Impact of Laboratory Molecular Diagnosis on Contemporary Diagnostic Criteria for Genetically Transmitted Cardiovascular Diseases: Hypertrophic Cardiomyopathy, Long-QT Syndrome, and Marfan Syndrome

A Statement for Healthcare Professionals From the Councils on Clinical Cardiology, Cardiovascular Disease in the Young, and Basic Science, American Heart Association

Barry J. Maron, MD, Chair; James H. Moller, MD, Cochair; Christine E. Seidman, MD; G. Michael Vincent, MD; Harry C. Dietz, MD; Arthur J. Moss, MD; Jeffrey A. Towbin, MD; Henry M. Sondheimer, MD; Reed E. Pyeritz, MD, PhD; Glenn McGee, PhD; Andrew E. Epstein, MD

Over the last several years, substantial progress has been achieved in defining the molecular basis for several genetically transmitted, nonatherosclerotic cardiovascular diseases.1–67 These advances in molecular biology have enhanced our understanding of the primary defects and basic mechanisms responsible for the pathogenesis of these conditions and their phenotypic expression, and in the process, new perspectives on cardiac diagnosis have been formulated. In the course of this scientific evolution, a certain measure of uncertainty has also arisen regarding the implications of genetic analysis for clinical diagnostic criteria.

New subgroups of genetically affected individuals without conventional clinical diagnostic findings have been identified solely by virtue of access to molecular laboratory techniques, creating a number of medical and ethical concerns regarding the possible clinical implications. Indeed, the extent to which such individuals should receive sequential evaluations and/or therapy or be subjected to employment or insurance discrimination, psychological harm, loss of privacy, or unnecessary withdrawal from competitive athletics is uncertain but remains a legitimate source of concern.68–71

It is therefore particularly timely and appropriate to analyze these issues in detail, specifically the extent to which molecular biology has revised traditional diagnostic criteria. The role of genetic testing in assessing prognosis and identifying high-risk subgroups or in defining basic disease mechanisms and pathophysiology is, however, largely beyond the scope of this scientific statement. As models for the present critique, we selected the 3 most common familial cardiovascular diseases for which gene defects have been identified, each of which is associated with autosomal dominant inheritance and a risk for sudden cardiac death: hypertrophic cardiomyopathy (HCM), long-QT syndrome (LQTS), and Marfan syndrome (MFS).

Hypertrophic Cardiomyopathy

Clinical Diagnosis (Phenotype)

HCM is a primary and usually familial cardiac disease characterized by complex pathophysiology and great heterogeneity in its morphological, functional, and clinical course.72–92 This considerable diversity is emphasized by the fact that HCM may present in all phases of life, from the newborn to the elderly. The clinical course is highly variable, with some patients remaining asymptomatic throughout life and others developing severe symptoms of heart failure; some die prematurely, either suddenly (often in the absence of prior symptoms) or owing to progressive heart failure.72–76 HCM appears to be a more benign condition in unselected patient populations, which are more representative of the overall disease spectrum,79–81,93 than in those patients who are part of preferentially selected and high-risk cohorts from a few tertiary referral centers.93 Recent observations suggest that the prevalence of HCM in the general population is probably higher than previously thought (≈0.2%, or 1 in 500).94 Therefore, HCM may be regarded as a cardiomyopathy resulting from a relatively common genetic defect.

Since the modern anatomic description of HCM by Teare in 1958,72 left ventricular hypertrophy traditionally has been regarded as the gross anatomic marker and the likely determinant of many of the clinical features and consequences observed in most patients with this disease.83,95,96 Because the left ventricular cavity is usually small or normal in size, increased left ventricular mass is due almost entirely to increased wall thickness.83,97,98 Consequently, the clinical diagnosis of HCM has been based on the identification by
2-dimensional echocardiography of the most characteristic morphologically expressed feature of the disease, ie, unexplained thickening of the left ventricular wall (usually asymmetrical in distribution) associated with a nondilated chamber, in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident (eg, systemic hypertension or aortic valve stenosis).73–76 LV indicates left ventricle; LVH, left ventricular hypertrophy; 2-D echo, 2-dimensional echocardiographic imaging; and AS, aortic valve stenosis. *Genotype-positive, phenotype-negative adults are uncommon but appear to be more frequently associated with certain genetic defects, such as mutations in the gene for myosin-binding protein-C.14,18

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Diagram summarizing the clinical and laboratory diagnosis of hypertrophic cardiomyopathy (HCM). Although it is possible to establish this diagnosis in the laboratory setting by mutational analysis, in the vast majority of instances HCM is identified clinically with 2-dimensional echocardiographic imaging (by virtue of a hypertrophied but nondilated left ventricle). Clinical diagnosis by this criterion can be confounded by associated cardiovascular diseases such as systemic hypertension or aortic valve stenosis, by evolution to the end-stage (or dilated) phase of HCM in which left ventricular wall thinning occurs, or if the subject is a highly trained athlete in selected sporting disciplines.14,28 LV indicates left ventricle; LVH, left ventricular hypertrophy; 2-D echo, 2-dimensional echocardiographic imaging; and AS, aortic valve stenosis. *Genotype-positive, phenotype-negative adults are uncommon but appear to be more frequently associated with certain genetic defects, such as mutations in the gene for myosin-binding protein-C.14,18

Molecular Diagnosis (Genotype)

It has been evident, even from the initial descriptions of the disease, that HCM is usually inherited as a mendelian autosomal dominant trait.100 Contemporary molecular genetic approaches were first applied to familial HCM in the mid-1980s.7 Over the last decade, molecular studies using linkage analysis have mapped a number of genetic loci responsible for HCM and in the process have provided insights into the considerable clinical heterogeneity characteristic of this disorder.3–5,8,14,15 The consequences of these different gene defects for patients appear to differ greatly and are not yet completely understood.

HCM can be caused by a mutation in any 1 of 5 genes that encode proteins of the cardiac sarcomere: β-myosin heavy chain (on chromosome 14),1,7,18–21 cardiac troponin T (chromosome 1),8–11 troponin I (chromosome 19),6 α-tropomyosin (chromosome 15),8,10,12,13 and cardiac myosin-binding protein C (chromosome 11).14–17,28 In addition, mutations in 2 genes encoding essential and regulatory myosin light chains have been reported in what may be an extremely rare form of HCM.22 This genetic diversity is further compounded by intragenic heterogeneity, with a total of more than 100 individual disease-causing mutations identified for these genes; the majority represent missense mutations in which a single amino acid residue is substituted with a different amino acid in the globular head or head-rod junction regions of the myosin molecule. Hence, it is apparent that the precise molecular defect responsible for HCM usually proves to be different in unrelated individuals.

Available data suggest that mutations in the β-myosin heavy chain gene (myosin is the primary contractile protein in thick filaments of myofibrils) may account for as much as 35% of familial HCM. All the known genetic myosin defects have proved to be missense mutations. Certain myosin mutations appear to carry more serious prognostic implications than others; some may be associated with a largely benign clinical course and near-normal life expectancy (eg, Val606Met),3,4,7,18 whereas others have been reported in a relatively small number of families showing decreased survival either due to sudden catastrophic events or due to heart failure (eg, Arg403Gln, Arg453Cys, Arg719Trp).3,4,7,18,19
Cardiac troponin T mutations\textsuperscript{8–11} account for an estimated 10\% to 20\% of familial HCM. Troponin T binds the troponin complex to tropomyosin and plays a major role in calcium regulation of cardiac contraction and relaxation. Several gene defects have been identified, including missense mutations and small deletions. Despite this diversity, the clinical manifestations of HCM associated with the 8 reported cardiac troponin T mutations are similar. Left ventricular hypertrophy has been described as relatively mild (subclinical in some adults), and life expectancy appears to be reduced.

Mutations in the gene for \( \alpha \)-tropomyosin, \textsuperscript{8,10,12,13,106} a thin filament component of the sarcomere that bridges troponin complex and actin filaments, are uncommon. In contrast to other genes that cause HCM, families with \( \alpha \)-tropomyosin thus far have demonstrated identical Asp175Asn mutations in which a hot spot with increased susceptibility to mutation has been observed at the nucleotide guanine residue 579.\textsuperscript{13} The few \( \alpha \)-tropomyosin pedigrees identified have shown favorable, near-normal life expectancies and great variability in phenotypic appearance.

Mutations in the gene for myosin-binding protein C\textsuperscript{14–17,28} (a structural component of the sarcomere that does not participate in contractile function) may account for an estimated 20\% or more of familial HCM. This gene defect appears to be associated with a relatively favorable clinical course, as well as a substantial proportion of genetically affected adults without phenotypic evidence of the disease on echocardiogram, ie, with normal wall thicknesses in each segment of the left ventricle and often with a normal 12-lead ECG.\textsuperscript{28} In addition, a pattern is evident that is suggestive of penetrance increasing with age, in which the initial phenotypic appearance of left ventricular hypertrophy may occur later in adulthood.

Although several disease-causing mutations have been defined for HCM, the clinical consequences of these gene defects and their contribution to disease incidence are not completely understood at present. All the gene defects taken together account for about two thirds of the pedigrees subjected to genotyping; however, other mutations involving additional genes that cause HCM await identification. For example, mutations in a gene on chromosome 7 remain to be defined.\textsuperscript{24} Indeed, it is possible that many other proteins implicated in filament assembly could account for familial HCM at other loci. Nevertheless, the fact that all disease-causing mutations for HCM defined to date involve genes that encode proteins of the cardiac sarcomere represents a unifying principle to explain the basic etiologic mechanisms responsible for this condition and, at present, permits us to regard this diverse clinical spectrum as a single disease entity and primary disorder of the sarcomere.

Although the aforementioned mutations are regarded as causing HCM, many of the primary structural abnormalities expressed as part of the disease phenotype do not substantially involve sarcomere proteins. These include mitral valve enlargement and elongation, anomalous papillary muscle insertion directly into the anterior mitral leaflet, abnormal intramural coronary arteries with thickened walls and narrowed lumen, and an increased volume fraction of the collagen matrix.\textsuperscript{86–88,90–92} Those observations, as well as recognition that much or most of the left ventricular wall is not involved by the hypertrophic process in many patients with HCM\textsuperscript{83,90} and that patterns of hypertrophy vary greatly within families,\textsuperscript{13,89} suggest that penetrance and variability in phenotypic expression are influenced importantly by factors other than the mutant genes, eg, modifier genes (such as angiotensin-I converting enzyme genotype DD)\textsuperscript{90,108} or environmental variables, including acquired traits such as lifestyle and exercise patterns.

**Conclusions**

In most affected adult patients, the diagnosis of HCM is most easily and reliably established by clinical examination, including careful 2-dimensional echocardiographic imaging. In those instances in which the clinical diagnosis is certain, establishing the precise genetic defect responsible for this disease by DNA analysis represents only a diagnostic confirmation. Nevertheless, molecular studies have the potential to enhance diagnostic reliability in HCM. Genotyping can play an important role in resolving ambiguous diagnoses, such as in subjects with a borderline or modest increase in left ventricular wall thickness, including some trained athletes with ventricular hypertrophy, and in patients with systemic hypertension who are suspected of having HCM.

In addition, the availability of DNA-based diagnosis has led to the identification of increasing numbers of children and adults with a preclinical diagnosis of HCM, usually in the context of genetic testing in selected pedigrees. These individuals have a disease-causing genetic mutation but no clinical or phenotypic manifestations of HCM such as left ventricular wall thickening on echocardiogram or cardiac symptoms (a variety of alterations, however, may be evident on the 12-lead ECG). On the basis of the available data, it appears likely that most such genotype-positive, phenotype-negative children will develop left ventricular hypertrophy while achieving full body growth and maturation.

The lack of phenotypic expression of left ventricular hypertrophy in genetically affected adults appears to be relatively uncommon and is largely confined to nonmyosin mutations, such as those reported in cardiac troponin T and particularly myosin-binding protein C. The frequency or timing with which these adults may subsequently develop the HCM phenotype is unknown. At present, there is no available evidence to justify precluding such genotype-positive, phenotype-negative individuals from most employment opportunities or life activities; however, a family history of frequent HCM-related death or the documentation of a particularly malignant genotype may justify efforts at risk stratification and possible restriction from competitive sports.

**Long-QT Syndrome**

**Clinical Diagnosis (Phenotype)**

The long-QT syndrome (LQTS; Romano-Ward)\textsuperscript{90,110} is an uncommon familial disease transmitted as an autosomal dominant trait, causing a predisposition to syncpe and sudden cardiac death (often related to emotional or physical stress, vigorous activity, or arousal stimuli). Sudden collapse is mediated through ventricular tachyarrhythmias such as polymorphic ventricular tachycardia (torsade de pointes) and ventricular fibrillation.\textsuperscript{29,111–113} The principal diagnostic and...
phenotypic hallmark of LQTS is abnormal prolongation of ventricular repolarization, measured as lengthening of the QT interval on the 12-lead ECG. This is usually most easily identified in lead II or V5, V6, or V3, but all 12 leads should be examined and the longest QT interval used; care should also be taken to exclude the U wave from the QT measurement. At present, manual measurement of QT interval is preferred over automated techniques because of the difficulties in detecting the end of the T wave that are commonly encountered in this disease. The QT interval should be adjusted for heart rate according to the Bazett formula (the QTc).

Other ECG alterations in LQTS include bradycardia, increased QT dispersion, and a variety of T-wave abnormalities in ion channel function are likely to contribute to electrophysiological instability. Indeed, it is now an aspiration to focus potential treatment strategies for LQTS.

Molecular Diagnosis (Genotype)

Since 1991, intensive laboratory investigation and a number of published reports have established LQTS to be a molecular structural disease with substantial genetic heterogeneity as well as complex pathophysiology involving several ionic currents. At present, 4 mutant genes encoding proteins of the cardiac ion channels have been identified as responsible for LQTS; a fifth locus on chromosome 4 has been reported, but this gene has not yet been identified. These mutant genes are believed to account for more than half of all patients with LQTS, and undoubtedly additional genes will be identified to explain the remaining patients affected with this disorder.

The first reported LQTS locus, on chromosome 11, responsible for ≈50% of genotyped LQTS cases, has now been established as a mutant KVLQTI gene, which encodes for the cardiac ion channel IKr. Approximately 40% of genotyped families have mutations of the α-subunit of the HERG gene on chromosome 7, which encodes for the cardiac potassium ion channel IKr. A small proportion of families (≈5%) have mutations of the sodium ion channel SCN5A gene on chromosome 3. A small proportion of families (≈5%) have mutations of the sodium ion channel SCN5A gene on chromosome 3.

<table>
<thead>
<tr>
<th>Table 1. LQTS Diagnostic Criteria*</th>
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<tr>
<td><strong>ECG findings</strong>†</td>
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<tr>
<td>A. QTc ≥480 ms1/2</td>
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<tr>
<td>460–470 ms1/2</td>
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<tr>
<td>450 ms1/2 (in males)</td>
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<tr>
<td>B. Torsade de pointes</td>
</tr>
<tr>
<td>C. T-wave alternans</td>
</tr>
<tr>
<td>D. Notched T wave in 3 leads</td>
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<tr>
<td>E. Low heart rate for age‡</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
</tr>
<tr>
<td>A. Syncope</td>
</tr>
<tr>
<td>With stress</td>
</tr>
<tr>
<td>Without stress</td>
</tr>
<tr>
<td>B. Congenital deafness</td>
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<tr>
<td><strong>Family history</strong></td>
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<tr>
<td>A. Family members with definite LQTS§</td>
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<tr>
<td>B. Unexplained sudden cardiac death &lt;30 years among immediate family members</td>
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Scoring: ≤1 point, low probability of LQTS; 2 to 3 points, intermediate probability of LQTS; ≥4 points, high probability of LQTS.

From Schwartz et al. In the absence of medications or disorders known to affect these electrocardiographic features. Resting heart rate below the second percentile for age. Definite LQTS is defined by an LQTS score ≥4.

In conclusion, LQTS is frequently unrecognized clinically, but it is an acknowledged cause of sudden death in young, apparently healthy people, including competitive athletes; indeed, because LQTS is unassociated with anatomic cardiac markers identifiable during life or at autopsy, its impact as a cause of premature death is probably underestimated. Even when a 12-lead ECG is available for interpretation, measurement of the QT-interval duration is subject to technical imprecision and interobserver and spontaneous variability, as well as the effects of age, sex, electrolyte alterations, central nervous system disorders, and certain drugs. These practical obstacles to reliable ECG measurement often make clinical identification of the LQTS phenotype difficult and sometimes elusive.

Diagnosis is easily confirmed when the QTc is markedly increased (eg, ≥0.50 seconds), but often QTc values are more modestly prolonged. Indeed, LQTS identification on ECG is often unavoidably based on small differences in the quantitative measurement of QT-interval duration. The “cut-off” value most commonly used previously to define an abnormally prolonged QTc interval was >0.44 seconds, but more recent genotype-phenotype correlations indicate ≥0.46 seconds to be more appropriate. In an effort to enhance diagnostic reliability, an elaborate point score system has been proposed that goes beyond QTc duration, incorporating other hallmarks of LQTS such as syncope and a family history of this condition (Table 1).
LQTS toward rectification of specific ion channel abnormalities.

Substantial intragenic heterogeneity has been established for LQTS, with >30 total mutations (mostly missense) now described in ~40 families, among which 1 mutational hot spot has been observed in HERG.234 Nevertheless, the recognition that mutations in 4 genes encode proteins formulating the cardiac sodium and potassium ion channels has provided fundamental insights into the genesis of arrhythmias. In addition, these observations have established a unifying concept for the etiology and pathophysiology of LQTS as a sarcolemmal ion channel defect affecting repolarization.30–33 This is similar to the circumstance that has evolved for HCM, in which the identification of several mutant genes encoding proteins of the cardiac sarcomere has created a working etiologic hypothesis.1,3,4,7,8,13–16

Of particular note is the observation derived from genetic linkage analysis studies in LQTS pedigrees that a wide range in QTc values occurs in individual family members as a consequence of gene mutations. Indeed, ~40% of chromosome 7 and 11 gene carriers show QTc values (0.41 to 0.47 seconds) that overlap with noncarriers.29 In this QTc range, phenotypic diagnosis from the ECG becomes imprecise. This segment of the LQTS population includes a subgroup (comprising 5% to 15% of all gene carriers), the majority of whom are males, who show false-negative QTc values of ≈0.44 seconds.29 Consequently, on the basis of molecular genetic studies, it is reasonable to conclude that QTc is not completely sensitive or specific for LQTS. When QTc ≥0.46 seconds is used, the positive predictive accuracy for QTc in LQTS is 96% in women and 91% in men; almost 100% positive predictive accuracy for LQTS can be achieved at QTc ≥0.47 seconds in males and QTc ≥0.48 seconds in females, in the absence of drugs or other conditions that independently lengthen QT interval. Negative predictive accuracy of almost 100% is present with a QTc ≤0.41 seconds in males and ≤0.44 seconds in females.29

Risk for adverse cardiac events appears to increase with greater QTc values, and patients with the most substantial QT prolongation (QTc >0.50 seconds) are those with the highest risk for subsequent cardiac events, including sudden death.112 Although the precise risks assumed by LQTS individuals with normal or borderline QTc intervals are unresolved, their clinical course is not necessarily innocent, because syncope and sudden cardiac death have occurred in some of these patients. Of note, in subjects with normal to borderline QTc, provocative tests such as treadmill or bicycle exercise115 and isoproterenol or epinephrine infusion have been advocated by some clinicians to provide an additional measure of resolution to an otherwise equivocal clinical diagnosis. However, this testing has not yet been validated for the diagnosis of LQTS in all patients. For example, patients with the SCN5A genotype appear to have a different response to exercise than those with the potassium ion genotypes.

Conclusions
Molecular diagnosis affords the potential to enhance diagnostic reliability in LQTS. The role for DNA diagnosis in this disease is substantial given the number of inherent difficulties that exist in identifying the LQTS phenotype solely from measurement of QT-interval duration on 12-lead ECG. Available genotype-phenotype correlations in LQTS show that a normal QTc does not exclude LQTS. Indeed, clinical diagnosis with measurement of QTc may be uncertain in as many as 50% of family members when false-negative, false-positive, and borderline values are combined. It is this substantial proportion of relatives in LQTS families for whom molecular diagnosis would potentially be most informative. Indeed, gene carriers with false-negative or ambiguous phenotypic diagnosis of LQTS are at some risk for clinical events. On the other hand, a false-positive clinical diagnosis may create unnecessary anxiety or result in inappropriate therapy. However, given the marked genetic heterogeneity of LQTS involving ≥5 genes and a multitude of mutations (and the expectation of even greater heterogeneity, with many mutations unique to single families or rarely found in other pedigrees), the possibility of comprehensive screening for LQTS genetic defects seems particularly difficult.

Marfan Syndrome
Clinical Diagnosis (Phenotype)
Marfan syndrome (MFS) is a systemic connective tissue disorder with autosomal dominant inheritance, first described in 1896 by Antoine Marfan.125 Life expectancy may be reduced, usually due to involvement of the cardiovascular system with progressive aortic root dilatation, dissection and rupture, or valvular regurgitation.126–133

Classically, the clinical diagnosis of MFS has been made on the basis of certain well-recognized and overt physical manifestations, most prominently involving the skeletal, ocular, and cardiovascular systems.57,126–129 In addition, the advent of echocardiography in the 1970s made identification of structural and functional cardiovascular abnormalities such as aortic dilatation, mitral valve prolapse, and valvular regurgitation much more accessible. Awareness of the true breadth of the MFS clinical spectrum has gradually evolved, and it is now obvious that not all affected individuals show classic features of the disease, that a diverse and complex constellation of abnormalities that are variable in severity (but difficult to measure) is consistent with this vast clinical continuum, and that many of the physical findings attributable to this disease are subtle or commonly encountered in the general population.

As a consequence of such variability in expression and diagnostic complexities, expert international panels have been convened on 2 recent occasions to clarify the criteria necessary for reliable identification of MFS.134,135 The Berlin nosology developed in 1988 was the first concerted effort to address this issue.134 Modifications proposed in the more recent Ghent criteria of 1996135 attempt to decrease the rate of false-positive diagnosis by increasing the quantity and specificity of the physical manifestations needed for diagnosis when a positive family history is present. The Ghent formula for the clinical diagnosis of MFS uses major and minor diagnostic criteria for each organ system135 (Table 2). The most prominent major criteria (ie, with high diagnostic specificity due to infrequent occurrence in other
TABLE 2. Requirements for Diagnosis of Marfan Syndrome (Ghent Criteria)*

For the index case:
- If the family/genetic history is not contributory, major criteria in ≥2 different organ systems and involvement of a third organ system.
- If a mutation known to cause Marfan syndrome in others is detected, 1 major criterion in an organ system and involvement of a second organ system.

For a relative of an index case:
- Presence of a major criterion in the family history, 1 major criterion in an organ system, and involvement of a second organ system.

Skeletal System

**Major Criterion** (Presence of ≥4 of the following manifestations is necessary to satisfy a major criterion):
- Pectus carinatum
- Pectus excavatum requiring surgery
- Reduced upper- to lower-segment ratio or arm span-to-height ratio >1.05
- Wrist and thumb signs
- Scoliosis of >20° or spondylolisthesis
- Reduced extension at the elbows (<170°)
- Medial displacement of the medial malleolus causing pes planus
- Protrusio acetabulae of any degree (ascertained on radiographs)

**Minor Criteria**
- Pectus excavatum of moderate severity
- Joint hypermobility
- Highly arched palate with crowding of teeth
- Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)

For the skeletal system to be considered involved, at least 2 of the components comprising the major criterion or 1 component comprising the major criterion plus 2 of the minor criteria must be present.

Ocular System

**Major Criterion**
- Ectopia lentis

**Minor Criteria**
- Abnormally flat cornea
- Increased axial length of globe
- Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

For the ocular system to be involved, at least 2 of the minor criteria must be present.

Cardiovascular System

**Major Criteria**
- Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva; or
- Dissection of the ascending aorta

**Minor Criteria**
- Mitral valve prolapse with or without mitral valve regurgitation;
- Dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, younger than age 40;
- Calcification of the mitral anulus younger than age 40; or
- Dilatation or dissection of the descending thoracic or abdominal aorta younger than age 50.

For the cardiovascular system to be involved, 1 major criterion or only 1 of the minor criteria must be present.

Pulmonary System

**Major Criteria**
- None

**Minor Criteria**
- Spontaneous pneumothorax; or
- Apical blebs

For the pulmonary system to be involved, 1 of the minor criteria must be present.

Skin and Integument

**Major Criteria**
- None

**Minor Criteria**
- Striae atrophicae (stretch marks) not associated with marked weight gain, pregnancy, or repetitive stress; or
- Recurrent or incisional herniae

For the skin and integument to be involved, 1 of the minor criteria must be present.

Dura

**Major Criterion**
- Lumbosacral dural ectasia by CT or MRI

**Minor Criteria**
- None

For the dura to be involved, the major criterion must be present.

Family/Genetic History

**Major Criteria**
- Having a parent, child, or sibling who meets these diagnostic criteria independently;
- Presence of a mutation in FBN-1 known to cause MFS; or
- Presence of a haplotype around FBN-1, inherited by descent, known to be associated with unequivocally diagnosed MFS in the family.

**Minor Criteria**
- None

For the family/genetic history to be contributory, 1 of the major criteria must be present.

*From De Paepe et al. 135*
conditions and in the general population) are as follows: a constellation of skeletal manifestations, including pectus carinatum or excavatum, reduced upper- to lower-segment ratio, or arm-span-to-height ratio >1.05, scoliosis, and reduced elbow extension; ectopia lentis; dilatation or dissection of the ascending aorta; lumbosacral dural ectasia; and inheritance of a genotype previously associated with classic MFS or an unequivocal family history.

Accurate identification of MFS has important implications from a number of clinical perspectives, particularly regarding prophylactic medication, surgery, and lifestyle restrictions. Consequently, a false-negative diagnosis is associated with certain clinical risks. Furthermore, because a diagnosis of MFS confers a variety of social, occupational, psychological, and economic consequences, a false-positive diagnosis also has unfavorable implications. Of note, the diagnosis of MFS may be facilitated by the consultative efforts of a clinical geneticist.

**Molecular Diagnosis (Genotype)**

The primary defect responsible for MFS, first described in 1991, resides in a gene (FBN1) localized to the long arm of chromosome 15 encoding the connective tissue protein fibrillin-1. Fibrillin is a structural glycoprotein component of microfibrils, which are extracellular components that participate in the formation of mature elastic fibers and which serve structural functions independent of elastin.

Linkage analysis has shown no locus heterogeneity for MFS; the cause-and-effect relation with the clinical Marfan phenotype has been confined to fibrillin mutations. Nevertheless, substantial allelic heterogeneity is evident, with 125 reported and unreported individual mutations (of several types, but mostly of the missense variety); nearly every genotyped family has a unique mutation in the fibrillin gene, with the most common single mutation identified in just 4 unrelated pedigrees. This intragenic heterogeneity and the large size of the gene have precluded the routine screening of mutations to establish the diagnosis of MFS.

Although patients with unequivocal phenotypic manifestations of MFS show FBN1 mutations, such gene defects have also been identified in individuals (or entire pedigrees) who do not satisfy contemporary diagnostic criteria for the Marfan phenotype or in patients with related but non-Marfan genetic syndromes. At present, subjects are not regarded as affected by MFS in the absence of proven MFS in another family member, and consequently such gene defects are of uncertain clinical significance. Ultimately, the greatest use of molecular testing will be to determine whether an individual with the potential to develop symptoms or die suddenly has inherited the genetic predisposition to develop the same Marfan phenotype unequivocally documented in other family members.

**Conclusions**

MFS fundamentally remains a clinical diagnosis, although in many instances this assessment is fraught with considerable difficulty and imprecision. No available genetic test can provide, in isolation, an unequivocal assignment of either affected or unaffected status for MFS.

Furthermore, the vast array of mutations in the fibrillin gene has made genotype-phenotype correlations unrewarding. Therefore, at present, genetic testing for MFS can only be regarded as an adjunct to diagnosis; when available, molecular data can be considered in conjunction with an assessment of the MFS phenotype and assimilated into the ultimate diagnostic assignment.

**Future Considerations for Molecular Diagnosis**

Availability of laboratory DNA-based diagnosis of certain genetically transmitted cardiovascular diseases has influenced the landscape of clinical diagnosis. The historical evolution of molecular biology over the last decade with regard to HCM, LQTS, and MFS has progressed from the identification of the first genetic defect to a much more complex phase in which substantial genetic heterogeneity has become increasingly obvious. In each instance, the molecular biology investigation has been performed at a few academic research laboratories with a particular interest in identifying new genes responsible for these diseases. However, the variety of different mutations now apparent in HCM, LQTS, and MFS, coupled with the time-intensive, demanding, and expensive techniques required for genetic analysis (as well as competing priorities for individual investigations), has created a circumstance in which the available resources of the few involved laboratories have become overwhelmed. Therefore, at present, DNA diagnosis of cardiovascular diseases permits only research-oriented genotyping of selected pedigrees and is not routinely available for clinical practice.

Consequently, we are in a period in which access to clinically relevant genetic diagnosis is limited. The impetus to produce widely available DNA diagnosis for patients with cardiovascular disease will probably require support from the commercial sector or governmental programs. Further initiatives will undoubtedly be focused on developing automated screening methods for rapid identification of known genetic mutations. Such direct mutational analysis would circumvent the classic but time-consuming methodology of linkage analysis, which requires detailed study of multiple relatives in large, informative pedigrees. Until these issues are resolved, diagnosis in the vast majority of patients with HCM, LQTS, and MFS will continue to be made largely by conventional clinical examination, usually with the aid of noninvasive testing, and in association with laboratory genetic analysis when such testing is selectively available and appropriate.

**Ethical Considerations**

A number of complex and sensitive ethical questions have arisen by virtue of the explosion of patient-related genetic data in many areas of medicine, including those cardiovascular diseases under discussion herein. The potential concerns, pitfalls, and risks implicit in the results of genetic testing include the following: (1) discrimination in employment or other life activities and in health, life, and disability insurance; (2) psychosocial difficulties and anxiety created by virtue of having a genetic disease; (3) ambiguity regarding
whether genetically affected subjects without phenotypic expression should be regarded as having cardiovascular disease solely on the basis of a molecular abnormality; and (4) the unresolved clinical significance of certain genetic laboratory data, particularly when effective preventive measures are lacking. The concern about inadvertently stigmatizing individuals and groups of patients through identification of genetic defects must be weighed against the perspective that a society founded on personal freedom and responsibility has the inherent responsibility to create a fully informed public, including those individuals with potentially relevant mutations.

Therefore, ethical considerations relevant to the diagnoses of the 3 familial cardiovascular disorders under discussion herein should be viewed with respect to these issues. First, because sufficient diagnostic findings are usually already evident clinically, the ethical implications of a molecular diagnosis such as MFS (and in many instances, HCM or LQTS) are not great and do not seem to differ substantially from those in the premolecular era for these patients. In such instances, the molecular DNA diagnosis is only confirmatory of the clinical diagnosis. Schools, employers, and insurance companies will have access to such information, if released by the patient or family.

We acknowledge, however, certain ambiguous areas related to genetic testing data in patients with HCM, LQTS, and MFS. Identifying a gene mutation in family members without overt phenotypic evidence of a disease usually provides information for which, at present, the clinical consequences are unresolved. For example, recognition of a disease-causing HCM mutation in a child or adult without left ventricular hypertrophy (or, similarly, a mutation in a member of a family with LQTS and normal QT interval) does not per se have obvious therapeutic implications, nor are the risks for adverse consequences known with certainty. There is also the potential for misapplication of such data, whereby aggressive therapeutic interventions (eg, implantable cardioverter-defibrillator) are recommended to young people when such treatment may be unwarranted.

This gap between our ability to test for a mutation and subsequently apply these data in a clinical context creates psychosocial and ethical complexities. In clinical practice, concerns may arise when a genetic test is obtained if the facts by which the results of that test may be interpreted are lacking. The criteria used to determine whether a diagnostic genetic test is appropriate in this context depend on its potential to benefit the patient in his or her lifetime to an equal or greater extent than other tests that are proposed.

Therefore, when subjects without overt evidence of cardiac disease agree to enter a research protocol for the purpose of pedigree genotyping, they should do so with sufficient informed consent in collaboration with the physician and/or genetic counselor. The patient and family should be counseled in advance regarding any limitations of test result interpretation and advised not to embark on genetic testing if they do not wish to know the results. If information gleaned from genetic testing is not of use in patient management strategies, this should be stated clearly and discussed with the patient within the context of the doctor-patient relationship and informed consent.

Indeed, there is a potential risk for patients in interpreting genetic data without access to formal counseling. In the case of minor children, the situations can be more complex. However, because substantial medical benefit can accrue to the young person if the diagnosis is certain, the parents should ultimately be responsible for this decision-making process, although the competent adolescent should be approached for consent. These ethical issues arising in the context of genetic cardiovascular diseases are perhaps not unlike some aspects of the debate currently evolving over BRCA mutations and the risk for breast and ovarian cancer.

As molecular technology improves, laboratory testing for genetic markers will become more available, and third parties (such as employers and insurance carriers) will request genetic information with increasing frequency. The number of genetically affected individuals with little or no phenotypic evidence of disease is likely to increase considerably, and such testing may be extended for the purpose of stratifying the risk for premature death in family members. However, there does not appear to be an obligation to provide such genetic information, obtained largely for investigative scientific purposes, to employers or to agencies such as schools, insurance carriers, and the military unless specifically requested by the patient and/or family. Indeed, genetic information can elicit powerful reactions, and even an unproven perception of high-risk status may, for example, jeopardize access to health insurance. However, some states have placed limits on discriminatory practices in health insurance, and pending federal legislation holds promise for greatly reducing such concerns for all citizens. All these perspectives may well evolve over time as we come to a better understanding of the clinical significance and implications of the specific gene defects in diseases such as HCM, LQTS, and MFS.

Final Perspectives

Hypertrophic cardiomyopathy, long-QT syndrome, and Marfan syndrome are each inherited as a mendelian autosomal dominant trait and demonstrate variable penetrance and expressivity. Although they are relatively uncommon in the general population, each not infrequently confers a predisposition for unexpected sudden cardiac death in the young. Over the past 8 to 10 years, the application of molecular biology and DNA-based technology to the study of genetically transmitted cardiovascular diseases has provided a measure of diagnostic clarification. Nevertheless, at present, most adult patients with these conditions can still be identified reliably by standard clinical diagnostic techniques.

By virtue of linkage or mutational analysis in selected pedigrees, genetically affected but phenotypically normal relatives have been identified, particularly within the HCM and LQTS disease spectrums. Indeed, it is the substantial proportion of relatives in LQTS families with borderline (or normal) QTc values for whom molecular diagnosis would potentially be most informative. Nevertheless, the precise clinical significance of these patient subsets with little or no phenotypic evidence of disease is currently uncertain, and longitudinal clinical data will be required to more definitively clarify the extent to which such
individuals ultimately evolve clinically overt disease manifestations and experience adverse cardiac events.

At present, the clinical utility of genetic testing for HCM, LQTS, and MFS is hampered by their substantial allelic heterogeneity and the time-intensive and costly nature of laboratory genotyping. Future initiatives directed toward molecular diagnosis of HCM, LQTS, and MFS will likely result from improved technology, gene sequencing, and the development of automated screening methods for more rapid identification of mutations. Such direct mutational analysis would have the distinct advantage of obviating the complex and time-consuming process of classic linkage analysis. In addition, with increased understanding of genetic mechanisms, it may be possible to target therapy to mitigate genetic defects or conceivably to correct molecular abnormalities. However, given the large number of genes and mutations already evident in HCM, LQTS, and MFS (and the realistic expectation for additional diversity), the future design of comprehensive molecular screening tests and therapy for these genetic cardiovascular diseases will continue to be a challenge.

Glossary
1. **Autosomal**: Mode of inheritance that is not sex linked.
2. **Chromosomes**: Morphologically distinctive nuclear structures, species specific in number and shape; assemblies of transcription units made up of DNA, RNA, and proteins that are precisely duplicated during cell division.
3. **Dominant**: Inheritance is dominant when the expected phenotype is expressed in the heterozygous state.
4. **Gene**: All nucleic acid sequences that are necessary to produce a peptide or an RNA; includes not only the coding sequences but also the regulatory sequences.
5. **Genotype**: The genetic constitution of an individual in terms of DNA sequences; genotyping an individual consists of studying the individual’s DNA sequence at a genetic position of interest.
6. **Linkage (genetic)**: Cosegregation of several alleles owing to their physical proximity; linkage analysis is a method of analysis of inheritance based on the search of a disease locus using markers.
7. **Locus**: Location, place where a gene is found.
8. **Mutation**: Change in a DNA sequence, most often used to qualify a change in the sequence of a gene.
9. **Phenotype**: Observable characteristics of an organism resulting from genomic expression, including morphological features, physiological properties, clinical syndromes, or proteins.
10. **Autosomal dominant**: The type of inheritance that is not sex linked; the mutant gene produces the phenotype in the heterozygous state, and the offspring of the affected individual are expected to receive the abnormal gene in 50% of cases.
11. **Genetic heterogeneity**: A disease has genetic heterogeneity when multiple different genes produce a similar clinical phenotype.
12. **Mutant gene**: A gene is considered to be mutated (ie, mutant) when a DNA sequence change occurs that changes the amino acid sequence of the encoded protein. The term is usually used when describing the genetic causes of a disease.
13. **Modifier gene**: A gene that affects another gene to modify the expression of that gene.
14. **Ion channel**: A channel through which ions, such as potassium (ie, potassium channel), sodium, calcium, or chloride ions, pass from 1 side of the membrane to the other side.
15. **Missense mutation**: A mutation in which the codon is mutated to direct the incorporation of a different amino acid; usually this is a single nucleotide change that changes the 3 nucleotide codons encoding 1 amino acid (the “normal” amino acid) into a codon encoding a different amino acid, hence changing the protein structure of the gene product.

References


Contemporary Diagnosis of Genetically Transmitted CVD


81. Abstract.


Impact of Laboratory Molecular Diagnosis on Contemporary Diagnostic Criteria for Genetically Transmitted Cardiovascular Diseases: Hypertrophic Cardiomyopathy, Long-QT Syndrome, and Marfan Syndrome: A Statement for Healthcare Professionals From the Councils on Clinical Cardiology, Cardiovascular Disease in the Young, and Basic Science, American Heart Association

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