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# Genetics and cardiomyopathy: Where are we now?

## ■ ABSTRACT

Many cases of cardiomyopathy have a genetic component: 90% of cases of hypertrophic cardiomyopathy are familial, and genetic factors may be responsible for 30% to 50% of cases of dilated cardiomyopathy. Clinical genetic testing for hypertrophic cardiomyopathy is becoming available, with significant implications for the clinician. This article gives an overview of how these genetic discoveries were made and how these new insights from genetics will affect clinical practice.

## ■ KEY POINTS

First-degree relatives of patients with hypertrophic cardiomyopathy or idiopathic dilated cardiomyopathy should undergo regular screening with electrocardiography and echocardiography.

A trained clinical genetic counselor should see the patient and obtain informed consent before genetic testing, as the legal and insurance implications of genetic testing are still evolving.

When a mutation that causes one of the cardiomyopathies is identified in a particular family, a negative test in a family member has excellent negative predictive value, while a positive test confirms the genetic diagnosis in borderline cases.

Routine clinical investigation is still the best way to stratify risk and to plan treatment.

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**G**ENETIC DISCOVERIES over the last decade have changed our understanding of the cardiomyopathies but are only beginning to change our clinical practice.

Although the underlying genetic causes of a number of these disorders have now been identified, routine genetic screening is available in only a few centers worldwide, and only for specific targeted genes for hypertrophic cardiomyopathy.

Then there is the question of what to do with the knowledge gained from the test. A simple, predictable genotype-phenotype correlation for a particular mutation has not proved clinically reliable in most cases, and the clinician must fall back on traditional clinical observations to calculate the risk for sudden death or other complications.

This article is designed to give the clinician an overview of the developments of the last decade, the terminology involved in genetics, and implications for clinical practice.

## ■ FOUR TYPES

Primary cardiomyopathies have been described as heart-muscle diseases of unknown cause.<sup>1</sup> There are four types (TABLE 1):

- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy
- Restrictive cardiomyopathy

These disorders are major causes of sudden cardiac death, heart failure, and need for cardiac transplantation. Population-based studies suggest that their prevalence is higher than clinically reported.<sup>2</sup>

Many cases have a genetic component.

TABLE 1

### Characteristics and prevalence of the cardiomyopathies vs hypertension, a common cardiovascular condition

DISORDER	PRESENTING SYMPTOMS	ECHOCARDIOGRAPHIC FINDINGS	PREVALENCE	GENE IDENTIFIED
<b>Hypertrophic cardiomyopathy</b>	Chest pain Arrhythmias Dyspnea	LV hypertrophy	1:500	10 genes, > 200 mutations
<b>Dilated cardiomyopathy</b>	Heart failure Arrhythmias	RV or LV dilatation	1:2,500	15 genes, > 20 mutations
<b>Arrhythmogenic RV cardiomyopathy</b>	Arrhythmias Heart failure	RV dilatation and dysfunction	1:1,000 to 1:5,000?	3 genes, > 8 mutations
<b>Restrictive cardiomyopathy</b>	Dyspnea Heart failure	LV stiffness Enlarged atria	Unknown	1 gene, 5 mutations
<b>Systemic hypertension</b>	Hypertension Dyspnea	Can cause LV hypertrophy	1:4	Mostly complex traits

LV = left ventricular, RV = right ventricular

**30% to 50% of cases of dilated cardiomyopathy are familial**

For example, 30% to 50% of cases of dilated cardiomyopathy are familial. Since the early 1990s, disease-causing mutations have been described in genes for myocardial sarcomeric proteins (which give muscle cells their contractile force) and cytoskeletal proteins (which give cells their structure; **FIGURE 1**). These disorders are usually monogenic, ie, with a single gene defect responsible. In contrast, in complex genetic traits such as hypertension, most cases probably result from environmental factors interacting with multiple genes.

#### ■ AN INTRODUCTION TO GENETICS

Genetic techniques developed over the last decade have revolutionized our understanding of the cardiomyopathies. The terminology used in genetics is complex and needs some introduction.

**Linkage analysis** involves studying large families in which at least 10 members have the disease in question. This technique allows geneticists to map a pattern of markers to the family disease, home in on particular small areas of the genome (*loci*) that have a high mathematical probability of containing the disease-causing change, and then directly sequence the area.

The Human Genome Project has sped up this technique somewhat, as each area is now crudely sequenced and geneticists have a better idea on where to focus.

The first breakthroughs in identifying disease-causing mutations in hypertrophic cardiomyopathy were by linkage analysis. For instance, researchers tracking a large Ohio family with a seven-generation pedigree with dilated cardiomyopathy determined that the likely genetic mutation was in chromosome 1, in an area known to contain the lamin A/C gene.<sup>3</sup>

**Candidate gene screening** is a logical extension of this technique, in which likely genes (often related structurally or functionally to previously identified proteins known to be involved in the disease in question) are targeted and sequenced. Thus, in 2000, after mutations in the gene for the sarcomere protein troponin T were identified as being involved in dilated cardiomyopathy,<sup>4</sup> candidate genes for troponin I and troponin C were sequenced as well and found to carry disease-causing mutations for dilated cardiomyopathy.<sup>5,6</sup>

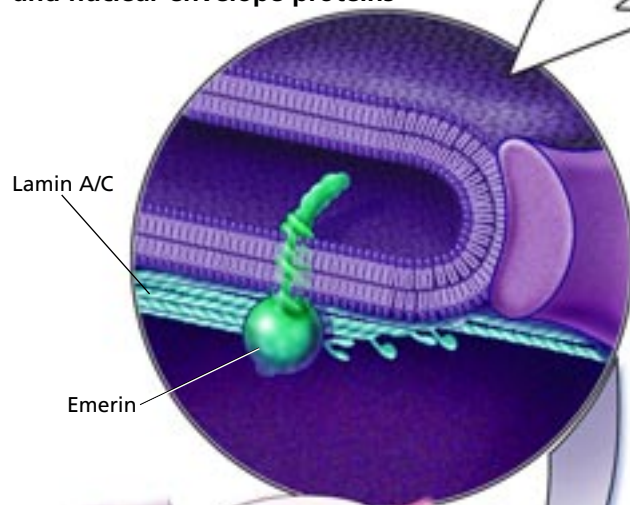
**Direct sequencing** means the detailed description of the exact nucleotide sequence coding for a particular protein. The geneticist needs to amplify the patient's DNA and also



## ■ The molecular basis of cardiomyopathy

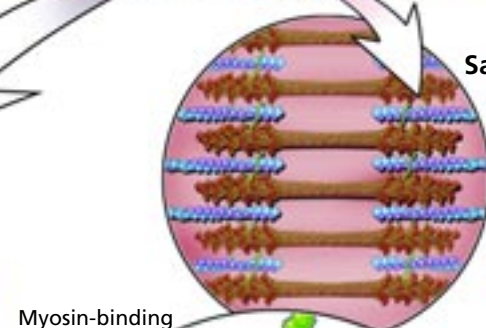
Genetic defects in cardiac proteins have been linked to different forms of cardiomyopathy, but the sheer number of mutations identified, which is rapidly growing, will make routine genetic testing problematic.

**Nuclear wall with cytoskeletal and nuclear envelope proteins**

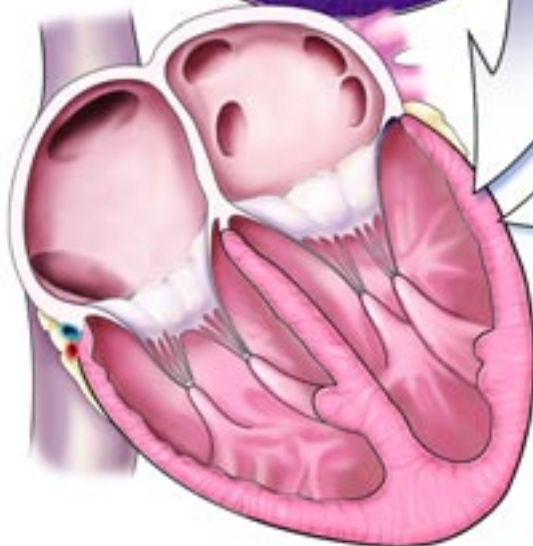
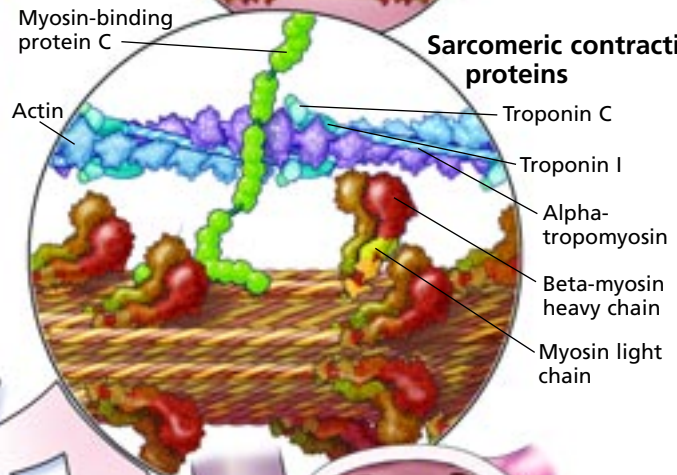


Cardiac cell

Sarcomere



**Sarcomeric contractile proteins**



**Dilated cardiomyopathy** can be caused by defects in cytoskeletal proteins, nuclear envelope proteins, or sarcomeric (contractile) proteins; more than 20 mutations have been identified so far.



**Hypertrophic cardiomyopathy** is caused by defects in sarcomeric contractile proteins; more than 200 mutations have been identified so far.

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FIGURE 1

must know the start and stop areas of each code for each **exon** (or coding section) of the gene. Thus, while the gene for cardiac troponin I has only 8 exons, the larger cardiac structural protein titin has 360 exons, each of which requires a separate amplification and sequencing run per patient. Therefore, it is not currently clinically feasible to directly sequence many of these genes on a regular basis as a clinical service for an individual patient.

A **mutation** is a definite proven disease-causing change in nucleotide sequence of a gene that causes a change in the amino acid sequence of a protein that alters its function or structure or truncates its size to a degree sufficient to be the prime cause of disease. Various types of mutations include *single nucleotide missense mutations*, *truncation* or *stop codon mutations* (in which the nucleotide change happens to signal a stop in the protein sequence at that point, leading to a shortened and dysfunctional protein), and *deletions*, in which a section of the coding sequence is missing, causing the protein to be dysfunctional.

A **polymorphism** in a gene is a sequence change found to varying degrees in the healthy population. Polymorphisms do not cause disease but may modify the response of the patient to a disease or drug or may create a tendency to disease in conjunction with other polymorphisms or environmental factors. For instance, the angiotensin-converting enzyme (ACE) deletion allele (ACE D), found in up to 30% of patients with dilated cardiomyopathy, is not the cause of disease but is associated with reduced survival. Patients with two copies of certain polymorphisms (ie, who are homozygous for them) in the beta-2 adrenergic receptor are at increased risk for hypertension and have increased responsiveness to beta adrenergic stimulation.<sup>7</sup> However, most polymorphisms are probably benign sequence variants—incidental single-nucleotide changes.

#### Proving that a mutation causes disease

Thus, one of the challenges of implementing the new technologies is to differentiate between a definite mutation and a benign polymorphism. Before any mutation can be accepted as causing disease, several proofs are required, including the following:

- Linkage analysis must show a statistically significant likelihood that the area of the gene contains the disease-causing mutation. The likelihood is expressed as a logarithm of odds score, or *Lod score*. A Lod score of more than 3.0 is conventionally taken as significant. The large Ohio family mentioned above<sup>3</sup> generated a Lod score of 13.2.
- The mutation must segregate with disease, ie, over several generations of a family every person who has the clinical disease must have the mutation.
- The mutation must not be present in healthy people. Usually, at least 100 ethnically matched controls must be tested to prove this.
- The protein sequence must have been conserved through evolution, ie, most other species must share the same sequence, demonstrating that the protein generated has such an important function that any mutation did not survive evolution over the long term.
- In laboratory or animal-based assays, the mutated protein must show a change of function.

#### Private mutations complicate screening

The last concept of importance in cardiovascular genetics is the problem of **private mutations**, whereby each family with a cardiomyopathy has its own specific mutation that is unique to that family, or nearly so.

For example, there are 10 sarcomeric proteins in cardiac muscle, but at least 200 different mutations in the 10 genes for these proteins are known to cause hypertrophic cardiomyopathy. This makes screening for a likely mutation very difficult, as each patient must potentially undergo screening of all 10 sarcomere genes for all possible mutations. The situation is even more complex in dilated cardiomyopathy, in which the number of candidate genes is expanding rapidly.

Technological advances are speeding up the process but still do not currently allow for routine genetic testing outside of a few centers worldwide.

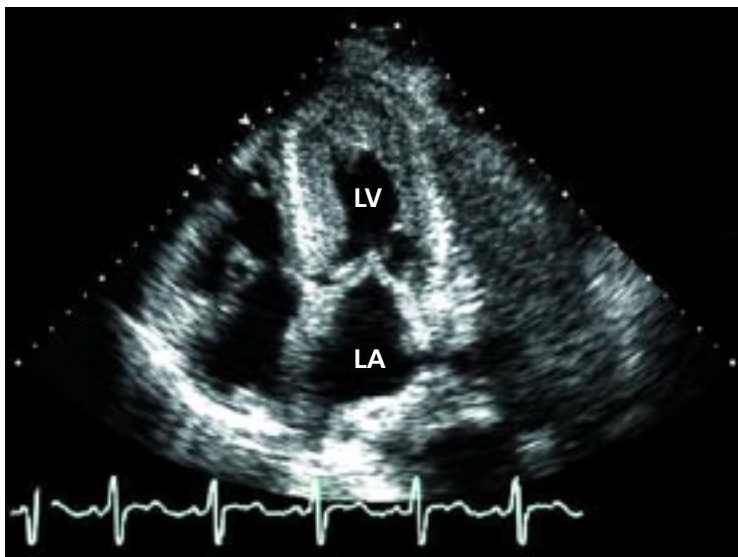
#### ■ CLINICAL VALUE OF A GENETIC TEST

When researchers in one of the large research programs around the country discover a disease-causing mutation in a patient with car-

**To date, more than 200 different hypertrophic cardiomyopathy-causing mutations have been reported**



## Hypertrophic cardiomyopathy



**FIGURE 2.** Two-dimensional transthoracic echocardiographic image in the apical four-chamber view of a patient with hypertrophic cardiomyopathy showing severe left ventricular hypertrophy. LV = left ventricle, LA = left atrium.

### Clinicians need to know the implications of a positive or a negative genetic test

diomyopathy and a family history of cardiomyopathy, it is relatively straightforward to check his or her relatives for that mutation (the family's "private mutation"). Clinicians will be seeing more patients undergoing genetic testing and will need to know the implications of a positive or a negative genetic test. Moreover, once the test moves from a research protocol to the clinical arena, the genetic laboratory needs to be certified and approved, and each family member must receive appropriate genetic counseling on the risks, meaning, and insurance implications of a negative or a positive test. The legal and insurance implications of a genetic diagnosis are still evolving.

A **negative test** is of excellent negative predictive value and reassures the family and clinician that the family disorder will not occur in that individual and will not be transmitted to future generations.

A **positive test** confirms the diagnosis and, in a person without symptoms, mandates continued clinical follow-up with electrocardiography (ECG) and echocardiography. Some gene-positive patients may never develop the disease: clinical penetrance can be as low as 50% for some genes in hypertrophic cardiomyopathy. However, patients who are

gene-positive but asymptomatic may still pass on the gene to the next generation. For advice on how to treat these patients, we need to examine each cardiomyopathy in turn.

### ■ HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is defined clinically as unexplained hypertrophy of the left ventricle.<sup>8,9</sup> The hypertrophy (**FIGURE 2**) is most commonly asymmetric and involves the interventricular septum.

Recent clinical studies have indicated that the prevalence is at least 1:500 in the general population.

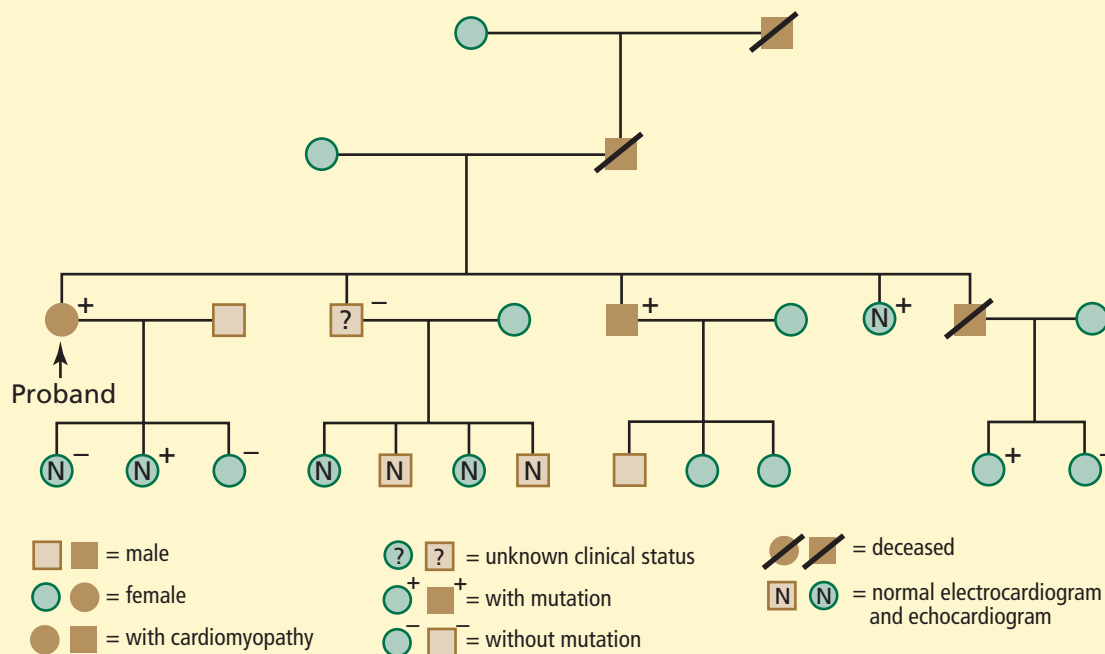
Presenting symptoms can include chest pain, palpitations, or syncope, but the disease can also be asymptomatic and discovered as a result of an incidental finding such as a murmur, eg, during a medical examination for insurance coverage or during clinical evaluation of a family. Tragically, the first sign can be sudden death, and hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in young adults. However, studies from several outpatient-based populations report that the incidence of sudden death in hypertrophic cardiomyopathy is lower than traditionally understood, at approximately 1% per year.

### Most hypertrophic cardiomyopathy is familial

Systemic evaluation of first-degree relatives has revealed that hypertrophic cardiomyopathy is familial in over 90% of cases. The pattern of inheritance is autosomal-dominant; thus, each child has a 50% chance of inheriting the gene. Major advances in mutation identification have been achieved over the last decade in family screening programs.

Hypertrophic cardiomyopathy is caused by mutations in genes for cardiac sarcomeric contractile proteins.<sup>10,11</sup> In adult disease, disease-causing mutations have been identified in the genes for 10 proteins, including beta-myosin heavy-chain, essential and regulatory myosin light-chain, alpha-tropomyosin, cardiac troponin T, troponin I, myosin-binding protein C, and actin. Rarer mutations in alpha-myosin, troponin C, and titin have also been described. To date, more than 200 differ-

## Dilated cardiomyopathy: A familial disease



**FIGURE 3.** A sample four-generation pedigree of a family with autosomal-dominant dilated cardiomyopathy.

ent mutations have been reported since the first genetic mutation was identified in 1989; many of them are private mutations confined to the proband and immediate family. About 10% of cases seem to be nonfamilial (sporadic), but are also caused mostly by sarcomeric protein gene mutations (usually new or “de novo” mutations).

Beta-myosin heavy-chain genetic mutations account for about 40% of adult cases, with more than 50 different mutations described. Cardiac myosin-binding protein C mutations occur in about 30% to 40%, especially in patients with late-onset hypertrophic cardiomyopathy, in whom electrocardiographic or echocardiographic features of hypertrophic cardiomyopathy may not always appear before the age of 40. The other mutations each account for 1% to 15% of adult cases.

The diagnosis of hypertrophic cardiomyopathy in an infant has different genetic implications than in an adult, and storage disorders and metabolic defects predominate in childhood hypertrophic cardiomyopathy. These are genetic defects, but are usually recessive.

### Other causes of adult hypertrophic cardiomyopathy

Though most cases of adult hypertrophic cardiomyopathy are due to sarcomere defects, patients with other disorders may also present with cardiac hypertrophy.

**Friedreich ataxia**, an autosomal-recessive disease involving sclerosis of the spinal cord, is often associated with hypertrophic cardiomyopathy, and its cardiovascular manifestations may precede the neurological symptoms by up to a decade in some cases.

**Noonan syndrome** (male Turner syndrome) is marked by short stature, a webbed neck, ptosis, and hypogonadism along with cardiac hypertrophy.

**Fabry disease** (alpha-galactosidase A deficiency) may account for up to 5% of cases of adult hypertrophic cardiomyopathy. This new observation is important, as Fabry disease is potentially reversible if treated with enzyme replacement therapy.<sup>12</sup> A serum enzyme assay may suffice as a screening test.

**Wolff-Parkinson-White syndrome** with hypertrophic cardiomyopathy, a nonsarco-

**Up to 5% of adult hypertrophic cardiomyopathy cases may be caused by Fabry disease**



mere disease with features of a storage disorder in the myocardium, is caused by mutations in the adenosine monophosphate kinase gene.

### Screening the family for hypertrophic cardiomyopathy

A detailed family pedigree (FIGURE 3) should be drawn up with the family's help, and a trained genetic counselor should be available to offer advice and explain the nature of genetic transmission.

Current best practice (defined by a consensus document from the American College of Cardiology and the European Society of Cardiology)<sup>13</sup> is to screen first-degree relatives of patients with adult-onset hypertrophic cardiomyopathy with ECG and echocardiography every year starting at age 12 and continuing through puberty. Screening is at variable intervals thereafter until early adulthood, by which time the disease should have manifested.

Some families have late-onset hypertrophic cardiomyopathy, and even if normal as young adults, family members are screened every 5 years. Data are limited in infants from families with adult-onset hypertrophic cardiomyopathy, but sudden death is very uncommon in the first decade, and it is not usual to screen children until the age of 12.

The cost-effectiveness of such screening programs has not been established.

By systematic family screening, we have identified severe hypertrophic cardiomyopathy in completely asymptomatic siblings and in middle-aged parents of young adults with hypertrophic cardiomyopathy, so an apparently negative family history is not a good guide. We have also identified gene-positive patients with normal ECGs and echocardiograms or with only subtle ECG changes. These patients clearly have hypertrophic cardiomyopathy in a molecular sense, and should be followed with serial ECGs and echocardiography.

There is no firm evidence that preemptive treatment of gene-positive patients who have asymptomatic or clinically mild hypertrophic cardiomyopathy will improve outcome, but certain families with troponin T defects may have a highly malignant risk of sudden death, and implantable cardioverter-defibrillators have been used prophylactically on a case-by-case basis. In these cases, a gene test helps: a

## Hypertrophic cardiomyopathy at a glance

The risk of inheritance in hypertrophic cardiomyopathy is 50%.

Screening with electrocardiography and echocardiography is recommended for all first-degree relatives of patients with hypertrophic cardiomyopathy.

There are 10 genes, and many private mutations (now > 200).

The genotype-phenotype relationship is not reliable.

Screen for Fabry disease (treat with enzyme replacement therapy).

gene test that confirms a troponin T defect clinches the diagnosis in cases in which minor electrocardiographic and echocardiographic changes do not fulfill current diagnostic criteria and in which the family history makes a firm diagnosis important.

### Genotype-phenotype correlation is not reliable

It was initially thought that specific mutations would predict specific clinical phenotypes—eg, severe left ventricular hypertrophy or asymmetric septal hypertrophy or apical hypertrophic cardiomyopathy—and would allow risk stratification on the basis of a gene test. For instance, it was initially observed that troponin T mutations in hypertrophic cardiomyopathy may be associated with minimal hypertrophy but a high rate of sudden death within affected families.

However, the genetic defects of hypertrophic cardiomyopathy are very variable in their expression, even among people with the same mutation within the same family. Therefore, a fixed predictable genotype-phenotype correlation for a particular mutation has not proved clinically reliable in many cases, and the clinician must fall back on traditional clinical investigations to stratify risk and plan treatment for patients.

It seems that other factors, genetic as well as environmental, must affect the degree of hypertrophy in hypertrophic cardiomyopathy. The primary genetic abnormality may lead to impaired contractility, release of growth factors, and compensatory hypertrophy. But environmental factors such as pressure overload may explain why the left ventricle is

**Screen first-degree relatives of adult-onset hypertrophic cardiomyopathy patients with ECG and echocardiograms starting at age 12**

## Dilated cardiomyopathy at a glance

Up to 50% of cases of idiopathic dilated cardiomyopathy may be familial.

Dilated cardiomyopathy is often autosomal-dominant, but penetrance (ie, clinical expression) is lower than in hypertrophic cardiomyopathy.

Screening with electrocardiography and echocardiography is recommended for all first-degree relatives.

Treat patients who have asymptomatic left ventricular dysfunction.

Many genes and many private mutations have been identified.

The genotype-phenotype relationship is not reliable.

**Only a few large centers currently offer genetic testing for hypertrophic cardiomyopathy**

selectively hypertrophied and the right ventricle is not, even though the abnormal protein is present in both chambers.

The degree of compensatory hypertrophy may vary, depending on other genetic modifiers. For instance, the ACE genotype DD polymorphism is more common in patients from hypertrophic cardiomyopathy families with a high incidence of sudden death. Perhaps this polymorphism may lead to an exaggerated response to cardiac hypertrophy.

### Difficulties in screening for hypertrophic cardiomyopathy mutations

Despite major advances in the molecular genetics of hypertrophic cardiomyopathy, genetic testing is currently confined to large centers with research-based protocols. The genetic heterogeneity of the condition, with up to 200 private mutations in 10 genes, makes it impractical at present to offer routine clinical genetic testing for all patients with hypertrophic cardiomyopathy.

Routine genetic testing will eventually become generally available but will pose a number of difficult issues. These include the ethics and practicality of preclinical screening, prenatal diagnosis, disclosure to insurance companies, and adequate pretest and posttest counselling. Therapeutic questions will also be raised: eg, should asymptomatic children with malignant mutations associated with a poor prognosis receive prophylactic therapy? There are currently no evidence-based answers to many of these questions.

## DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is a condition of unknown cause characterized by unexplained dilatation and impaired systolic function of the left ventricle or both ventricles<sup>14</sup> and increased myocardial mass. Patients may present with heart failure, palpitations, or sudden death.

Clinically, dilated cardiomyopathy is the most common of the cardiomyopathies, accounting for over 90% of all cases referred to specialized centers. It is the most common single reason for cardiac transplantation in the young. Population-based studies suggest a prevalence of up to 1:2,500. However, the true prevalence is probably higher, as asymptomatic patients are likely to escape detection.<sup>2,15</sup>

The cause of dilated cardiomyopathy remains poorly understood and may be very heterogeneous, but in recent years genetic factors have been suggested as responsible for 30% to 50% of cases. Other contributing factors include hypertensive heart disease, autoimmune disease, and toxins such as alcohol.

Viral myocarditis may be important in childhood, but in adults the relationship between myocarditis and dilated cardiomyopathy is unclear, and the lack of consistency of viral studies has confounded attempts to isolate specific disease pathogens. Interferon-beta has been used in small studies to eliminate viral replication in patients with biopsy-proven myocarditis, dilated cardiomyopathy, and a high viral load, but larger studies are awaited to clarify the full clinical significance of these observations.<sup>16</sup> Diagnosing myocarditis is problematic owing to sampling limitations and variations in histopathological diagnostic criteria.


### Dilated cardiomyopathy is often familial

Careful family screening suggests that dilated cardiomyopathy is genetically transmitted in up to 50% of cases, mostly with an autosomal-dominant inheritance pattern, with a lesser number of autosomal-recessive, X-linked, or mitochondrial disorders.

### Screening the family for dilated cardiomyopathy

Systematic family screening may show echocardiographic abnormalities in 25% of





relatives of patients with dilated cardiomyopathy; the abnormalities include dilated cardiomyopathy and isolated left ventricular enlargement. Large-scale screening programs suggest that 10% to 25% of such patients with left ventricular enlargement will develop clinical dilated cardiomyopathy with symptomatic heart failure, arrhythmias, or thromboembolism within 5 years.<sup>15</sup> Patients with left ventricular enlargement have histological abnormalities comparable to changes seen in dilated cardiomyopathy, and have abnormal metabolic exercise capacity and abnormal circulating cytokine profiles.<sup>17</sup>

These observations strongly suggest that familial dilated cardiomyopathy is a slowly progressive disorder, appearing clinically after several decades of “gestation.” Therefore, screening programs have been recommended for all first-degree relatives of patients with idiopathic dilated cardiomyopathy. As with hypertrophic cardiomyopathy, the expression of disease may vary widely from individual to individual in affected families, and mild disease in a parent does not guarantee mild disease in the next generation.

Those with asymptomatic left ventricular systolic dysfunction should be treated with ACE inhibitors<sup>18</sup> and probably beta-blockers (although clinical trial evidence for the latter is lacking). Those with isolated left ventricular enlargement but normal systolic function should be followed with serial ECGs and echocardiography. A normal screening ECG and echocardiogram in an adult family member is reassuring, and the family member does not usually need routine follow-up.

### **Genetics of dilated cardiomyopathy**

The first disease-causing gene mutations to be identified in dilated cardiomyopathy were in the cytoskeletal protein dystrophin in patients with combined dilated cardiomyopathy and skeletal muscle disorders such as Duchenne and Becker muscular dystrophies. Then, mutations in patients with pure autosomal-dominant familial dilated cardiomyopathy were described in 1998.

Mutations have been described in genes encoding for cytoskeletal proteins such as desmin, taffazin, D-sarcoglycan, and metavinculin,<sup>19,20</sup> and for nuclear envelope proteins



# **NO ONE GOES THROUGH MEDICAL SCHOOL TO PRACTICE INSURANCE.**

Remember graduating from college and passing your MCATs, then spending the next four years of your life getting through classes like clinical epidemiology, neurology and radiology so you could practice medicine? Today's financially driven managed care environments make having a practice difficult. Hurrying patients in and out of the office to make a quota and going into negotiations to prescribe treatments that don't coincide with a patient's policy aren't practicing medicine. We'd like to prescribe a solution: Move your profession to the United States Air Force. Get back to what's important — practicing medicine. To request more information, please visit our website at [AIRFORCE.COM](http://AIRFORCE.COM) or give us a call at 1-800-423-USAF.

such as emerin and lamin A/C.<sup>21</sup> These cytoskeletal proteins are important for structural integrity and for force transmission. Although some cytoskeletal protein mutations produce both cardiac and skeletal muscle disease, most such mutations produce pure cardiac dysfunction. Lamin A/C mutations have been associated with Emery-Dreifuss muscular dystrophy (X-linked), but also with autosomal-dominant dilated cardiomyopathy and conduction disease. Lamin A/C mutations may be associated with a more malignant form of dilated cardiomyopathy, with a higher incidence of sudden death.

More recently, other sarcomere protein gene mutations (previously identified only in hypertrophic cardiomyopathy) have been identified as the cause of dilated cardiomyopathy in several large families, with mutations in the troponin T and beta-myosin heavy chain genes. These may interfere with interactions between myosin and actin, or within the troponin complex, and thus diminish force generation. Why some sarcomere mutations produce hypertrophy and others produce dilatation remains unclear. Mutated proteins in the troponin complex (troponin T, I, and C) may account for up to 6% of cases of familial dilated cardiomyopathy.

In 2004, new mutations were described in the gene for phospholamban<sup>22</sup> (a calcium pump) and, somewhat unexpectedly, for a subunit of the cardiac adenosine triphosphate-sensitive potassium channel.<sup>23</sup>

#### **Dilated cardiomyopathy is genetically heterogeneous**

Fifteen disease genes have been identified for dilated cardiomyopathy in four different types of proteins, none of which accounts for a large proportion of cases. These findings further complicate the search for a unifying theory of dilated cardiomyopathy and widen the scope of any candidate gene-based approach for the individual patient. Dilated cardiomyopathy continues to be the most genetically heterogeneous of the cardiomyopathies, and a routine clinical genetic test is unlikely to be available in the near future.

For the clinician, it is recommended that first-degree relatives be screened with ECG and echocardiography. Asymptomatic

systolic dysfunction should be treated with ACE inhibitors and probably beta-blockers. There is no evidence that treating gene-positive family members who have normal ECGs and echocardiographs is of any benefit.

#### **■ ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY**

Arrhythmogenic right ventricular cardiomyopathy is defined as a heart muscle disease of the right ventricle, of unknown origin. It is characterized by progressive “fibro-fatty” tissue replacement of the myocytes and extracellular matrix of the right ventricular myocardium. The fibro-fatty scarring typically involves the right ventricle but can also involve the left ventricle.

The clinical presentation of arrhythmogenic right ventricular cardiomyopathy can be arrhythmias, syncope, and sudden death. Symptomatic palpitation or dizzy spells and blackouts are usually due to multiple incidents of ventricular ectopy or ventricular tachycardia. Ventricular tachycardia usually has the pattern of left bundle branch block. This can occur spontaneously but is more common during exercise.

The diagnosis may be made by the incidental finding of multiple ectopic beats on a routine ECG or by echocardiographic screening. Echocardiographic changes are subtle in early disease. Cardiac magnetic resonance imaging provides the best chance to image infiltration of fibro-fatty tissue in the myocardium.

Sudden cardiac death can be the first presentation of the disease. Heart failure, both right and left, can occur late in the course of disease. Left ventricular systolic impairment is a poor prognostic sign.

Most patients with arrhythmogenic right ventricular cardiomyopathy present in the third and fourth decades of life. The prevalence is unclear, but may be between 1:1,000 and 1:5,000. In parts of Italy, arrhythmogenic right ventricular cardiomyopathy is the most common cause of sudden death in young athletes.

Treatment is with antiarrhythmics and implantable cardioverters-defibrillators for

**Arrhythmogenic right ventricular cardiomyopathy may be a disorder of cell-to-cell junction proteins**

ventricular tachycardia, and diuretics if right heart failure intervenes.

### Genetics of arrhythmogenic right ventricular cardiomyopathy

Familial disease is common, with an autosomal-dominant inheritance pattern in most cases; thus, it is appropriate to screen first-degree relatives with ECG, echocardiography, and Holter monitoring. A high level of incomplete penetrance makes identification of such patterns difficult.

An autosomal-recessive pattern has also been described on the Greek island of Naxos, in which homozygotes have arrhythmogenic right ventricular cardiomyopathy, wooly hair, and palmoplantar keratoderma. A major breakthrough was the report in 2000 that Naxos disease is due to a deletion mutation in the gene for plakoglobin, a cell-to-cell junction protein (ie, a protein that connects myocytes).<sup>24</sup> Now other proteins are implicated, such as the cardiac ryanodine receptor.<sup>25</sup> This provided the first important insights into the pathogenesis of the disease and suggests that arrhythmogenic right ventricular cardiomyopathy may be a disorder of cell-to-cell junction proteins.

Light microscopy of plakoglobin mouse models shows layers of cells with poor apposition. It has been hypothesized that wide intercellular spaces may form in humans with arrhythmogenic right ventricular cardiomyopathy, in which fat is deposited. Alternatively, this fatty and fibrous tissue may form as part of a repair process replacing apoptotic myocardial cells.

The timing and development of fibrofatty replacement is also poorly understood, and family screening studies are identifying patients with milder phenotypes, which suggest variable penetrance and variable age of onset of disease in arrhythmogenic right ventricular cardiomyopathy.

### ■ RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy is a rare myocardial disease with impaired ventricular filling and reduced diastolic volumes, normal systolic function, and normal or near-normal myocardial thickness. The disease presents with


symptoms of progressive left-sided and right-sided heart failure. The overall prognosis is poor, especially when the onset is in childhood, and patients often require cardiac transplantation.

Although several inherited and acquired disorders may cause restrictive cardiomyopathy, such as amyloidosis (primary and secondary) and sarcoidosis, many cases are still classified as idiopathic. Familial restrictive cardiomyopathy has been reported, but recent reports highlight for the first time that patients with seemingly “pure” idiopathic restrictive cardiomyopathy may have mutations in the gene for cardiac troponin I, and restrictive cardiomyopathy may represent an overlap with hypertrophic cardiomyopathy in many familial cases.<sup>26</sup> Because the troponin I gene is small, it may become feasible to develop clinically relevant genetic screening in this context.

Biopsy of the right ventricle has an important clinical role in restrictive cardiomyopathy and can help rule out other potentially treatable causes of cardiomyopathies such as sarcoidosis and amyloidosis. When heart failure occurs in a patient with normal or near-normal myocardial thickness and preserved systolic function, pericardial disease should also be considered.

### ■ NEEDED: BETTER UNDERSTANDING OF GENES AND THEIR TRIGGERS

In the future, a clinically applicable genetic test is most likely to be useful in disorders such as arrhythmogenic right ventricular cardiomyopathy, in which the phenotype can be apparently mild but the outcome malignant. The best example of a really useful genetic test in cardiology is in arrhythmic disorders such as long QT syndrome and familial catecholaminergic ventricular tachycardia, in which a small group of relatively small candidate genes can be screened to look for a disorder in which the first clinical manifestation may sadly be the last.

To improve the management of patients with cardiomyopathy and their relatives, additional genes will have to be identified, and may allow better understanding of the precise molecular and physiological mechanisms that trigger the disease. 

**Penetrance may be incomplete in arrhythmogenic right ventricular cardiomyopathy mutations**



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