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Genetic determinants of QT interval variation and sudden cardiac death

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Electrocardiographic QT interval prolongation or shortening is a risk factor for sudden cardiac death. The study of Mendelian syndromes in families with extreme long and short QT interval duration and ventricular arrhythmias has led to the identification of genes encoding ion channel proteins important in myocardial repolarization. Rare mutations in such ion channel genes do not individually contribute substantially to the population burden of ventricular arrhythmias and sudden cardiac death. Only now are studies systematically testing the relationship between common variants in these genes — or elsewhere in the genome — and QT interval variation and sudden cardiac death. Identification of genetic variation underlying myocardial repolarization could have important implications for the prevention of both sporadic and drug-induced arrhythmias.

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Introduction

Sudden cardiac death (SCD) and resuscitated sudden cardiac arrest are commonly due to ventricular arrhythmias and claim more than 300 000 lives annually in the United States [1]. SCD is a complex trait with multiple environmental (e.g. smoking) and genetic contributors. Although multiple SCD risk factors such as age, male sex, reduced left ventricular ejection fraction, hypertension, diabetes, tobacco use, body mass index and most importantly acute coronary syndromes have been identified, prediction of SCD risk in individuals in the general population is poor owing to the non-specific nature of these risk factors and the heterogeneous nature of SCD. Efforts to identify SCD risk factors have therefore focused on high-risk groups, ranging from those with

strong clinical risk factors such as reduced left ventricular ejection fraction following myocardial infarction or those with strong genetic factors such as families with congenital long or short QT syndromes (LQTSs and SQTs, respectively). Family history of SCD is a potent risk factor in the general population, suggesting a role for genetic variation in determining risk [2,3]. Owing to obvious difficulties in recruiting victims of SCD from the general population, limited sample sizes have hampered efforts to identify prevalent genetic risk factors to date.

Electrocardiographic QT interval duration is more tractable because of its widespread availability in large collections and substantial evidence of heritability. QT interval duration is measured from the beginning of the QRS complex to the end of the T wave and corresponds to the myocardial depolarization and repolarization time. The QT interval is a potent quantitative SCD risk factor when prolonged or shortened both in the general population [4] and in families with congenital LQTSs [5–12] or SQTs [13–15]. Moreover, QT interval prolongation and resultant ventricular arrhythmias upon exposure to cardiac and non-cardiac medications is a major barrier to drug development and has led to the costly withdrawal from the market of several widely used medications such as cisapride and terfenadine [16]. Thus, identification of contributors to genetic variation in QT interval duration could have a broad impact on biomedical science.

In this review, focusing on reports since 2004, the allelic architecture of Mendelian and complex traits is considered as it informs the methods used to identify genetic determinants of SCD and QT interval variation. We review recent advances in the understanding of various aspects of QT duration: congenital LQTSs and SQTs; the relationship of LQTSs and sudden infant death syndrome (SIDS); the heritability and genetic basis of SCD; the genetic determination of QT interval variation in the general population; and the genetic basis of drug-induced QT prolongation and arrhythmias.

Allelic architecture of human diseases

The genetic architecture of a disease is defined by the frequency and number of genetic variants and the strength of their effects on disease risk. For most common diseases such as SCD, the genetic architecture is almost entirely unknown. The heterogeneous substrates and triggers of SCD and the difficulty in collecting large numbers of well-phenotyped SCD victims have been major barriers to defining this architecture.

2 Genetics of disease

Congenital LQTSs and SQTs, marked by extreme derangements of myocardial repolarization — very long or short QT interval — and SCD from *torsade de pointes*, comprise a small but well-defined subset of SCD. Strong aggregation within families has enabled the identification of hundreds of rare mutations of strong effect, mostly in ion channels (Figure 1a). These mutations are generally individually rare and typically confined to individual families, as demonstrated originally by Splawski *et al.* [17] and more recently by Tester *et al.* [18] and Napolitano *et al.* [19] (see www.fsm.it/cardmoc/ for an up-to-date catalog of reported variants). Presumably, negative selection has prevented such poorly tolerated mutations from rising to appreciable frequencies, at least until the modern era of improved diagnosis and preventive therapies. Notable exceptions include recently reported potassium channel gene ‘founder’ mutations in Finland [20] and in South Africa [21]. In such cases, however, the founding of a population by a relatively small number of individuals results in widespread if distant relatedness: carriers of a specific mutation are part of one big family. Unfortunately, outside of these founder populations, no common LQTS or SQT variants have been identified that contribute individually to any of the Mendelian QT syndromes or to SCD, with the exception of the 1102Y *SCN5A* variant (see below).

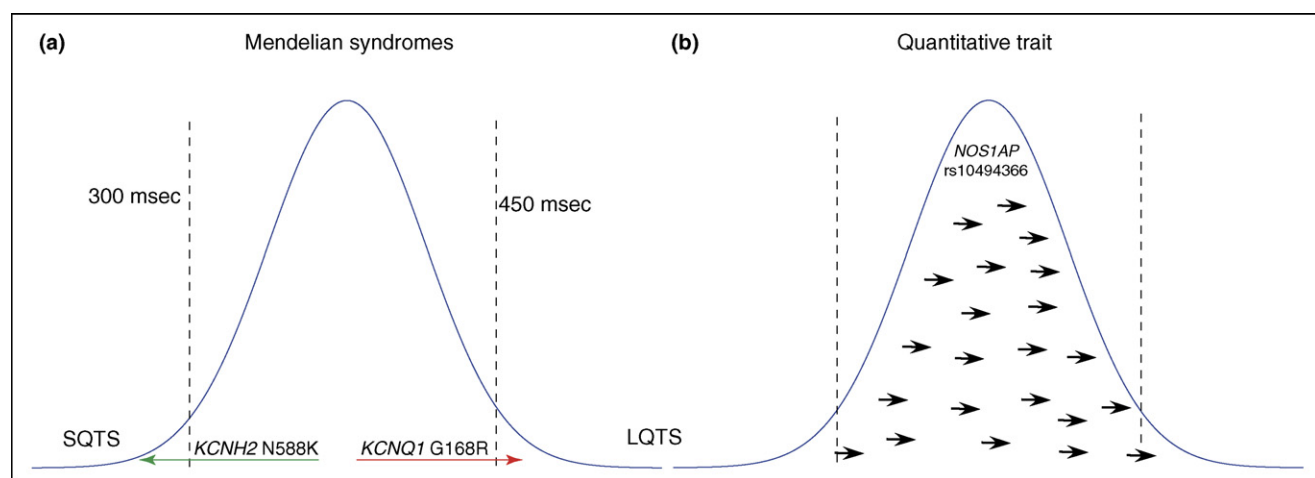
Linkage methods have been particularly effective in identifying disease-causing loci implicated in congenital

LQTS, ultimately leading to the identification of nine genes, four of which are also associated with SQTs (Table 1). The strength of the effect of the underlying mutations, the relatively low background rate in the general population, and the high penetrance have all contributed to the great success of linkage analysis for the study of Mendelian diseases such as LQTS and SQTs [22]. However, linkage methods are not well suited to detecting common variants of modest effects or to the general population of SCD victims from families with much less aggregation of SCD. Association methods are more powerful for detecting the more modest effects presumed to exist for many common diseases of late onset — such diseases are immune to the negative selection against stronger variants causing Mendelian QT syndromes before reproductive age. However, these methods require large numbers of subjects to detect their more modest effects (Figure 1b). Having reviewed the allelic architecture of SCD and its implications for the genetic tools best suited to dissect it, we now review Mendelian LQTS and SQTs.

Congenital long and short QT syndromes

Congenital LQTS is characterized by prolonged QT interval duration and SCD due to *torsade de pointes* — polymorphic ventricular tachycardia with prolonged QT interval duration. The majority of LQTS families in which the disease has an identifiable cause — approximately 75% of all cases — have mutations in ion channels

Figure 1



QT variants in Mendelian syndromes and quantitative traits. **(a)** Mendelian syndromes such as congenital long QT syndrome (LQTS) and short QT syndrome (SQTs) have been found to result from loss-of-function and gain-of-function mutations, respectively, in potassium channels — for example, those encoded by *KCNQ1* and *KCNH2* — that underlie I_{Ks} and I_{Kr} repolarizing currents (see Table 1). Such mutations exert strong influences on the delay or hastening of myocardial repolarization as manifest by significantly longer or shorter QT intervals, reaching thresholds of >450 msec or <300 msec. **(b)** By contrast, the continuous QT interval in minor homozygotes compared with major homozygotes of a recently identified common allele of *NOS1AP* (minor allele frequency is 38%) is reproducibly increased by 4–8 msec throughout the entire distribution of ‘normal’ values (see text). Although LQTS and SQTs mutations result in strong derangements of myocardial repolarization with resultant ventricular arrhythmias, they are individually rare and do not contribute to a substantial proportion of variability of QT duration in the general population. Whether the high frequency of common variants of modest effect such as the *NOS1AP* variant translates into a significant influence on the population burden of sudden cardiac death is a hypothesis currently being tested.

Table 1

Genes found to contribute to congenital long QT and short QT syndromes

Gene	Gene Name	Gain of function	Loss of function	Syndromes	Other disorders
<i>KCNQ1</i>	Potassium voltage-gated channel, KQT-like subfamily, member 1 (I_{Ks})	SQT2 [14]	LQT1 [7]	Associated deafness (JLN) [62], SIDS [33]	Familial atrial fibrillation (GOF) [63], drug-induced QT prolongation/TdP [64]
<i>KCNH2</i>	Potassium voltage-gated channel, subfamily H (eag-related), member 2 (I_{Kr})	SQT1 [13]	LQT2 [6]		Drug-induced QT prolongation/TdP [65]
<i>SCN5A</i>	Sodium channel, voltage-gated, type V, α subunit (I_{Na})	LQT3 [11]	Brugada [24]	SIDS [34]	Familial heart block [66], congenital sick sinus syndrome [67]
<i>ANK2</i>	Ankyrin 2, neuronal		LQT4 [68]		
<i>KCNE1</i>	Potassium voltage-gated channel, Isk-related family, member 1 (I_{Ks})		LQT5 [10]	Associated deafness (JLN) [69]	
<i>KCNE2</i>	Potassium voltage-gated channel, Isk-related family, member 2 (I_{Kr})		LQT6 [5]		Familial atrial fibrillation (GOF) [70]
<i>KCNJ2</i>	Inwardly rectifying potassium channel (I_{K1})	SQT3 [15]	LQT7 [71]	Andersen-Tawil syndrome (periodic paralysis, facial dysmorphism)	Familial atrial fibrillation (GOF) [72]
<i>CACNA1C</i>	Calcium channel, voltage-dependent, L type α 1C subunit (CaV1.2)	LQT8 [8]	SQTS [23]	Timothy syndrome (congenital heart disease, dysmorphism, syndactyly) [8]	
<i>CAV3</i>	Caveolin 3	LQT9 [12]		SIDS [73]	

Shown are the effects of gain-of-function (GOF) or loss-of-function (LOF) mutations on disease. Syndromes in which ventricular arrhythmias have been found in association with other traits are identified. Other disorders reported to result from mutations in the same LQTS/SQTS genes are also shown. Abbreviations: TdP, *torsade de pointes*.

involved in the cardiac myocyte action potential (Table 1) [17,18]. The action potential is a tightly orchestrated event resulting from the joint and timed action of multiple ion channels including depolarizing sodium and calcium currents and repolarizing potassium currents. LQTS results from either loss-of-function mutations in potassium channel genes (e.g. *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2* and *KCNJ2*), thus delaying repolarization, or gain-of-function mutations in sodium (*SCN5A*) and calcium channel genes (*CACNA1C*), thus sustaining depolarizing current (Table 1). Interestingly, Mendelian SQTSs have recently been identified and result from gain-of-function potassium channel mutations or loss-of-function calcium channel mutations [13–15,23]. Loss-of-function mutations in the *SCN5A* sodium channel gene result in Brugada Syndrome with clear repolarization abnormalities manifest in the right precordial leads of the electrocardiogram but typically without long or short QT interval duration [24].

Unfortunately, the proportion of sudden deaths in the general population attributable to LQTS or SQTS is low and the contribution of individual mutations — typically private to the families in which they arise — is close to zero. Molecular characterization of large numbers of affected LQTS families, as in a report by Napolitano *et al.* [19] in 2005, has demonstrated that mutation-carrying relatives of probands often have milder prolongation of the QT interval, overlapping the normal range. Penetrance of mutation-carrying relatives of probands was

reported to be 60%. Whether sporadic or unrecognized familial LQTS-mutation carrying individuals have a wider prevalence in the general population is being clarified by accumulating case study data. In 2004, Chugh *et al.* [25] reported an autopsy study of 12 unexplained sudden death victims — none had apparent structural heart disease — from a collection in Minnesota in which sodium and potassium channel genes were examined and two individuals harboring the same previously reported disease-causing variant in *KCNH2* were identified. In 2004 and 2007 Tester *et al.* [26,27] reported an autopsy study of 49 young cases of sudden unexplained death in which putative disease-causing mutations in ion channels and the ryanodine receptor were identified in 17 (35%) of individuals. It remains to be seen whether ion channel mutations contribute to sudden cardiac death in individuals with coronary artery disease and other structural heart disease.

Sudden infant death syndrome and long QT syndrome

SIDS is a devastating syndrome of death that occurs within the first year of life but without any apparent cardiovascular or pulmonary cause. It has an incidence in the United States of 0.03–0.1% [28]. Although multiple environmental risk factors are known, including prone sleeping, bed sharing and premature birth, risk stratification tools for targeted preventive measures have been elusive. A notable exception is the worldwide public health 'Back to Sleep' campaign to encourage parents

4 Genetics of disease

to put babies to sleep in the supine position, which has had a notable impact on the rates of SIDS generally [29].

It was proposed in 1976 that congenital LQTS might contribute to a substantial fraction of SIDS cases [30,31]. In 1998, Schwartz *et al.* [32] reported an impressive prospective population-based study establishing the association of SIDS with QT interval prolongation. They studied a population-based sample of 33 034 newborns in Italy with electrocardiograms (ECGs) on the third or fourth day of life and reported 24 SIDS cases by one year of follow-up. Twelve of 24 SIDS cases were found to have a corrected QT interval >97.5th percentile, and the odds of SIDS was 41-fold greater for infants with a corrected QT >97.5th percentile compared with infants with a corrected QT \leq 97.5th percentile. Thus, this study raised the possibility that genetic mutations contributing to prolonged QT interval duration could mark SIDS as a *forme fruste* of congenital LQTS [32]. Additional early data from case reports demonstrated that mutations in known LQTS genes could be found in SIDS cases [33,34].

In 2005, Tester *et al.* [35] reported a study of 93 SIDS cases in whom one sodium and five potassium channel genes were screened and 5.1% of 58 white infants and 2.9% of 34 black infants had likely causal mutations. In 2006, Plant *et al.* [36] reported a study of 133 African-American SIDS cases compared with 1056 controls focused on the SCN5A S1102Y variant that has been reported to be associated with ventricular arrhythmias in African-American adults (see below). The investigators found the frequency of 1102Y homozygosity to be 2.3% in cases compared with 0.1% in controls, suggesting a substantially increased risk of SIDS owing to homozygosity for this allele [36]. In 2007, Schwartz's group [37] reported a study of 201 SIDS cases from Norway in whom five potassium genes, *SCN5A* and *caveolin 3* were screened. After elimination of likely non-functional variants, 9.5% (95% CI: 5.8–14.4%) of the 201 SIDS cases were felt to be attributable to mutations among the seven LQTS genes studied. Thus, an appreciable fraction of SIDS cases is attributable to an early and aggressive manifestation of LQTS.

Some have advocated screening of infants for prolonged electrocardiographic QT interval to identify increased risk of death from SIDS or LQTS at older ages, but this has not been widely accepted. In support of this approach are the ease and low cost of non-invasive ECG screening, the availability of effective therapies such as β -adrenergic blocking therapies and implantable defibrillators, and the devastating impact of neonatal death [38]. However, these must clearly be set against the cost of population-based screening of many infants, most of whom will not die suddenly, the psychological and social impact on families and individuals of false-positive screening results — by definition 2.5% of children exceed the

97.5th percentile for corrected QT — and the potential morbidity of β -blockers or serial defibrillators [39].

Heritability of sudden cardiac death in the general population

Several population-based epidemiologic studies have identified risk factors for SCD, including antecedent myocardial infarction, tobacco use, hypertension, hypercholesterolemia, diabetes, heart rate, left ventricular hypertrophy, dietary factors and time of day [2,40,41]. Unfortunately, the factors that contribute significantly to risk of SCD are prevalent and non-specific and, to date, high-risk population subsets include only a small fraction of those who go on to die suddenly [42]. A positive family history of SCD imparts a substantial risk of SCD. Friedlander *et al.* [3] reported a relative risk for SCD of 1.57 for a first-degree relative with a history of myocardial infarction or SCD after adjustment for other SCD risk factors. Using multivariable models, Jouven *et al.* [2] found a relative risk of 1.80 for SCD in individuals whose mother or father had died from SCD, compared with individuals with no parental history of SCD. History of SCD in both parents increased the relative risk to 9.4 [2].

The aggregation of coronary artery disease risk factors among SCD risk factors and the strong influence of acute myocardial infarction raise the question of whether SCD and its heritable risk factors can be distinguished from myocardial infarction determinants alone. Two recent reports address this question directly. In 2006, Kaikkonen *et al.* [43] reported a study of SCD victims in Finland without past history of myocardial infarction and with autopsy-proven acute coronary syndrome — fresh intracoronary thrombus, plaque rupture or erosion, intraplaque hemorrhage or >75% left main coronary artery stenosis. Thus, the authors excluded individuals who might have died suddenly from arrhythmias due to LQTS or primary cardiomyopathies. Remarkably, the odds of having a first-degree relative with SCD were 2.2 times greater among SCD victims during acute coronary syndrome than for healthy controls and 1.6 times greater than for acute myocardial infarction survivors. The odds of having two or more first-degree relatives with SCD were 11.3 times greater than for controls and 3.3 times greater than for acute myocardial infarction survivors.

In 2006, Dekker *et al.* [44•] reported a study in the Netherlands of 330 cases of resuscitated ventricular fibrillation (VF) arrest within the first 12 hours of an acute and first ST elevation myocardial infarction (STEMI) without co-existent structural heart disease, compared with matched STEMI controls without VF. Individuals with a history of SCD in a parent or sibling had 3.3 times the odds of VF compared with individuals with no family history of SCD even after adjustment for SCD risk factors, including degree of ST segment elevation.

It is perhaps reasonably assumed that acute myocardial infarction is such a strong and generic arrhythmogenic stimulus that heritable factors would play little role in SCD determination. In fact, as demonstrated by Kaikkonen *et al.* [43] and Dekker *et al.* [44^{*}], the opposite is true: in the setting of the defined and stereotyped stimulus of acute myocardial infarction, family history of SCD plays an even stronger role in producing cardiac arrest. Arrhythmic death is the leading cause of death, most commonly in the setting of acute coronary events. Whether or not heritable factors that influence SCD in non-coronary event settings have identical impacts on SCD during coronary events, it is clear that genetic factors play a role in SCD generally. Studies are only now beginning to identify genetic risk factors for SCD in the general population.

Common genetic variants and SCD

In 2002, Splawski *et al.* [45] reported a study of the *SCN5A* gene in a heterogeneous collection of clinical syndromes, including cardiac arrhythmias, syncope and QT prolongation. The investigators found that the frequency of the S1102Y minor allele (referred to as S1103Y in some reports referencing an alternate transcript) among 23 African-American arrhythmia cases was substantially higher than in 100 population-based African-American controls (57% versus 13%, respectively, with $p = 0.00003$), consistent with an odds ratio of 10.8.

In 2005, Burke *et al.* [46] reported an African-American autopsy series in Maryland in which 289 population-based sudden unexpected deaths were categorized as one of the following: 1) controls who died of non-cardiac causes; 2) controls with marked cardiac structural disease including coronary atherosclerosis or acute thrombosis and severe cardiomyopathy; 3) subjects with only mild left ventricular hypertrophy (i.e. apparently inadequate to explain SCD); or 4) subjects with no morphologic cardiac abnormalities (termed unexplained arrhythmias). The investigators found the frequency of heterozygosity for 1102Y to be substantially higher in groups 3 and 4 (20% and 28%, respectively) compared with control groups 1 and 2 (6% and 4%, respectively). Thus, convincing evidence supports a role for a common *SCN5A* variant in SCD or arrhythmia risk in the general population of people of African ancestry. The frequency of 1102Y in populations of European or Asian ancestry is close to zero.

In 2006, Sotoodehnia *et al.* [47] reported that the common Gln27Glu polymorphism (major allele frequency of 57% in whites, 81% in blacks) was associated with SCD. They observed in a prospective nested case-cohort study that Gln27 homozygous white and black individuals from the Cardiovascular Health Study had a 56% higher hazard of SCD than those with one or two Glu27 alleles ($p = 0.003$). In an independent case-control collection from the emergency medical system in King County and Seattle,

Washington (Cardiac Arrest Blood Study), Gln27 homozygous white individuals were shown to have a 64% increased hazard of SCD ($p = 0.04$). These results suggest that common genetic variation in *B2AR* imparts a modest contribution to SCD risk. Attempts to replicate this finding are ongoing.

To date, no other common variants in known candidate genes have been convincingly shown to influence SCD risk. Barriers to discovering such common variants include the heterogeneous SCD phenotype and obvious difficulties in recruiting large samples of subjects for the study of a lethal disease, with up to two-thirds of cases not recognized to have cardiovascular disease before SCD [48].

QT interval variation in the general population

We and others have been pursuing the genetic determinants of QT interval variation in unselected population-based samples with the goal of identifying alleles that might contribute incrementally to SCD or drug-induced arrhythmia risk. We have shown that continuous electrocardiographic QT interval duration across the entire range of values in the unselected Framingham Heart Study is heritable, with at least 35% of the variability of age-, sex- and heart rate-adjusted QT due to additive genetic effects [49]. We found suggestive evidence of linkage (LOD score 2.84) to a chromosome 3 locus that contains the *SCN5A* gene. Common variants that might underlie this suggestive linkage signal are currently being studied. In 1998, Busjahn *et al.* [50] reported a study of 66 dizygotic twins in which they found modest evidence of linkage to the loci containing *KCNQ1* and the LQT4 locus (subsequently attributed to the *ANK2* gene). No signal of linkage to the *SCN5A* locus was observed although power was quite limited.

In 2005, Pfeufer *et al.* [51] reported a linkage-disequilibrium-based association study of four potassium channel genes in the KORA S4 population-based collection from Augsburg, Germany. The authors found evidence of association of one common single nucleotide polymorphism (SNP) in *KCNQ1* (intronic SNP rs757092) and two in *KCNH2* (missense SNP K897T/rs1805123 and intronic SNP rs3815459). The association of the QT interval with the K897T polymorphism, found to have different channel properties in some assays [52], is supported by earlier work in a smaller German sample by Bezzina *et al.* [53], and subsequent work by a smaller study in a French sample by Gouas *et al.* [54], but it contradicts an earlier finding in a small sample of Finnish women [55]. The other variants await replication.

Until recently, all association studies of continuous QT interval duration had focused on recognized candidate genes on the basis of their involvement in Mendelian

6 Genetics of disease

LQTSs. Genome-wide association studies enable the systematic testing of a large fraction of common genetic variation using fixed genotyping arrays and are thus not restricted to association testing of known candidate genes. We and collaborators recently identified a novel myocardial repolarization gene using such a method. Beginning with a small sample of 200 subjects assayed for 88 500 genotypes, top associations were tested in sequentially larger samples ultimately including more than 7500 unrelated individuals of European ancestry [56]. Unequivocal evidence was found for association of a common variant (minor allele frequency of 36–38%) in the nitric oxide synthase 1 adaptor protein (*NOS1AP*) gene, explaining approximately 1.5% of QT interval variation with p-values of 10^{-3} , 10^{-7} and 10^{-11} in three independent samples. Before this study, *NOS1AP* was not known to have any involvement in myocardial repolarization. Ongoing efforts to replicate the QT association in samples of other ancestry, to test for its association with SCD risk and to examine its role in myocardial repolarization in animal and human models are underway. Much larger genome-wide association studies of QT interval duration will have greater power to detect variants of more modest genetic effects and promise to identify additional novel genes and pathways involved in myocardial repolarization.

Beyond their role in unselected population samples, common variants influencing QT interval duration could have stronger influences on specific host backgrounds associated with ‘reduced repolarization reserve’, a concept advanced by Dan Roden in 1998 [57]. Such host factors could include acute myocardial infarction, severe left ventricular hypertrophy or exposure to QT-prolonging medications. A study in 2005 by Crotti *et al.* [58] reported a family in which a *KCNH2* mutation with limited penetrance was associated with QT prolongation only in the company of the K897T missense polymorphism of *KCNH2*. This study thus supports the concept that common polymorphisms act as modifiers of a Mendelian trait. Whether common polymorphisms interact with other clinical or genetic backgrounds to increase arrhythmia risk remains to be demonstrated.

Drug-induced QT prolongation and arrhythmias

An area of particular interest is the problem of drug-induced QT prolongation and resultant ventricular arrhythmias. In 2005, Straus *et al.* demonstrated that use of any non-cardiac QT-prolonging medications was associated with a 2.7-fold increase in SCD in an unselected population sample in the Netherlands [59]. The search for the determinants of drug-induced arrhythmias can focus on the medications themselves or on patients.

On the drug side of the equation, a ‘thorough QT/QTc study’ is required by the US Food and Drug Adminis-

tration in phase I screening for QT prolongation in drug-exposed subjects. Preclinical screening for binding of medications to the promiscuous HERG channel (encoded by the *KCNH2* gene) is a routine part of drug development but is poorly predictive of the risk of serious arrhythmias. Late loss of drugs from the development pipeline and the costly post-marketing withdrawal of non-cardiac medications such as terfenadine and cisapride has been a major impediment to drug development. Improved prediction of liability to cardiac arrhythmias is actively being sought by the pharmaceutical industry.

On the patient side of the equation, several non-specific clinical risk factors for drug-induced arrhythmias have been recognized: female sex, older age, heart failure, left ventricular hypertrophy and even menstrual phase [16]. To date there has been no success in identifying prevalent genetic risk factors. Several case studies have identified individuals with putative LQTS mutations among drug-induced arrhythmias. In reports in 2000 by Sesti *et al.* [60] and in 2002 by Yang *et al.* [61] a case series of 95 individuals with drug-associated *torsade de pointes* was described in which five mutations in potassium channel subunits were identified. The identification of common variants that modify risk of drug-induced cardiotoxicity could enable the prospective identification of the vulnerable patient. Although an exciting possibility, this is currently far from reality. Ongoing efforts to define the contribution of common genetic variation to inter-individual differences in QT prolongation upon exposure to medications might change this.

Conclusions

The human being is a messy model organism for genetic research. Animal models offer a uniform genetic background on which to selectively alter a single gene of interest. Until recently, variability in overall genetic background arising from random mating in the human population has obscured all but the most extreme genetic signals. Mendelian syndromes in which the relationship of genotype to phenotype is nearly 1:1 have been crucial to improving our understanding of normal electrophysiology and the derangements that contribute to familial sudden death syndromes. However, the recent development of methods such as genome-wide association studies in sufficiently large samples promises to supplement the accumulated Mendelian mutation compendium with common polymorphisms that contribute incrementally to risk of SCD and drug-induced arrhythmias. Continued efforts to clarify in model organismal and cellular systems will be required to determine what novel repolarization genes such as *NOS1AP* are doing. The exciting additional advantage of identifying common variants of even modest effects, beyond offering new entrées into human physiology, is that they can be incorporated with prevalent clinical factors into increasingly sophisticated models to predict risk for SCD and drug-induced arrhythmias. The

promise of the human genome project can thus be brought to bear on one of the leading causes of death in the developed world.

Update

In late 2006, an interesting paper by Imboden *et al.* [74] reported that among 1534 offspring of a genotyped parent with an LQTS mutation in either *KCNQ1* or *KCNH2*, the frequency of mutation transmission regardless of affection status was 57% compared to 43% with no mutation transmission. Under Mendelian inheritance, a 50% transmission frequency is expected. The authors interpreted this finding to indicate evidence of positive selection for mutations that in later life contribute to sudden death, in contrast to the expectation that such mutations would be subject to negative selection. It is also possible that some ascertainment bias underlies the transmission ratio distortion. Interestingly, the common allele of the *NOS1AP* gene that is associated with shorter QT interval duration shows evidence of positive selection in HapMap samples of European ancestry (<http://www.hapmap.org/>). One wonders whether genetic variants that alter myocardial repolarization might also have important effects in other tissues or at an early stage of development such as fertilization, in which flux of ion channels is crucially important [75].

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8 Genetics of disease

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