Abstract—Genetic approaches have succeeded in defining the molecular basis of an increasing array of heart diseases, such as hypertrophic cardiomyopathy and the long-QT syndromes, associated with serious arrhythmias. Importantly, the way in which this new knowledge can be applied to managing patients and to the development of syndrome-specific antiarrhythmic strategies is evolving rapidly because of these recent advances. In addition, the extent to which new knowledge represents a purely research tool versus the extent to which it can be applied clinically is also evolving. The present article represents a consensus report of a meeting of the European Working Group on Arrhythmias. The current state of the art of the molecular and genetic basis of inherited arrhythmias is first reviewed, followed by practical advice on the role of genetic testing in these and other syndromes and the way in which new findings have influenced current understanding of the molecular and biophysical basis of arrhythmogenesis. (Circulation. 1999;99:518-528.)

Key Words: death, sudden • genetics • arrhythmia • molecular biology • electrophysiology

Clinical cardiologists who manage arrhythmias are increasingly faced with new complexities in management decisions. The once obscure science and jargon of medical genetics is assuming a much more prominent position in the mainstream medical literature, with almost weekly reports of new mutations to explain what once seemed to be very obscure diseases. This rapidly expanding knowledge base places the clinician (who usually trained when the concepts were not a major component of the medical school or fellowship training curricula) at a disadvantage in making day-to-day decisions with respect to managing common symptoms, such as unexplained syncope or heart failure. Even entertaining a diagnosis such as the congenital long-QT syndrome (LQTS) or hypertrophic cardiomyopathy used to be a medical curiosity. Now, with increased public and physician awareness of these and even more esoteric conditions, the questions in patient management have become more common and more complex. They include not only broad questions such as “How can I establish (or better yet, rule out) a diagnosis?” but also more specific issues such as “Should this patient undergo genetic testing? Where? How? And how can I interpret the results?”

The first and second parts of this article attempt to answer these questions. They neither teach molecular genetics nor provide an exhaustive review of the current state of the art of molecular and genetic cardiology relevant to arrhythmias. Rather, they try to put into a very practical perspective the ways in which ongoing progress in genetics may affect day-to-day clinical management.

The recognition that diversity in cardiac electrophysiology, and indeed in many aspects of cardiac function, can be attributed to variable expression of specific genes or variability in the function of their protein products has the potential to alter the way in which we think about normal and abnormal electrical heart function. The third part of the article reviews the potential for a genetic approach to understanding diversity
in cardiac function, focusing in particular on ion channels and gap junction proteins as the central players in normal and abnormal electrophysiology. Moreover, integration of molecular function into a single cell and of single cells into cellular networks reveals a multitude of interactions that eventually determine the generation and conduction of the cardiac action potential and therefore arrhythmogenesis.

This text is the outcome of a workshop convened by the Study Group on Molecular Basis of Arrhythmias of the Working Group on Arrhythmias of the European Society of Cardiology.

**Part I: Inherited Arrhythmogenic Disorders**

**Long-QT Syndrome**

LQTS is a familial disease characterized by abnormally prolonged ventricular repolarization and high risk of malignant ventricular tachyarrhythmias, often but not always occurring in the setting of high adrenergic activity, ie, physical or emotional stress. Two major clinical syndromes have been characterized on the basis of the pattern of transmission of the disease: a more common autosomal dominant form with a pure cardiac phenotype (Romano-Ward) and a rarer autosomal recessive form characterized by the coexistence of cardiac abnormalities and congenital deafness (Jervell and Lange-Nielsen).

**LQTS Genes**

Five loci have been associated with the Romano-Ward LQTS, and they are located on chromosomes 3, 4, 7, 11, and 21 (Table). As illustrated in Figure 1, 4 LQTS disease genes, each encoding an ion channel protein, have been identified: **SCN5A**, encoding the cardiac sodium channel (chromosome 3p21-p23); **HERG**, encoding the **I** channel protein (chromosome 11p15.5); **KvLQT1**, encoding the **I** channel protein (chromosome 7p12); **KCNJE1**, encoding **mink**, an ancillary subunit for the **I** channel complex (chromosome 21). Although the prevalence of each variant of LQTS has not been precisely defined, LQT1 is the most frequently encountered form, whereas LQT3 and LQT5 are rare.

**Mutations in LQTS Genes**

Most of the mutations identified to date in LQTS genes are missense mutations. These mutations are not confined to a single location but rather are located at various positions within each gene in different families. Thus, in most affected families, LQTS is due to a distinctive, or “private,” mutation. This remarkable genetic heterogeneity probably contributes to variability in the clinical presentation.

A few mutational “hot spots” (ie, specific positions within a gene mutated in multiple families) have been identified in **KvLQT1** and **HERG**. Unrelated kindreds worldwide with

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<th>Disease</th>
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<tr>
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<td>Muntoni et al&lt;sup&gt;70&lt;/sup&gt;</td>
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**CDDC** indicates conduction defect and dilated cardiomyopathy; **FAIb**, familial Afib; **LQTS (F-IVF)**, LQTS, Romano-Ward type; **LQTS (JLN)**, LQTS, Jervell and Lange-Nielsen type; **ARVD**, arrhythmogenic right ventricular cardiomyopathy; and **F-IVF**, familial idiopathic ventricular fibrillation.

the same mutation can therefore be studied to test the logical hypothesis that they share common clinical or epidemiological features. Contrary to expectations, initial studies indicate that substantial phenotypic heterogeneity remains even with an identical LQTS gene abnormality. This, in turn, suggests that variable expression of as-yet-unidentified “modifier genes” contributes to the clinical manifestations of the disease.

The Jervell and Lange-Nielsen (autosomal recessive) variant of LQTS (in which affected subjects have especially long QT intervals) arises in individuals who inherit abnormal KvLQT1 or minK alleles from both parents. The abnormal allele can be the same (usually in consanguineous families)19,20 or different (compound heterozygosity).16 Thus, parents of subjects with Jervell and Lange-Nielsen carry LQTS mutations, although most (but not all) are asymptomatic. Recently, a family with apparently autosomal recessive LQTS without deafness has also been identified.21 These findings all suggest an effect of gene dosage to determine phenotype (2 abnormal alleles appear to be worse than 1) and also highlight the extraordinary variability in LQTS phenotype.22–25 The location of the mutations within the gene (eg, close to the regions encoding specific structures such as the pore, the voltage sensor, the S1-S6 region, or the N- or C-terminal portions) or the type of mutation (the nature of the amino acid substitution, missense mutation versus deletions or insertions) may also play a role.

Functional Consequences of Mutations

The channels carrying $I_{Ks}$ and $I_{Kr}$ are multimeric; that is, alleles from both parents are thought to contribute to the channel complexes. When mutations in KvLQT1, KCNE1, or HERG are expressed alone or with wild-type alleles in oocytes or in other cell lines, they exhibit “loss of function,” ie, the total current carried by the defective channel complexes is reduced. Some of the mutations not only reduce current but also modify channel kinetics. Many HERG and KvLQT1 mutations have been defined as “dominant negative” because when the mutant protein is coexpressed with the native protein,13,14,26,27 the resulting defect in current exceeds 50%. One explanation for this phenomenon is that incorporation of a single abnormal protein subunit into the tetrameric channel structure is sufficient to alter the overall behavior of the current.

By contrast, mutations in the SCN5A channels cause a “gain of function.”10,11 These mutations produce a persistent late $I_{Na}$ that is not present physiologically and that is due to defective inactivation. In most described mutations, the $I_{Na}$ is increased because of late reopenings of the channels, whereas in the 3-amino-acid deletion (ΔKPQ), long-lasting bursts of channel activity are also present. These mutations also differ in severity, with the ΔKPQ deletion being associated with a quantitatively larger increase in late sodium inward current.11 It is generally difficult to develop specific therapies for loss of function (eg, the $K^+$ channel defects described above). By contrast, the gain of abnormal function exhibited by mutant SCN5A gene products raises the possibility that a cure could be accomplished by pharmacological agents that inhibit the gained function, ie, block the late $I_{Na}$. Indeed, some data suggest that these currents are especially sensitive to block by mexiletine or lidocaine.10,11

Genotype-Phenotype Correlations

The different time- and voltage-dependence of the ionic currents involved in LQTS may help explain some aspects of the variable phenotype and raise the possibility of gene-specific treatment. Indeed, available data on several hundred genotyped patients indicate the existence of gene-specific differences in the triggers for cardiac events.28 Exercise-related events dominate the clinical picture in $I_{Kr}$-related LQTS (LQT1).24 $I_{Kr}$ is the predominant $K^+$ current in conditions of high sympathetic activity, particularly at shorter cycle lengths. Thus, reduced $I_{Kr}$ will be predicted to lead to inadequate action potential shortening with adrenergic stress and thereby account for the high prevalence of arrhythmic events in these patients during exercise. By contrast, most LQT3 patients experience events during sleep or at rest; they are also able to markedly shorten their QT interval during exercise.29 In this case, it seems likely that the presence of
normal K⁺ currents produces normal action potential shortening during exercise; however, at rest, defective inactivation of \( I_{\text{Na}} \) will result in an increase in the plateau inward Na⁺ current. This apparently nice distinction between LQT1 and LQT3, however, is complicated by the reality that LQT2 patients also tend to display events both at rest and during exercise, thus pointing to the persistent limitations in current understanding.

There is an emerging sense that gene-specific therapy may be feasible for some forms of LQTS. This relates both to pharmacological therapy and to advice regarding lifestyle. A disorder based on disturbed inactivation kinetics of the sodium channel (LQT3) seems likely to respond to a sodium channel blocker. Indeed, in LQT3 patients, the QT interval seems to shorten more than in LQT1 and LQT2 patients in response to mexiletine, but individual exceptions do exist, and significant shortening of QT intervals by sodium channel blockers has been reported in some LQT2 patients. It is also possible that although mexiletine or similar drugs shorten QT in LQT3, \( \beta \)-blockade might still be necessary to suppress arrhythmias. Because the amplitude of \( I_{\text{Ks}} \) increases when extracellular potassium concentration is increased, attempts have been undertaken to increase K⁺ levels in LQTS patients. To date, QT interval has been shown to shorten significantly in LQT2 patients, but neither LQT1 nor LQT3 patients have yet been tested with this approach. Because \( I_{\text{Ks}} \) function is normal in the latter subjects, elevating potassium to increase \( I_{\text{Ks}} \) should shorten QT in them as well. The putative role of \( I_{\text{Ks}} \) in cardiac physiology suggests an especially favorable effect of \( \beta \)-blockade and the avoidance of vigorous increase in heart rate (ie, competitive sports) in LQT1 and LQT3. These examples demonstrate that gene-specific therapy may be feasible in LQTS. However, it should be emphasized that long-term trials are not yet available and that at present, \( \beta \)-blockers remain the first-choice therapy.

**Drug-Induced LQTS**

It has long been postulated that drug-induced LQTS might represent a genetically mediated “forme fruste” of LQTS. Recent studies have identified relatively large numbers of individuals who carry “silent” mutations on LQTS genes. Thus, these persons, whose LQTS mutations by themselves produce an alteration in repolarizing currents that is insufficient to prolong the QT interval at rest, may be especially sensitive to any drug that affects K⁺ currents. The combination of even a modest degree of \( I_{\text{Ks}} \) blockade, induced by a variety of drugs used for multiple purposes, and such silent mutations could thereby produce the major prolongation in action potential that triggers the onset of torsades de pointes. Indeed, occasional patients with typical drug-induced LQTS and underlying mutations on LQTS genes have now been identified. However, this phenomenon is sufficiently rare that genetic testing in patients with drug-induced LQTS is not yet warranted in the absence of other indications (eg, family history, long baseline QT).

**Familial Hypertrophic Cardiomyopathy**

Hypertrophic cardiomyopathy is transmitted as an autosomal dominant disease. Its clinical phenotype is characterized by unexplained and inappropriate clinical left and/or right ventricular hypertrophy, which may be severe (4 to 5 cm), mild, or even absent. Characterization of the distribution of left ventricular hypertrophy is arbitrary, but by convention, hypertrophy is considered to be either asymmetrical septal, concentric, or predominantly distal ventricular hypertrophy. Any pattern of hypertrophy may be seen, however, including hypertrophy confined to the posterior or free wall. Characteristic histological features include myocyte disarray surrounding areas of increased loose connective tissue.

Clinically, there is marked hemodynamic heterogeneity among patients with familial hypertrophic cardiomyopathy (FHC). Systolic function may be hyperdynamic (with or
without obstruction), “normal,” or impaired (10% to 15%). Diastolic dysfunction is the usual physiological abnormality, although the precise abnormality of ventricular filling and compliance is extremely variable.

FHCM-related arrhythmias occur both at the ventricular and at the atrial levels. Importantly, sudden cardiac death in FHCM is not necessarily caused by ventricular arrhythmias. Atrial fibrillation (AFib) in the presence of an accessory pathway, bradyarrhythmias, and ischemia all may lead to sudden death. In patients with β-myosin heavy chain-related FHCM (likely the majority), hypertrophy itself does not seem to be the main determinant of malignant ventricular arrhythmia. One caveat in interpreting electrophysiological changes in these settings is that a common secondary response to injury (such as pressure overload or coronary occlusion) is cardiac hypertrophy, which in diseased hearts then produces further functional changes, notably in calcium handling. Thus, the extent to which any of the observed electrophysiological alterations are primary or secondary to the response to the disease process requires further study.

**FHCM Genes**

As illustrated in Figure 2, there is considerable genetic heterogeneity in FHCM. Mutations in 7 sarcomeric protein genes have been identified in families with FHCM (Table). These are (1) β-myosin heavy chain on chromosome 14,37 (2) cardiac essential myosin light chain on chromosome 3,38 (3) cardiac regulatory myosin light chain on chromosome 12,38 (4) cardiac troponin T on chromosome 1,39 (5) α-tropomyosin on chromosome 15,39 (6) cardiac myosin-binding protein C on chromosome 11,40,41 and (7) cardiac troponin I on chromosome 19.42 An additional locus has been identified on chromosome 7 in a large family with both FHCM and cardiac preexcitation (Wolff-Parkinson-White syndrome [WPW]).43

The prevalence of the different gene abnormalities in FHCM is being delineated. To date, information in <100 genotyped families suggests that mutations in β-myosin heavy chains and myosin-binding protein C are more common than the others. In addition to this locus heterogeneity, there is, as in LQTS, marked allelic heterogeneity for all the recognized disease genes, and to date, >85 different mutations have been reported (for reviews see References 34, 44, and 45). The majority of mutations are missense mutations, although for the cardiac myosin-binding protein C gene, most of the mutations lead to an early stop codon resulting in truncated mutant proteins.46

Functional studies of mutant myosin indicate that sarcomeric contractile performance is depressed.47–49 This, in turn, suggests that myocyte hypertrophy characteristic of FHCM reflects a compensatory response. The molecular (or other) determinants of myocyte disarray and myocardial fibrosis (interstitial and replacement) remain unclear. It may well be that these latter responses relate to the type of mutation (eg, greater with troponin-related disease) and that sudden death and clinical arrhythmia are the clinical consequences of extensive disarray and fibrosis.

**Genotype-Phenotype Correlations**

Information on the genotype-phenotype relation in FHCM is still preliminary, because the published data on genotyped patients relate to only a few hundred individuals from centers that may reflect different referral biases. It is nevertheless clear that the phenotype varies not only with the type of mutation but also within individuals bearing the same mutation. The 403 codon in β-myosin is a hot spot for mutations; the arginine-to-glutamine mutation is associated with a poor prognosis, whereas the arginine-to-tryptophan mutation appears to be more benign.50–52 Current practice suggests that if ECG and 2-dimensional echocardiography are normal by age 25 years, then the patient can be safely reassured that he or she will not develop clinical FHCM. However, myosin-binding protein C mutations appear to be associated with age-related penetrance during adult life.40,41,53 Further information confirming the impression that adult onset of disease is an important feature seen with myosin-binding protein C mutations would thus have a significant impact on management and counseling. The disease caused by troponin T mutations appears to be associated with mild or absent hypertrophy, a 20% to 25% incidence of nonpenetrance, and a high incidence of premature sudden death (possibly greater in young men, although the numbers are small), which can occur even in the absence of significant clinical left ventricular hypertrophy.54–56

**Arrhythmogenic Right Ventricular Dysplasia**

Arrhythmogenic right ventricular dysplasia (ARVD) is a recently recognized familial cardiomyopathy.57 The disease is characterized by fibrofatty replacement of the right ventricular myocardium and life-threatening ventricular tachyarrhythmias originating from the right ventricle. Occasionally, the left ventricular myocardium is involved as well. Disease progression is associated with left ventricular involvement (50%), atrial dilation, and arrhythmias with embolic risk. Malignant ventricular arrhythmias are a common manifestation of the disease. Inducibility and reproducibility in the clinical electrophysiological laboratory is high, suggesting that reentrant mechanisms related to the distinctive structural changes are likely. The disease appears to be especially common in Northeastern Italy (prevalence, 1:1000), with an autosomal dominant inheritance (30%). An autosomal recessive variant of ARVD that is associated with a distinctive extracardiac phenotype (woolly hair and palmoplantar keratoderma) has been reported from the island of Naxos in Greece.58

**Molecular Basis of ARVD**

To date, 4 loci for autosomal dominant ARVD have been identified, 2 of which are in close proximity on chromosome 14 (14q23-q24 and 14q12-q22).59,60 A third locus was located on chromosome 1 (1q42-q43).61 and the fourth on chromosome 2 (2q32.1-q32.2).62 (Table). The autosomal recessive syndrome variant of ARVD has been linked to a locus on chromosome 17 (17q21), within the gene encoding a keratin, a reasonable candidate for the entity.58 Further advances will facilitate recognition of the nonarrhythmic clinical presentations and the broader phenotype of ARVD/Naxos disease (Table).

**Dilated Cardiomyopathy**

Dilated cardiomyopathy (DCM) is a genetically and clinically heterogeneous disease63 that can affect newborns, children,
adolescents, adults, and the elderly. The disease may be associated with other organ or muscle abnormalities or present as a pure disorder. Malignant life-threatening ventricular arrhythmia and atrial arrhythmia with serious impact on cardiac function are frequently associated with the disorder. As in FHCM, sudden death in DCM may also be caused not only by ventricular arrhythmias but also by bradyarrhythmias. Whenever spontaneous ventricular arrhythmias have been clinically documented, the inducibility and reproducibility of the arrhythmia in electrophysiological studies is usually low, favoring the possibility of a predominant role for nonreentrant mechanisms.64,65 At least 30% of cases of DCM are inherited (ie, familial DCM), with a significant percentage of the remaining cases being acquired (ie, myocarditis, ischemic heart disease, etc). Inherited DCM may have autosomal dominant, autosomal recessive, X-linked, or mitochondrial transmission (Table).

**Molecular Basis of DCM**

To date, genes for X-linked DCM and autosomal dominant DCM (ADDCM) have been mapped, demonstrating genetic heterogeneity.66 The genes for 2 X-linked cardiomyopathies have been identified: the dystrophin gene, which is also responsible for Duchenne and Becker muscular dystrophy,67,68 and G4.5 in Barth syndrome (X-linked cardioskeletal myopathy with neutropenia, abnormal mitochondria, and 3-methylglutaconic aciduria).69 Multiple mutations in both genes have been reported as well.68–72

Dystrophin is a large cytoskeletal protein that is found on the inner face of the sarcolemma and attaches at its N-terminal domain to F-actin in the matrix and to the dystrophin-associated glycoprotein (DAG) complex (an oligomeric transmembrane protein) at its C-terminal domain. The protein encoded by the G4.5 gene is called “tafazzin,” but its function is still unknown.

Genes for autosomal dominant DCM have been mapped to 6 different loci thus far. “Pure” DCM has been localized to 1q32, 2p31, 9q13, and 10q21-q23,73–76 whereas DCM with conduction defects has been mapped to 1p1-1q177 and 3p22-3p25.78 Recently, mutations in cardiac actin79 located on chromosome 15q14 have been identified; therefore, actin is thus far the only known gene for ADDCM. On the basis of this finding, Olson et al79 have now proposed that DCM is a consequence of defective transmission of force in cardiac myocytes leading to heart failure.

**Idiopathic Ventricular Fibrillation and the Brugada Syndrome**

Another interesting group of patients that has become a target for genetic studies is represented by those individuals with so-called idiopathic ventricular fibrillation (ie, patients with a normal heart who experience cardiac arrest with documented VF).80 A subgroup of these patients experience sudden death (which may occur in families), apparently have no structural heart disease, and have right precordial ST-segment elevation, sometimes with right bundle-branch block (RBBB; Brugada syndrome).81 These ECG characteristics may depend on exaggerated transmural differences in action potential configuration, especially in the right ventricular outflow tract. This could arise from dysfunction of a number of ion currents, such as \( I_{\text{Ca,L}} \), L-type \( \text{Ca}^{2+} \) current \( [\text{Ca(L)}] \), and \( I_{\text{Na}} \).

At least 1 variant of the Brugada syndrome is caused by defects in the sodium channel gene (SCN5A), ie, the same gene implicated in LQT3.82 In the Brugada syndrome, the mutations identified apparently lead to a loss of function, whereas in LQT3, most cause a gain of function. Thus, LQTS and the Brugada syndromes appear to be separate allelic disorders.

The evidence that not all patients with Brugada syndrome have defects on the cardiac sodium channel (S.G. Priori et al, 1998, unpublished observations) suggest that, in analogy with the other inherited cardiac diseases, genetic heterogeneity is also present in Brugada syndrome.

**Atrial Fibrillation**

Perhaps the most common arrhythmia requiring intervention is Afib. Data are now emerging from a number of laboratories on the potential molecular basis of electrophysiological changes observed in atria that have been fibrillating for hours to days and those that have been fibrillating for weeks to months.83–87 They all share a marked shortening of refractoriness, most likely reflecting decreased action potential duration early during Afib. Available data suggest that a major mechanism is decreased inward current through L-type calcium channels and possibly sodium channels.88 Later during the “remodeling” that appears to accompany chronic Afib, changes in expression and/or distribution of connexin proteins and/or other ion channel proteins, as well as changes in cellular ultrastructure, may play a role.

Inherited Afib is considered uncommon and has been reported with autosomal dominant transmission. Recently, familial Afib has been mapped to 10q22-q24 (a region of \( \approx 11 \text{ cM} \)) in 3 families.89 Expansion of the previously identified kindreds has allowed further refining of the map position and limitation of the gene critical region.

A fascinating issue concerning Afib is its association with other disorders, such as DCM, FHCM, and LQT4 and the possibility that a mutation in a gene responsible for 1 of these associated disorders could cause familial Afib. For instance, is it simply circumstantial that a familial DCM locus76 and the mapped Afib locus are within the same relatively small region of 10q21-q24? Is there something different about the clinical course, and thus the causative gene responsible for LQT4,8 in which prolonged QTc appears to be associated with a high incidence of Afib and slower heart rates than typically seen in LQTS? Could this be a different type of gene (ie, not an ion channel) or a new channel disorder?

**Progressive Familial Heart Block**

Two forms of progressive familial heart block (PFHB),90 which differ in their ECG characteristics, have been reported. The first, PFHB-L, is defined on ECG by evidence of bundle-branch disease such as RBBB, left anterior hemiblock, left posterior hemiblock, or complete heart block with broad QRS complexes. Progression of disease occurs with changes in the ECG going from a normal ECG to RBBB to complete heart block. Typical manifestations of the disease are syncope, sudden death, and Stokes-Adams attacks. The
second form of PFHB, known as PFHB-II, presents with complete heart block and narrow QRS complexes and is believed to occur as a result of AV nodal disease with AV block and an idiomodal escape rhythm. Typically, these patients present with sinus bradycardia and left posterior hemiblock and develop syncope and Stokes-Adams attacks.

Genetically, PFHB-I is better studied than PFHB-II and appears to be inherited in autosomal dominant fashion. Brink and Torrington91 studied 3 South African families with PFHB-I, including one 9-generation kindred, for linkage analysis. In 86 family members (39 affected), linkage was identified on chromosome 19 at 19q13.2-19q13.3, and the gene was localized to within 10 cM of the kallikrein locus. Confirmation of this localization was subsequently reported by De Meeus et al92 in a large Lebanese family. Other candidate genes within the mapped region include apolipoprotein C2, creatine kinase–MM, myotonic dystrophy, troponin T, and the histidine-rich Ca2+-binding protein (a luminal sarcoplasmic reticulum protein). Myotonic dystrophy, creatine kinase–MM, and apolipoprotein C2 have been excluded as the causative genes.

Familial WPW Syndrome

Familial WPW has rarely been reported, but an inherited form of WPW associated with FHCM has been described and its locus mapped to chromosome 7q3.45 It is unknown whether a single defect is responsible for both aspects of the syndrome or whether 2 genes are located in close proximity (ie, contiguous gene syndrome) and thus frequently cosegregate. In the latter case, familial WPW could be caused by a single gene defect on chromosome 7. However, other associations of FHCM and WPW have also been identified. For example, Kimura et al42 found mutations in the cardiac troponin I gene (on chromosome 19) in patients with FHCM and WPW. Furthermore, some children with mitochondrial abnormalities and metabolic disease (Pompe disease) associated with FHCM also have been noted to have WPW. Therefore, it currently appears that WPW may have multiple different genetic pathogenesis.

Part II: Molecular Diagnosis of Inherited Arrhythmogenic Disorders

Role of DNA Screening in Diagnosis of Inherited Arrhythmogenic Diseases

The potential of making a genetic diagnosis makes it possible to consider the role of genetic testing in routine clinical practice. Applications could include preclinical diagnosis and identification of patients who might benefit from prophylactic treatment for sudden death. For this approach to become a reality, however, several conditions must be met: the development of routine clinical DNA diagnostic testing facilities; a sufficiently large database to determine risk in relation to genotype, as well as the recognized heterogeneity in phenotype; an estimate of the efficacy of available treatments; and a consideration of the cost implications.

Molecular diagnosis has the potential to define with 100% sensitivity and 100% specificity the genetic status of any member of an affected family. However, for this potential to become fully expressed, it is necessary that all the genes and all the mutations within these genes causing a given disease be identified. This is not yet even close to reality for any of the inherited arrhythmogenic diseases discussed here. As a consequence, physicians still generally have to rely on clinical criteria to establish these diagnoses.

For some diseases, not even the specific affected gene(s) are known. In these cases (eg, familial Afib, progressive familial AV block), the available genetic information is derived from linkage studies and provides only data as to which chromosomal region the disease gene is located on. If this region is large, it may take years before the gene responsible for the disease is located. Thus, at this stage of knowledge, molecular screening for these entities is limited to research activities; it is not possible to consider genotype-phenotype correlations, and most importantly, the nature of the defect underlying the disease remains undefined. Linkage studies can nonetheless provide the important information on whether only 1 gene is associated with the disease or whether genetic heterogeneity exists (ie, several genes accounting for a disease).

When a gene responsible for a disease is identified, it then becomes possible to search for specific mutations. The organization and the sequence of the disease genes are often not entirely known, and thus, mutations are usually searched for (at least initially) only in portions of the gene. As a consequence, a positive finding (ie, the identification of a mutation) is diagnostic, whereas a negative finding in a linked gene suggests that mutations may be present in an unexplored region of the gene (or that the linkage is incorrect). The diagnostic power of molecular screening is further limited (for all arrhythmogenic disorders discussed here) by the presence of genetic heterogeneity and the lack of identification of all of the genes responsible for the disease.

Implications of Molecular Diagnosis on Patient Management

When the genetic bases of FHCM and LQTS were elucidated, one hope of molecular biologists and clinicians alike was that it would have become possible to reach, in a relatively short time, some important goals in the establishment of genotype/phenotype correlations. In this respect, valuable information would be the ability to categorize mutations as mild versus severe to guide the therapeutic approach on the basis of the predicted risk. For the time being, this goal has not been achieved, and we are still far from being able to predict adverse or favorable prognosis on the basis of the genetic defect.

A major goal in LQTS and FHCM is to have sufficient genotyped patients to understand the diagnostic, functional, and prognostic implications of the different mutations. A problem in genetic testing in LQTS and FHCM is that the disease-associated gene and specific mutations are still being identified. This research information is not yet widely implemented in commercial laboratories, and the resource demands for such an effort on a routine (or “service”) basis are generally beyond those available to the research laboratories engaged in the problem.
Genetic Testing for LQTS
When should genetic testing be considered in dealing with LQTS patients? The cardiologist will confront 3 clinical scenarios.

The first situation is the patient who has a definite diagnosis based on established clinical diagnostic criteria. Here, genetic testing is not absolutely necessary, because the cardiologist has most of the elements necessary to decide about initiation of therapy. However, genetic testing could be useful, because, depending on the gene (and ultimately even the specific mutation) identified as responsible for the disease, modifications in management may be suggested. Examples discussed above include the addition of mexiletine in LQT3 or lifestyle modifications such as limitation of strenuous or competitive exercise in LQT1. It should be pointed out, however, that in symptomatic patients with an established diagnosis of LQTS, implementation of therapy with β-blockers should not be delayed while waiting for results of genetic screening.

A second scenario occurs when the diagnosis of LQTS is only suspected or the patient has a borderline diagnosis based on clinical criteria. Under these circumstances, genetic testing could be very useful in establishing the diagnosis, because identification of a mutated LQTS gene would convert a suspected diagnosis into a certain one and would remove the cardiologist’s hesitation in making therapeutic choices. However, the failure to identify a mutation does not rule out the diagnosis (because only a minority of mutations have been identified to date). Although genetic testing in this situation is not yet widely available, techniques to automate screening for the hundreds of possible known mutations are now being developed and will probably be available in the next 5 to 10 years.

A third scenario is an apparently asymptomatic relative of a patient with LQTS. Here, genetic testing can be especially useful if the disease-causing mutation has previously been identified in the proband. Otherwise, the same issues arise as those in evaluating the borderline LQTS diagnosis.

Genetic Testing for Hypertrophic Cardiomyopathy
Similar considerations apply in FHC. From the clinical perspective, comprehensive screening of the disease-causing genes would be both inappropriate and impractical at this time. Specific clinical situations exist in which DNA diagnosis is likely to have an important impact on management. For example, sudden death/resuscitated VF in association with normal or near-normal heart weight and/or mild morphological features in the young should lead to testing for mutations in the cardiac troponin T gene. Premature sudden death in association with obvious morphological features in the young has been associated with the Arg403Glu and Arg453Cys mutation in the β-myosin heavy chain gene, and these mutations could be tested in this clinical context. Identification in the proband of troponin or myosin heavy chain mutations that are associated with poor prognosis would permit an early or even a preclinical diagnosis in family members with the potential for lifestyle modifications (avoidance of competitive exercise) and prophylactic treatment (amiodarone or implantable cardioverter-defibrillator) to prevent sudden death.

Genetic Testing for Autosomal Dominant DCM, Arrhythmogenic Right Ventricular Dysplasia, Familial Afib, and Progressive Familial AV Block
Until specific genes are discovered and characterized, molecular diagnosis should be considered a research tool only in large families in which linkage analysis may be performed.

Genetic Testing for DCM
In both X-linked DCM and Barth syndrome, definite diagnosis at the molecular level may be useful clinically, because both are rapidly progressive and severe disorders. In the case of X-linked DCM, in which anticongestive and antiarrhythmic management initially and cardiac transplantation shortly thereafter are lifesaving, determination of a mutation could help diagnose presymptomatic male gene carriers. In Barth syndrome, therapeutic options are less clear-cut, but a definitive diagnosis in family members and potentially in fetuses could be similarly useful.

The recent identification of mutations in the actin gene opens the opportunity to perform family screening for mutations; however, until the prevalence of actin-related ADDCM is defined, the cost/benefit ratio of actin gene screening cannot be defined.

Genetic Testing for Brugada Syndrome
The identification of mutations in the cardiac sodium channel in families with Brugada syndrome opens the possibility of screening patients with the disease. The importance of the identification of the defect obviously consists of the ability to identify the carriers before they become symptomatic. This is particularly important for a disease in which the first manifestation is often cardiac arrest. However, because not all patients with Brugada syndrome have mutations in the sodium channel (S.G. Priori et al, 1998, unpublished observations), the cost/benefit ratio of mutation screening in the sodium channel gene cannot be defined until the prevalence of the genetic variant of the form associated with sodium channel defects is defined.

Ethical Aspects of Molecular Screening
Important ethical aspects are involved when DNA screening is considered in families affected by a congenital disease. Discussion of the information that could be provided by genetic testing with families is a most important first step. The experience of the team, which should include an appropriately trained genetic counselor, is of critical importance. Counseling in arrhythmogenic disorders is to help the patient decide whether he or she should undergo genetic screening at all. The considerations involved when an individual is deciding whether or not to be tested are as follows.

The patient should be given information on (1) the sample required, (2) use of the sample, (3) results of the test performed, (4) implications of these results for management of the patient and family, and (5) who will have access to the results.
The patient should use this information to decide whether to give or withhold consent. There should be no coercion by anyone (healthcare team, family members, insurance companies).

The consent form that patients sign should include statements that (1) all blood samples are coded to prevent identification and (2) the results of screening will be communicated only to the patient and that no disclosure will be made to third parties (not even family members) without the patient’s written consent. Asymptomatic patients should have the option of providing samples (e.g., for family study) but not being informed of the results.

**Reimbursement and Cost Issues**

At the present time, DNA screening for arrhythmogenic disorders is not considered a routine test, and therefore, costs are not usually covered by insurance. Linkage to isolate the disease gene can be performed in large families. When small pedigrees or single patients in whom linkage cannot be applied are studied, the only approach for DNA screening is the systematic search for known mutations in any disease-linked gene. As discussed above, clinical evaluation may help in selecting gene(s) to be screened first. Depending on the size of the gene and on the number of genes to be screened, costs may be substantial ($1000 US per gene screened in each family). Currently, costs are covered almost exclusively by research funding of the laboratories involved in the field. The development of automated screening and identification of more mutations may change this in the near (?) future.

**Appendix**

This article summarizes the outcome of a workshop held at the European Heart House C, Sophia Antipolis, France, October 2–5, 1997. The need for the workshop was proposed by Silvia G. Priori. It was organized by the Study Group on Molecular Basis of Arrhythmias of the Working Group on Arrhythmias of the European Society of Cardiology, and its funding was administered by the Working Group itself. The workshop was cochaired by Silvia G. Priori and André G. Kébler. The final preparation and organization of the manuscript were the responsibility of André G. Kébler, Silvia G. Priori, Dan M. Roden, and Peter J. Schwartz.

**References**


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Parts I and II
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