0.87	None	Na ⁺ /K ⁺ ATPase β-subunit	↓ QT interval	56
1p <i>RNF207</i>	rs846111	0.28	G603A	Ring finger protein	↑ QT interval	55, 56
16p <i>LITAF</i>	rs8049607	0.49	None	Tumor necrosis factor	↑ QT interval	56
17q <i>LIG3</i>	rs2074518	0.46	None	DNA ligase III	↓ QT interval	55, 56

* Most variants are non-coding.