Sudden cardiac death in patients younger than 35 years of age is primarily due to genetic causes. Familial hypertrophic cardiomyopathy accounting for 30% to 40% is associated with structural heart disease while the Brugada syndrome and the long QT syndrome (LQTS) are associated with normal cardiac function. This is a review of the genetics of supraventricular and ventricular arrhythmias. Atrial fibrillation is mapped to nine chromosomal loci and four genes are identified. Adenosine monophosphate-activated protein kinase is one gene responsible for Wolf-Parkinson-White syndrome. The LQTS and the Brugada syndromes are due to defects primarily in cardiac sodium and potassium ion channels. The role of single nucleotide polymorphisms in predisposing to arrhythmias in acquired disorders such as hypertrophy is discussed. (J Am Coll Cardiol 2006;47:9–21) © 2006 by the American College of Cardiology Foundation

The past decade has been golden for cardiovascular diseases with the elucidation of several genes responsible for familial cardiomyopathies and the ion channelopathies. However, these diseases, referred to as single gene disorders, were amenable to chromosomal mapping of the gene locus through conventional genetic linkage analysis. In these disorders, a single gene predominates in the expression of the phenotype. However, even with single gene disorders, there are modifier genes, which have a significant influence on the phenotype but would not be detected by this conventional technique. There is suggestive evidence that arrhythmias such as atrial fibrillation occurring in association with acquired structural heart disease are more likely in those individuals with genetic predisposition (1,2). This is particularly pertinent in polygenic diseases such as coronary artery disease and hypertension (3,4). Locating and identifying modifier genes and genes that predispose but do not per se induce the phenotype has not been feasible due to lack of appropriate statistical models and high throughput genotyping technology. While both of these problems are still with us, there are currently methods making it possible and practical to pursue such research goals.

The sequencing of the human genome has brought with it a wealth of information as well as enabling the development of high throughput technology. It is now recognized that 99.9% of the three billion bases that comprise the human genome are identical (5,6). Thus, about three million bases account for all of the differences between human beings including one’s resistance or vulnerability to disease. The current and future challenge is to identify these differences referred to as single nucleotide polymorphisms (SNPs). Currently, it appears there are over 15 million SNPs circulating in the population from which three million can be selected to be passed on by each parent to their offspring. A major project referred to as the HapMap project is ongoing to map the chromosomal location of these SNPs and generate haplotypes involving multiple SNPs that tend to be inherited as blocks or units (7). The effect of SNPs on a particular phenotype may be through haplotypes containing several SNPs rather than a single SNP. To identify these SNPs or haplotypes on a genome-wide basis for a particular phenotype such as atrial fibrillation would require hundreds of thousands of DNA markers, which, until recently, would be prohibited (6). Chips are now available with hundreds of thousands of SNPs such as the Affymetrix 500,000 chip (Affymetrix, Santa Clara, California) to perform these studies. Secondly, such high-density DNA markers make it possible to utilize mathematical models to identify associations with polymorphisms that have minimal effect on the phenotype (5,6,8). It is now possible to genotype 100 DNA samples for 500,000 genotypes over a period of a few hours. This has ushered in a new era for detecting genetic variants that affect human disease.

GENOMIC IMPLICATIONS FOR DIAGNOSIS AND TREATMENT OF SUDDEN CARDIAC DEATH (SCD)

Sudden cardiac death remains a worldwide scourge. There are considerable data to indicate the proximate cause of SCD is electrical due to cardiac conduction defects or dysrhythmias. In the U.S. over 400,000 and in Canada over 50,000 die annually from SCD (9). It is of note that this number has not changed for the past three decades. Thus, treatment for SCD has not been as progressive as in other forms of cardiac disease, indeed one may say it has been regressive. A major landmark study evaluating drugs in the treatment of arrhythmias was the international clinical trial referred to as Cardiac Arrhythmia Suppression Trial (CAST) (10). The major and unexpected finding was that most of the drugs used in the trial were shown to be pro-arrhythmic. Quinidine, a drug used for decades in the
treatment of supraventricular and ventricular arrhythmias was shown to prolong the QT interval and induce ventricular arrhythmias and SCD. Therapy had to be developed empirically without knowing the molecular basis for the disease or the molecular mechanism of the drug. Current knowledge of ion channels facilitates the development of drugs without known adverse effects such as prolongation of the QT. It is expected that genetic defects, many of which involve ion channels, will help to identify molecular mechanisms for arrhythmias, which are also applicable to arrhythmias caused by acquired disease. There is some encouragement with the overlap between the mechanism responsible for ventricular tachycardia of familial long QT syndrome (LQTS) and that induced by quinidine in acquired disorders.

Young individuals who die with monogenic disorders such as Brugada syndrome or prolonged QT syndrome are usually asymptomatic, and SCD is their first and often last symptom. In the future, when appropriate therapy becomes available to prevent SCD in the asymptomatic individuals, genetic screening will be a prerequisite (e.g., Brugada syndrome, LQTS, and so on). Gene testing on the basis of family history or an incidental electrocardiogram (ECG) finding (e.g., insurance) followed by appropriate therapy is likely to be a future routine to prevent SCD. Most of SCD over the age of 35 years occurs in association with acquired structural heart disease and symptoms. There is, however, the concern of who is vulnerable for SCD. One hope is identifying which half is vulnerable. One hope is to detect SNPs that predispose to SCD. Identifying molecular defects responsible for arrhythmias should lead to novel therapies specifically designed to target the abnormality. Identification of the defect in the cholesterol receptor of familial hypercholesterolemia leads to the development of drugs (statins) to inhibit cholesterol synthesis. These drugs are now the mainstay of treatment to prevent coronary artery disease in the general population. Pharmacogenetics and pharmacogenomics will assist in selecting the drug and determining the dose on an individual basis to minimize adverse side effects. Determining who is at risk for arrhythmias and SCD is a problem common to those with structural or electrical cardiac disease. The person without structural heart disease (Brugada syndrome) is perhaps at a greater disadvantage because they are more likely to be younger and less likely to have a reason to visit the physician.

THE FREQUENCY AND PREVALENCE OF GENETIC-INDUCED ARRHYTHMIAS

In considering the role of genetics and arrhythmias, one must pause as to the frequency and prevalence of the genetic-induced arrhythmias. Throughout the world, SCD occurring in the young adult (<35 years) whether associated with structural or nonstructural heart disease is predominantly due to genetic defects. Familial hypertrophic cardiomyopathy (HCM) with a prevalence of 1 in 500 is the most common cause of SCD in the young (12). While there are no population studies on the prevalence of the genotype, estimates based on the phenotype, which usually underestimates the genotype, show it is very common for a genetic disorder. It is estimated over 12 million individuals in the world carry the genetic defect for HCM. There are over 600,000 individuals with this genetic defect in the U.S. and 60,000 in Canada. Brugada syndrome, another familial cause of SCD in the young, is the most common cause of SCD occurring in individuals without structural heart disease (13). Wolff-Parkinson-White syndrome (WPW) is the second most common cause of supraventricular arrhythmias in the Western world and the most common cause in China (14). The role of WPW in SCD remains controversial. In those studies in which the cardiac conduction system was evaluated, WPW was a major cause of SCD, particularly in infants (15). Wolff-Parkinson-White syndrome, while always a genetic disease, appears to be mostly sporadic rather than familial. In a recent study, 30% of patients with atrial fibrillation with or without structural heart disease had a family history of atrial fibrillation (16). Offspring with even a single parent having atrial fibrillation will have 85% increased risk of developing atrial fibrillation (16). For single gene disorders, many genes with their corresponding mutations have been identified, and the appropriate technology could be assembled soon to screen populations at risk of having these genetic defects.

THE ROLE OF GENETICS IN ACQUIRED ARRHYTHMIAS

In the middle-aged and elderly population, which accounts for most of SCD, the cause is almost always associated with structural heart disease predominantly due to coronary artery disease. What is the role of genetic defects in these individuals? While no gene or polymorphism has yet been definitely identified to induce arrhythmias, there is increasing evidence that genetic predisposition contributes significantly to acquired arrhythmias (17). For example, a recent finding shows that atrial fibrillation occurring with structural and nonstructural heart disease is associated with a

Abbreviations and Acronyms

AMPK = adenosine monophosphate-activated protein kinase
AP = action potential
HCM = hypertrophic cardiomyopathy
ICD = implantable cardioverter-defibrillator
LQTS = long QT syndrome
SCD = sudden cardiac death
SNP = single nucleotide polymorphism
SQTS = short QT syndrome
WPW = Wolff-Parkinson-White syndrome
family history of atrial fibrillation in 30% of patients (16). Much of susceptibility to acquired disease is thought to be encoded primarily by SNPs that span the human genome. Even in single gene disorders, there are modifying genes (SNPs), which modulate the phenotype resulting from the interaction of the environment with the genotype. A third group of genes modulating arrhythmias in acquired and inherited diseases, particularly coronary artery disease or heart failure, are those whose expression is reprogrammed by the underlying disease. An excellent and well-characterized example is cardiac compensatory hypertrophy in response to pressure overload as occurs in hypertension, valvular disease, or heart failure. In pathological hypertrophy as opposed to physiological hypertrophy, expression of a host of genes is up-regulated as part of the so-called fetal program (18). The extent of hypertrophy may, in part, depend on the presence or absence of certain alleles. For example, regardless of the cause, if the patient is homozygous for the DD allele of the angiotensin-converting enzyme gene as opposed to the I-form, hypertrophy will be more extensive and the propensity for SCD greatly increased (19). Hypertrophy that deteriorates into dilated cardiomyopathy induces the expression of other genes, which could alter the predisposition to atrial or ventricular arrhythmias and SCD. All of the association studies suggesting genetic predisposition remain suspect because of the small sample size (6), but the technology is now available to pursue studies with adequate sample size. The availability of genome-wide scans with 500,000 SNPs properly selected is likely to add a new dimension to our search for genetic predisposition and modifier genes.

GENETIC SCREENING FOR PREDICTION AND PREVENTION OF ARRHYTHMIAS

Genes themselves do not engage in the work of the cell, but rather their end product, the protein, performs the function of the organism. In single gene disorders of adults, the most common mutation is a missense. This is a genetic defect in which a single base has been substituted for another resulting in the encoding of a different amino acid, which, if occurring in an important domain of the protein, will be associated with a gain- or loss-of-function. Other less common defects would be a loss or gain of a base resulting in a protein with many amino acids altered or the coding may be changed to a start or stop codon resulting in a truncated protein. Genetic defects occurring in non-protein coding regions will be manifested primarily as increased or decreased expression of the protein. Thus, the major functional change in the protein is loss- or gain-of-function due to an alteration in the amino acid composition or the expression of the protein. While genetic screening is pivotal in the prevention of genetic disease, it unfortunately is not the only variable that must be considered. Genetic screening determines the presence or absence of the genetic defect and thus whether there is a risk of developing the disease. Screening for polymorphisms in polygenic disorders determines whether there is a risk of increased susceptibility for arrhythmias. Other critical features must be considered as we move into the genetic revolution and apply this information to the care of patients. Despite having the genotype at birth, several factors modulate whether the phenotype will ever develop and to what extent. First, is the feature of penetrance which the risk of developing the phenotype in an individual with the genetic defect. In the case of single gene disorders, those that are autosomal dominant have a high penetrance of probably 70% to 80% but seldom complete. Thus, a percentage of individuals despite having the defective gene do not develop the disease. The other modifier is referred to as expressivity defined as the variability in phenotypic manifestations that occur across a population despite being due to the same genetic defect. The onset of the phenotype is often age-dependent. The severity of the phenotype and whether it develops are also influenced by environmental factors such as exercise, temperature, gender, and other factors. Nevertheless, solutions to these problems will be facilitated with routine genetic screening and increased experience. Present knowledge clearly indicates that a multidisciplinary approach is required in the future to identify these genetic abnormalities and utilize them for treatment and prevention. It does require careful clinical characterization, genetic expertise, functional analysis, and genetic counseling along with drug discovery to significantly impact this worldwide scourge.

GENETICS OF SUPRAVENTRICULAR ARRHYTHMIAS

Atrial fibrillation. Atrial fibrillation is the most common sustained cardiac arrhythmia. It occurs in about 6% of the population over the age of 60 years. It is estimated there are over 3 million people with persistent atrial fibrillation in the U.S. (20), which will increase to 5.6 million by 2050 (21). At age 40 years and over, the chance of developing atrial fibrillation in men and women is about 25% (22). It is associated with significant morbidity and mortality, accounting for over one-third of all strokes over the age of 60 years (23). In a recent Framingham Heart study of 2,243 participants, 681 had at least one parent with atrial fibrillation (16). This indicates 30% of all patients with atrial fibrillation, with or without structural heart disease, have a family history of the disease (16). The relative risk of atrial fibrillation was increased 85% in individuals with at least one parent with a history of atrial fibrillation (16). We identified the first locus for familial atrial fibrillation on chromosome 10 (10q22), confirming the inheritance of this disease (24). Currently, seven chromosomal loci have been mapped and four of the genes identified. The genetic features of each of these loci are summarized in Table 1, and a brief discussion will follow of each of the genes.

KCNQI gene. KCNQ1, the first gene, was identified (25) in a four-generation Chinese family showing autosomal dominant inheritance. The locus was mapped to chromosome 11.
A third gene was identified in 30 unrelated Chinese kindreds of atrial fibrillation showing a missense mutation in the potassium channel subunit KCNJ2 (28). KCNJ2 encodes for the Kir 2.1 channel, which mediates potassium current in the heart. It is an inward rectifier, which induces early repolarization. The gene exhibited a missense mutation with G to A at nucleotide 277 corresponding to a valine to isoleucine at residue 93 (V93I). Functional analysis again showed that this mutant gene shortens the atrial AP duration and the atrial effective refractory period. Several investigators with multiple families had shown KCNJ2 is not responsible for atrial fibrillation in their families (26), suggesting this is an uncommon cause for atrial fibrillation. A second locus was identified by the same Chinese investigators (27) on 21q22 encoding for another potassium channel subunit (KCNE2). The mutation was shown to involve a C to T transition at nucleotide 79 of the gene for KCNE2. This resulted in an arginine to cysteine at residue 27 (r27C), which is present in all affected individuals but not in healthy individuals. Mode of transmission was again, autosomal dominant. Functional studies, again, showed that the mutant shortened the atrial AP duration and the atrial effective refractory period. The penetrance appeared to be incomplete although difficult to assess from the limited number of studies performed.

**Table 1. Genetic Loci Responsible for Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene</th>
<th>Mode of Inheritance</th>
<th>Mutation</th>
<th>Effect on Function</th>
<th>Physiological Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>11p15.5</td>
<td>KCNQ1</td>
<td>AD</td>
<td>S140G</td>
<td>Gain of function</td>
<td>↓ AAP ↓ ARP</td>
</tr>
<tr>
<td>21q22</td>
<td>KCNE2</td>
<td>AD</td>
<td>R27C</td>
<td>Gain of function</td>
<td>↓ AAD ↓ ARP</td>
</tr>
<tr>
<td>17q</td>
<td>KCNJ2</td>
<td>AD</td>
<td>V93I</td>
<td>Gain of function</td>
<td>↓ AAD ↓ ARP</td>
</tr>
<tr>
<td>7q35–36</td>
<td>KCNH2</td>
<td>AD</td>
<td>N588K</td>
<td>Gain of function</td>
<td>↓ AAP ↓ ARP</td>
</tr>
<tr>
<td>5p13</td>
<td>Unknown</td>
<td>Recessive</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>6q14–16</td>
<td>Unknown</td>
<td>AD</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>10q22</td>
<td>Unknown</td>
<td>AD</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

AAP = atrial action potential duration; AD = autosomal dominant; ARP = atrial effective refractory period.

KCNH2 gene exhibited a missense mutation at nucleotide 17645 with C going to G resulting in the substitution of asparagine for lysine at residue 588 (N588K). All affected members upon electrophysiological testing showed a shortening of the atrial and ventricular refractory periods with inducibility of atrial and ventricular fibrillation. The mutation confers a gain-of-function with a shortening of the atrial AP duration and the effective atrial refractory period. Genetic defects provide insight into the mechanism for atrial fibrillation. There are several consistent features of the genetics of atrial fibrillation:

1) Genes identified all encode for subunits of potassium channels.
2) All mutations confer a gain-of-function.
3) All of the mutations shorten the atrial AP duration and the atrial effective refractory period.

Atrial fibrillation is thus a channelopathy whereby the genetic defects provide an ideal substrate for re-entry arrhythmias. The consistency of the mechanism whereby genetic defects induce atrial fibrillation should provide specific targets for the development of novel drug therapy.

**Polymorphisms That Predispose to Atrial Fibrillation in Individuals With Structural Heart Disease**

Atrial fibrillation occurs mostly in association with acquired diseases such as coronary heart disease, value disease, or heart failure. In a recent study (1) involving 250 patients with structural heart disease and atrial fibrillation, 250 controls expression of polymorphisms N235T, G-6A, G-217A of the angiotensin-converting enzyme gene were significantly increased in patients with atrial fibrillation over that of controls with a p value of 0.01, 0.005, and 0.002, respectively. The odds ratio for atrial fibrillation was 2.5 with M235/M235 + M235/T235 genotype, 3.3 for the G6/G6 genotype, and 2.0 for the G217/G217 genotype. Similar associations have been made with polymorphisms in the connexin 40 gene. This gene encodes a cardiac gap junction protein, which mediates electrocoupling of cardiomyocytes (2). The polymorphisms in the promoter region upstream of the gene, which are −44A and −44AA genotypes, were more frequent in subjects with atrial fibril-
ation exhibiting a risk ratio of 5.3 and 6.2, respectively, for atrial fibrillation. In another study (35), 108 patients with acquired atrial fibrillation compared to controls showed the K38G alleles of connexin 40 exhibited an odds risk ratio for atrial fibrillation of 1.8 in patients with more than one K38G allele. These studies suggest that polymorphisms predispose to atrial fibrillation when occurring in association with these diseases. It is important to recognize that these studies are case control association studies, and it is inadequate to make definitive conclusions. The sample size is too few and would require confirmation of the larger sample size and also better matching of controls with affected individuals. However, the availability recently of genome-wide scans with hundreds of thousands of SNPs will, in the future, make it possible to perform genomic studies to identify SNPs that predispose to diseases such as atrial fibrillation. This is expected to be a major onslaught of genomic technology in the next few years.

**Paroxysmal supraventricular tachycardia.** Wolff-Parkinson-White syndrome is the most common form of paroxysmal supraventricular tachycardia in China and the second most common cause in the Western world (14,36). The incidence of WPW is about 1 in 3,000 of the population. This syndrome, named after the individuals described in 1930, has remained as a paradigm of a model for re-entry arrhythmias. In this disease, there is an accessory bundle of muscle tissue, which connects the atrium to the ventricle bypassing the atrioventricular node. Conduction through the accessory bundle is usually retrograde but under unusual circumstances may be antegrade at very rapid rates of 150 beats/min. Rapid heart rates, whether retrograde or antegrade, if sustained lead to heart failure or even ventricular tachycardia and SCD. The most common form of tachycardia associated with WPW is paroxysmal supraventricular tachycardia with rates of 120 to 160 beats/min. The role of WPW in SCD is difficult to assess. Autopsies performed to assess cause of death do not examine the specialized conduction system of the heart and thus would not detect WPW. In studies in which the conduction system was evaluated, WPW was found to account for 33% of patients who died suddenly without structural heart disease (15). The prevalence of familial WPW appears to be low with most due to a sporadic genetic defect; WPW is a genetic disease in that the formation of an accessory conducting bundle or lack of remodeling of an existing bundle requires genetic regulation. It is perhaps analogous to cancer, which is an obligatory genetic disease, but the familial form appears less common.

In 2001 we identified a family with WPW and showed (37) the gene responsible for the disease in this family encodes for the gamma 2 subunit of the enzyme adenosine monophosphate-activated protein kinase (AMPK). The gene is referred to as PRKAG2 located on chromosome 7q36 and is inherited in an autosomal dominant pattern; AMPK consists of three subunits, alpha, beta, and gamma, with each subunit encoded by a distinct gene. The gamma subunit has a binding site for AMP, which is essential for enzymatic activity. The mutation consists of a substitution of glutamine for arginine at residue 302. Six mutations have since been described in several families all of which are missense mutations except for one, which is an insertion (38). The penetrance based on the few families so far studied is in the range of 70% to 80%. The phenotype consists of pre-excitation on the ECG, varying degrees of conduction defects, frequently cardiac hypertrophy, and excessive glycogen storage in the myocytes without sarcomere or myocyte disarray (39). The most common arrhythmia associated with WPW is that of paroxysmal supraventricular tachycardia with a narrow QRS. In the remaining 20%, the arrhythmia is generally atrial fibrillation. In this syndrome, however, the incidence of atrial fibrillation is much higher in the range of 40% to 50%; AMPK is a sensor of the body’s ATP level and is activated by an increase in the ratio of AMP to ATP (40,41). The availability of ATP is increased by AMPK through increasing glucose absorption, inhibiting glycogen synthesis, increasing fatty acid oxidation, and decreasing fatty acid synthesis. Transgenic mice expressing either the R302Q mutation (39) or the N4881 mutation (42) exhibit a typical phenotype as observed in humans for this disease. The mechanism whereby AMPK leads to accessory pathways or alters conduction remains to be determined. In one study, it has been shown that R302Q mutation inhibits the cardiac sodium inward current (41). Utilizing these transgenic models, studies are now being performed to determine alternate forms of therapy. It also serves as a model to elucidate AMPK's role in the development of the heart and, in particular, that of the specialized cardiac conduction system. The accepted form of treatment currently in patients with familial WPW is ablation of the accessory bundle. Therapy to prevent the excessive glycogen storage may require replacement of AMPK enzyme.

**GENETICS OF VENTRICULAR ARRYTHMIAS**

**Brugada syndrome.** There remains a large group of individuals who develop idiopathic ventricular fibrillation unassociated with any structural heart disease. In 1995, a disease now referred to as Brugada syndrome (43) was described, which is associated with SCD at a very young age and is responsible for a significant proportion of sudden infant death syndrome. Brugada syndrome is characterized by a history of sudden death and a typical ECG pattern of ST-segment elevation in leads V1 to V3 (Fig. 1) (13). It is claimed to be responsible for up to 12% of all sudden deaths and approximately 20% of deaths occurring in patients with structurally normal hearts. In the Western world, the prevalence of this disease appears to be in the order of 1 in 5,000 individuals. In Southeast Asia, the disease is more prevalent being a leading cause of death in males under the age of 40, second only to car accidents (13). This disease exhibits an autosomal dominant pattern of inheritance indicating it affects men and women equally, and 50% of the...
offspring will inherit the gene and be at risk of developing arrhythmias and SCD. This also means only one copy of the gene is defective, and it acts as a dominant positive or negative. All of the mutations identified have been in a subunit of the sodium cardiac channel (SCN5A).

The subunit referred to as SCN5A has a genomic structure consisting of 28 exons spanning approximately 80 kb on chromosome 3p21 with a dinucleotide repeat polymorphism in exon 16. The gene encodes for a protein with 2,016 amino acids. Sodium channels, like most ion channels, are part of a complex. The pore forming alpha subunit is encoded by SCN5A, and up to three beta subunits have been described, as well as other attachments to the cytoskeleton such as caveolas. The mutations identified responsible for the Brugada syndrome have been primarily missense mutations. More than 60 mutations have been described in the SCN5A of which all have been localized to the protein coding sequences. Screening for these mutations show they account for only about 25% of patients with Brugada syndrome. This indicates there may be other mutations in the SCN5A gene and most likely mutations in multiple other genes. Most of the genes responsible for the ion channels of the cardiac AP have been cloned and are available as good candidates to screen for these mutations. The mutations identified in SCN5A have been associated with a loss of current either by creating a truncated protein or by increasing sodium channel inactivation. One of the mutations, an insertion, occurred in the splicing donor site of intron 7. Recently, the first intronic mutation in SCN5A was described, which involved a four base pair insertion in exon 27. This led to a truncated protein and a non-functional channel. Brugada syndrome and LQTS can both be caused by defects in the SCN5A but are opposite in function, namely, the former is due to loss of function leading to an accelerated inactivation of the sodium channel resulting in more rapid depolarization. Patients with Brugada syndrome on becoming febrile are more likely to develop arrhythmias and SCD. It is evident there are many more mutations and other genes yet to be discovered considering that over 75% of cases are not due to known mutations. A second locus has been mapped to chromosome 3 indicating at least another gene; however, that gene has not been identified. Genetic screening, currently not available, will be essential for the management of this disease because most of these people do not have symptoms. Even when someone is identified to have a history of this disease, it will be necessary to determine which 50% of the offspring have the mutation and are vulnerable to arrhythmias and SCD. Genetic screening is necessary for appropriate genetic counseling as well as to implement preventive therapy when it becomes available. In the meantime, it is important to recognize that most drugs are not effective in this syndrome. An implantable cardioverter-defibrillator (ICD) is essentially the only recommended form of therapy.

![Figure 1. Variation in the precordial lead ST and T waves in a patient with Brugada syndrome. Reprinted with permission from Fuster V, Alexander RW, O'Rourke RA. Hurst's The Heart. 11th edition. McGraw-Hill Companies, 2004.](image-url)
LQTS Clinical features. The congenital LQTS is an inherited disease characterized by prolongation of ventricular repolarization, which is manifested by prolongation of the QT interval on the ECG (47). It is associated with a high risk of sudden death from ventricular arrhythmias. There are two forms of the disease, one autosomal dominant and the other recessive (48). The autosomal dominant form is far more common, and the rare recessive form is associated with deafness. Clinically, the syndrome is characterized by syncopal episodes, malignant ventricular tachycardia, and fibrillation. The majority of patients with LQTS are asymptomatic and are either discovered incidentally based on ECG, family history, or having survived an episode of syncope or severe ventricular arrhythmias. The prognosis of untreated patients is considered to be quite poor. It is claimed that about one-fifth of untreated patients presenting with syncope die within 1 year and 50% within 10 years (13). Long QT syndrome can also be acquired due to a long list of drugs, primarily antiarrhythmics, antidepressants, and phenothiazides. In addition, electrolyte imbalance such as hypokalemia, hypomagnesemia, and hypocalcemia, can also cause LQTS. These drugs and electrolyte abnormalities play a major triggering role in ventricular arrhythmias and SCD in patients with the inherited LQTS.

Pathogenesis of familial LQTS. Long QT syndrome is now known to be due to nine different genes (Table 2). Of the nine genes identified, seven encode potassium channel subunits, one, a sodium channel, and, most recently, a mutation encoding for ankyrin B, a scaffolding protein. The latter is the only non-channel disease gene thus far described (49).

In LQTS, prolongation of the AP (Fig. 2) may be due to an increase in the phase of depolarization or a decrease in the current that induces repolarization. The molecular defect is determined by the specific genotype, but the final common pathway is prolongation of the AP and decreased repolarization reserve (47). This results in diminished ability of the ventricular myocyte to respond to stress such as hypoglycemia, hypomagnesemia, and drugs that prolonged the AP. The sodium and potassium channels share opposite affects on the AP duration. The sodium channel depolarizes the cell with most of the activity occurring during the upstroke of the AP. An increased amount of current active during the plateau phase would prolong depolarization and lengthen the AP. Potassium channels when active tend to restore the internal negativity of the cell and shorten the AP. If potassium currents predominate during the plateau, repolarization will occur shortening the AP as opposed to sodium currents if they predominate during plateau, it prolongs the AP. In LQTS due to defects in a potassium channel, there is a loss-of-function, whereas in LQTS due to defects in sodium channel gene, there is a gain-of-function. Both are due to autosomal dominant patterns of inheritance indicating only one copy of the mutated gene is necessary to produce the clinical syndrome.

The pathogenesis of LQTS due to defects in the ion channels may be summarized as follows: mutations in the potassium channel lead to inadequate opening and decreased outward current; mutations in the sodium channels lead to inadequate closing of the channels and excessive sodium inward current. This results in an imbalance with an inadequate maintenance of the electrical gradient reflected in prolongation of the AP reflected by long QT interval on the ECG.

Genotype-phenotype correlations. The role of genetics with respect to prognosis and therapy for LQTS remains to be defined. Studies relating a single mutation to survival or to clinical events as well as therapy have not shown a clear-cut stratification (50). This may, in part, relate to lack of adequate sample size and the genetic background on which that particular mutation is interacting. Attempts, however, to relate a particular gene to survival and how it interacts with gender and the duration of the QT interval have been performed (48). In the study by Priori et al. (48), investigators assess the risk of the first cardiac event before the age of 40 years and before initiating therapy in 580 patients. The study involved 355 patients with a mutation in the KCNQ1 gene, 176 patients with a mutation in the KCNH2 gene, and 49 individuals with a mutation in the SCN5A gene. These represent the most common causes of the familial LQTS. Results, as illustrated in Figures 3A, 3B, and 3C, indicate the cumulative event-free survival was

<table>
<thead>
<tr>
<th>Arhythmia</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>11p15</td>
<td>KCNQ1</td>
<td>~50%</td>
</tr>
<tr>
<td>LQT2</td>
<td>7q35</td>
<td>KCNH2</td>
<td>30%-40%</td>
</tr>
<tr>
<td>LQT3</td>
<td>3q21</td>
<td>SCN5A</td>
<td>5%-10%</td>
</tr>
<tr>
<td>LQT4</td>
<td>4q25</td>
<td>ANK2</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT5</td>
<td>21q22</td>
<td>KCNE1</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT6</td>
<td>21q22</td>
<td>KCNE2</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT7</td>
<td>17</td>
<td>KCNJ2</td>
<td>Rare</td>
</tr>
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Table 2. Genetic Loci Responsible for Long QT Syndrome

<table>
<thead>
<tr>
<th>Arhythmia</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT</td>
<td>11p15</td>
<td>KCNQ1</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT</td>
<td>21q22</td>
<td>KCNQ2</td>
<td>Rare</td>
</tr>
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quite different among the three groups with the highest event rate occurring in KCNH2 and SCN5A. Analysis for gender within each subgroup showed that gender had no influence on patients with a mutation in the KCNH2 gene, whereas female patients with a mutation in the KCNH2 gene had a higher risk than male patients, and there was a trend towards a higher risk among patients with a mutation in the SCN5A. Thus, a first cardiac arrest or sudden death was highest among female patients with a mutation in the KCNH2 gene (0.82 per year) and male patients with a mutation in the SCN5A gene (0.96 per year). Thus, the role of gender varies according to the genetic locus. Correcting for the QT interval showed significant differences among the three subgroups. The mean QT was 466 ± 44 ms among patients with a mutation at the KCNQ1 gene, 490 ± 49 ms among those with a mutation in the KCNH2 gene, and 496 ± 49 ms among those with mutations in the SCN5A gene. In each subgroup, the QT interval was longer in those who were symptomatic. The number of genetically affected patients with a normal QT interval was significantly higher in the KCNQ1 group (36%) than in the KCNH2 group (19%) or the SCN5A group (10%). Analysis of the event-free survival, taking into account the quartile of corrected QT interval, showed progressive decrease in survival at longer QTc values. These data illustrate an interaction of the particular gene with gender and the duration of the QT interval.

**GENETIC IMPLICATIONS FOR THE THERAPEUTIC MANAGEMENT OF LQTS**

Despite the large number of mutations (300) responsible for LQTS, there is still limited correlation with respect to specific therapy. It is evident that mutations in the KCNH2 or SCN5A genes are associated with more cardiac events. Given the risk stratification provided by the three parameters previously discussed, the investigators (48,50) recommend that prophylactic treatment is warranted in male and female patients with a mutation in the KCNQ1 gene who have a QT above 500 ms or more, male patients with a mutation in the KCNH2 gene who have a QT of 500 ms or more, all female patients with a mutation at the KCNH2 gene irrespective of the QT, and all patients with a mutation in the SCN5A gene.

Schwartz et al. (51,52) reported cardiac events more frequently occur during exercise (62%) and only rarely during sleep and rest in LQT1 patients. Swimming is also a common trigger in the LQT1 syndrome (52). In contrast, in LQT3 patients, cardiac events predominantly occur during sleep and rest (39%) while exercise-induced events are rare.
In LQT2 patients, cardiac events occur equally during exercise or rest (51). Interestingly, a subtle startle in a form of auditory stimulus is more likely to precipitate arrhythmias in LQT2. Exercise or mental stress more often triggers ventricular arrhythmias in LQT4 patients (49). In LQT7, hypokalemia is more likely to trigger ventricular arrhythmias as well as periodic paralysis. Thus, patients with these specific syndromes can be advised to avoid this form of activity. Several studies have concluded that beta-blockers are far more effective in LQT1 than LQT2 or LQT3. Because it is more common to have a lethal event in LQT3 than in LQT1 or LQT2, some have suggested that an ICD implantation is to be encouraged in patients with LQT3 syndrome (53). In 2002, Moss et al. (52) suggested LQT2 patients with mutations in the pore region of the KCNH2 gene have increased risk of arrhythmias over that of mutations in the non-pore region. This has been disputed by Zareba et al. (54), but a more recent Japanese study reports findings similar to that of Moss et al. (55). Many patients with LQTS do not respond to beta-blockers or other forms of drug therapy and thus would be candidates for an ICD. Nevertheless, in asymptomatic patients with borderline prolonged QT, the decision remains difficult to insert an ICD. The investigators strongly recommend that instituting therapy in patients at low risk of becoming symptomatic before the age of 40 years should be individualized. Further studies are required in such patients before a robust recommendation can be developed.

**THE ROLE OF GENETICS IN DRUG-INDUCED LQTS**

Long QT syndrome as a cause for ventricular tachycardia and sudden death is more commonly associated with acquired disorders than that of the familial LQTS. A major cause of acquired long QT is drugs (56). The predominant mechanism whereby the QT interval is prolonged, whether it be genetic or acquired, is prolongation of sodium influx or more commonly delayed outflux of potassium ions. There are over 20 potassium channels expressed in the heart, most of which participate in the AP (57). Antiarrhythmic drugs can also induce long QT primarily those in class 1A (e.g., quinidine) or class 3 (e.g., sotolol). Of the 25 drugs for which a mechanism has been elucidated, 24 of them are blockers of the potassium channel, which delays repolarization. It is well recognized these drugs induce prolonged QT only in individuals who are susceptible. It is the aim of pharmacogenetics and pharmacogenomics to determine the genetic basis for this susceptibility. One obvious avenue of investigation is to determine whether these susceptible individuals have a mutation in one of the channel proteins that is aggravated by drugs. The extent to which this occurs remains to be determined as screening for familial long QT mutations remains experimental and time-consuming. A recent study showed 10% to 15% of individuals with drug-induced LQTS harbor ion channel gene mutations or SNPs that predispose to the LQTS (58). Most of the mutations or SNPs found so far that predispose to long QT are in the potassium channels (59). Gene variants associated with acquired arrhythmias according to Anantharam et al. (60) can be classified as indirect, direct, and compound. Indirect are mutations that impair the potassium channel at baseline but do not affect drug sensitivity and are not associated with any prolongation of the QT interval until
drug administration is superimposed upon this inherited impairment. An example would be A116V-MIRPI with quinidine (61). Another example is an Asian-specific SNP (G643S) in the KCNQ1 gene, which has been shown to induce LQTS (62). The prevalence of G643S is 11% in the Japanese population and was first identified after a patient being on a class IA antiarrhythmia agent. Another example of an SNP predisposing to prolonged QT, which appears to be ethnic-related, is that of the S1102Y SNP found more commonly in the African population (63). This SNP in the SCN5A gene increases the risk of cardiac arrhythmias in the presence of drugs such as amiodarone. It is found primarily in West African, Caribbean, and African American populations. It does not in itself cause LQTS but only in the presence of other aggravating factors.

Direct mutations are perhaps the most difficult because they do not affect potassium current but increase sensitivity to drug blockade (64). An example of this is T8A-MIRPI SNP present in 1.6% of the U.S. population was first identified in a patient taking a combination of sulfamethoxazole and trimethoprim. This SNP increases the sensitivity of the sodium channel to blockage by the sulfa drugs. The third category compound mutations are those that impair channel function at baseline and also increase sensitivity to the drug. An example is the Q9E MIRPI channel, which was discovered in a female patient after taking clarithromycin, which precipitated torsades de pointes. Women are more vulnerable to develop prolonged QT than men if caused by drugs that block the potassium channel (64). Ultimately, if we are to avoid sudden death associated with prolonged QT, it will be necessary to screen for all known mutations and SNPs that predispose to long QT.

An equally fruitful area is the role of heredity with respect to the pharmacokinetics of these drugs. Most of these drugs are eliminated from the bloodstream by the cytochrome CYP2D6 system in the liver which again, depending on which particular polymorphism is inherited, can increase or decrease the blood concentration of that particular drug. Ultimately, it will be possible to determine whether someone is a rapid or slow acetylator of these drugs, and the appropriate drug dose can be modified. It is well recognized in the case of procainamide that fast acetylators of this drug are less likely to develop the lupus syndrome (56). Similar studies are well recognized for the development of neuropathy in response to isoniazid therapy (56).

SQTS

This is a rare disease associated with accelerated atrial and ventricular depolarization and a high propensity for atrial and ventricular arrhythmias (13). Mutations have been identified in three genes, all of which are a gain-of-function. The syndrome usually occurs in structurally normal hearts. The syndrome is recognized by a short QT on the surface ECG. Three loci have been identified referred to as SQTS1 and SQTS2 and SQTS3 (65); SQTS1 is caused by a gain-of-function mutation in the KCNH2 gene encoding an alpha subunit of the potassium channel. The SQTS2 is caused by a gain-of-function mutation in the KCNQ1 gene encoding the alpha subunit of the potassium channel. The SQTS3 was reported recently (65) due to a gain-of-function mutation in the KCNH2 gene encoding for the inwardly rectifying potassium channel, which accelerates repolarization and shortens the AP duration. It is of some physiological significance that a loss of function mutation in these genes is associated with the opposite effect, namely, delayed repolarization, which induces familial LQTS. The mechanism for arrhythmias in the SQTS is yet to be determined. The prevalence of the SQTS has, until recently, been considered rare. There is increasing evidence that many cases of ventricular fibrillation and SCD previously considered idiopathic may be due to SQTS. A rare disease referred to as Anderson syndrome (66) is due to a loss-of-function mutation in the gene encoding for a potassium channel subunit, which is associated with muscle paralysis, long QT, and ventricular arrhythmias. It is of interest that quinidine, a drug that prolongs the QT interval, has been shown to favorably affect this disease and is recommended as treatment to prevent malignant arrhythmias.

FAMILIAL CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

This is inherited in autosomal dominant and recessive forms occurring without evidence of structural myocardial disease (67,68). It is characterized by bidirectional and polymorphic ventricular tachycardia in response to vigorous exercise. This frequently deteriorates into ventricular fibrillation and death. Patients usually present with recurrent syncope, seizures, or sudden death associated with prolonged QT, it will be necessary to screen for all known mutations and SNPs that predispose to long QT.

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TISSUE GENE PROFILING USING MICROARRAYS TO SEARCH FOR GENES THAT INDUCE OR PREDISPOSE TO VENTRICULAR AND ATRIAL ARRHYTHMIAS

The human genome is estimated to contain about 25,000 distinct genes. Identification of these genes and their function remains to be determined. Regulation of gene expression, recognized to play a major role in the response of the body to environmental stimuli including disease, is of critical importance in the diagnosis and treatment of disease. Genetic regulation of organ differentiation is perhaps even less understood. DNA or RNA microarray (73,74), a relatively new technique consisting of thousands of genes etched into a chip, can be used to identify genes via hybridization to complementary base pairing. Microarray chips are now available with essentially all of the genes represented by expressed sequence tag or oligonucleotide. This technique is being utilized to determine which genes are expressed in certain tissues and the extent to which their expression is regulated in response to a variety of stimuli. It is well recognized in animal models and in human disease that atrial fibrillation, once it occurs, tends to be self-perpetuating and is associated with significant tissue remodeling of the atria (75). Studies being performed in the goat (76) and in human atrial tissue removed at the time of surgery (77) show a distinct gene expression profile associated with atrial remodeling in response to atrial fibrillation. A variety of genes have been observed to be up-regulated while others are down-regulated during this remodeling process (78). It has also been shown in animal models that once atrial fibrillation is converted to sinus rhythm, this pattern will return to that of the normal atrium (76). This provides an opportunity to assess these genes for polymorphisms as well as perform genomic function analysis to determine genes that play a pathogenic role in sustaining atrial fibrillation. Such studies, while in their primitive state, are ongoing. Another area of interest is atrial fibrillation that occurs after cardiac surgery in about 20% of individuals (77). Are they predisposed to genetic factors? The ability to scan with a chip containing 25,000 genes should accelerate finding genes pivotal to the disease.

Similarly, it is well recognized that ventricular hypertrophy increases one's risk of sudden death two- to four-fold regardless of the stimulus (18). The mechanism whereby ventricular hypertrophy increases risk to arrhythmias have not been determined. It is thus reasonable to assume that certain genes with polymorphisms that predispose to sudden death may be up-regulated in hypertrophy, which accounts in part for the vulnerability to arrhythmias. Microarray analysis, again, has already shown there is a differential display of genes in the atria and ventricle, and with the development of hypertrophy the fetal program of genes is up-regulated along with a variety of other genes (18). The microarray also provides the opportunity to classify genes in clusters as well as identify sets of genes that play a role in cell signaling. Thus, if a particular gene with an SNP is shown to be important, one can assess for SNPs in other such genes that are part of the signaling network. Nevertheless, it will significantly accelerate our ability to relate and associate genes with certain responses to the environment such as remodeling with atrial fibrillation or hypertrophy in response to ischemic heart disease.

FUTURE OF GENOMICS IN CARDIOVASCULAR ARRHYTHMIAS

While cardiac arrhythmias may be associated with or without structural heart disease, the defect always involves some aspect of the electrical conduction system of the heart. The structural component is, of course, the sinus node, specialized atrial tracts, atrioventricular node, and bundle of HIS with the Purkinje system. After conducting within this specialized electrical transmission, the current must pass into other cells such as myocytes. The important components are predominantly ionic currents, ion channels, structural proteins, and gap junctions. Most of the genetic defects currently identified involve some aspect of the subunits of the ion channels. We now recognize at least 429 genes that encode ion channel proteins in the human (79).

Of these, 170 encode potassium channels, 38 are for calcium channels, 29 are for sodium channels, 58 are for chloride channels, and 15 are glutamate receptors (80). It is of interest that ion channels represent only about 5% of the molecular targets of modern medicine (81,82). It is now recognized that in addition to the role of ion channels regulating membrane potential they also regulate many other functions including cell volume and hormone secretion (83,84). The complexity of these channels, such as the voltage-gated cardiac potassium channels, is such that several domains exist within the integrated channel protein. In addition to the pore domain, there are the domains that provide ion selectivity, opening and closing of the gate together with the sensing units whether it be voltage or chemical. The elucidation of mutations causing disease is rapidly enhancing our understanding of the topography and sequences involved with each domain. Approaches by the pharmaceutical industry to develop designer drugs for those domains, while in its infancy, are rapidly developing.

The characteristic feature of the electrical activity of the heart is the AP of the atria and ventricles due to depolarization and repolarization with the characteristic long plateau phase involving multiple ion channels. Many of these channels have now been cloned and will serve as prime candidates for the identification of genetic defects in the future. The major currents involved in the atrial and ventricular AP are indicated in Figure 2. Cardiac electrical activity is thus a complex process, which integrates the electrical activity of multiple molecules. Any variant in either of these molecules whether it is due to SNPs or greater defects can significantly alter cardiac activity. It is well recognized that structural heart disease, associated with either hypertrophy or cardiac dilatation, can structurally affect electrical transmission or through altered gene expression induce arrhythmias. Hypertrophy is well documented to increase the propensity for SCD by about four-fold.
Structural heart disease is associated with excessive fibrous tissue, which has a lower velocity of conduction and could lead to re-entry arrhythmias. Common genetic variants have been shown to increase the risk of cardiac arrhythmias, and most recent studies show that even common genetic variant in genes referred to as SNPs can alter cardiac electrical manifestations in certain populations. Atrial fibrillation is associated with significant morbidity in the aging population. Ventricular fibrillation is a lethal arrhythmia responsible for over 600,000 deaths each year in the Western world. Both atrial and ventricular fibrillation remain the most challenging of rhythm disorders.

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