Molecular Genetic Insights into Cardiovascular Disease

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The recent application of molecular genetic tools to inherited forms of cardiovascular disease has provided important insight into the molecular mechanisms underlying cardiac arrhythmias, cardiomyopathies, and vascular diseases. These studies point to defects in ion channels, contractile proteins, structural proteins, and signaling molecules as key players in disease pathogenesis. Genetic testing is now available for a subset of inherited cardiovascular diseases, and new mechanism-based therapies may be available in the near future. This remarkable progress and the implications it may have for more common forms of cardiovascular disease are reviewed here.

Human molecular genetic technology has changed the way that biomedical researchers approach clinical problems. The goal of the molecular geneticist is to identify genes that, when mutated, contribute to disease. Once a disease gene has been identified, the structure and function of the encoded protein can be studied, the functional consequences of disease-associated mutations examined, and the molecular mechanism defined. The pathogenesis of disease can then be studied at the cellular and organ levels in animal models. Human molecular genetics also offers the promise of improved disease diagnosis, prevention, and treatment through genetic testing and mechanism-based therapy.

Cardiovascular disease presents a particular challenge to molecular geneticists because it is often multifactorial in origin, resulting from the interplay of genetic and environmental factors. For many forms of cardiovascular disease, the relative importance of genetic factors is poorly defined, but for others, genetic factors clearly predominate. Lessons learned from the study of predominantly genetic disorders can provide important insight into the pathogenesis of, and potential therapies for, more common cardiovascular disorders. Here, we describe recent advances in the application of molecular genetics to the study of inherited cardiovascular disease.

Inherited Cardiac Arrhythmias

Cardiac arrhythmias are responsible for most of the 250,000 sudden cardiac deaths per year in the United States (*1*). Presymptomatic diagnosis of life-threatening arrhythmias is difficult, and medical therapy has been ineffective. Ironically, some antiarrhythmia medications have increased the incidence of arrhythmia (*2*). Until recently, the molecular and cellular mechanisms underlying inherited arrhythmias were an enigma.

Long QT disease (LQT) is an inherited cardiac disorder that causes increased risk of sudden death from ventricular arrhythmias. LQT can affect any population but is commonly observed in young, otherwise healthy people. Electrocardiograms of individuals with LQT show an abnormality in cardiac repolarization known as a prolonged QT interval. This clinical observation, coupled with animal studies showing that stimulation of the autonomic nervous innervation of the left side of the heart prolongs the QT interval and produces arrhythmias, led to the hypothesis that LQT is caused by an imbalance in cardiac autonomic innervation. As a result, therapy for LQT has focused on the autonomic nervous system, including left cervical sympathectomy and treatment with β-adrenergic receptor antagonists. Unfortunately, these treatments do not prevent arrhythmia in all patients nor do they resolve the underlying repolarization abnormality.

Recent molecular genetic studies indicate that the autonomic nervous innervation of the heart is not central to the pathogenesis of autosomal dominant LQT. Instead, these studies have established that LQT results from mutations in genes that encode cardiac myocyte ion channels. Within the past year, three LQT genes have been identified: *SCN5A* on chromosome 3, *HERG* on chromosome 7, and *KVLQT1* on chromosome 11 (*3*, *4*) (Table 1). A fourth LQT locus has been mapped to chromosome 4, and at least one additional locus exists (*5*). *SCN5A* encodes the cardiac sodium channel, a protein that was well characterized before the genetic findings. Physiologic analyses of HERG have demonstrated that its gene encodes α subunits that form channels responsible for I_{Kr}, a cardiac delayed rectifier potassium current (*6*). The

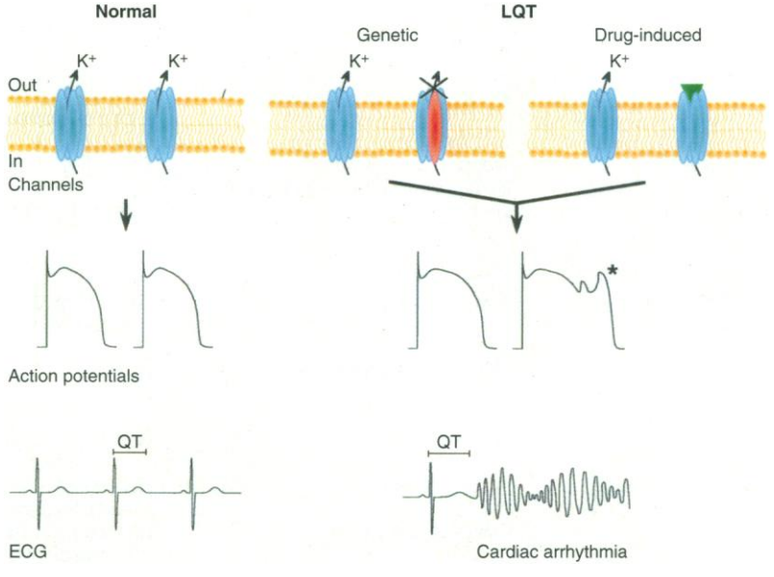

Fig. 1. A molecular mechanism for cardiac arrhythmia in LQT. Normally, the opening of potassium channels terminates the action potentials of cardiac myocytes (left). The time required for repolarization of the ventricles can be measured as the QT interval of the body surface electrocardiogram (ECG). Normal cardiac rhythm is characterized by synchronized depolarization and repolarization of the ventricles. In inherited LQT, dysfunction of the cardiac myocyte HERG potassium channel produces a prolonged action potential (middle) and sometimes premature secondary depolarizations (asterisk). Similarly, drugs that block HERG channels can prolong action potentials (right). Prolonged repolarization is detected as a longer QT interval on the ECG. This physiologic abnormality increases the risk of life-threatening cardiac arrhythmias.

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physiologic properties of the protein encoded by *KVLQT1* are not yet defined, but the amino acid sequence predicted by the complementary DNA suggests that this protein is the first member of a novel class of potassium channels (*4*).

LQT-associated mutations in SCN5A cause a gain-of-channel function. Normally, this sodium channel initiates myocellular action potentials, then closes and remains closed (inactivated) for the remainder of the action potential. The inactivation gate of mutant SCN5A channels is destabilized, resulting in repetitive channel opening and a prolonged action potential (*7*). A different molecular mechanism is responsible for HERG-induced LQT. Normally, activation of the HERG potassium channel contributes to termination of the cardiac action potential. LQT-associated mutations in HERG result in reduced channel function, leading to action potential prolongation. At least two distinct molecular mechanisms account for reduced HERG function in the setting of LQT. In the first, LQT-associated intragenic deletions of one HERG allele can result in the synthesis of aberrant subunits that do not coassemble with normal subunits into the functional tetrameric form. The net effect is a 50% reduction in the number of functional channels, a partial loss-of-function mechanism. In the second mechanism, missense mutations lead to the synthesis of HERG subunits with single amino acid substitutions. Channels formed from the coassembly of normal and mutant HERG subunits have reduced or no function. The result is a greater than 50% reduction in HERG channel function, a dominant negative effect (*8*).

Despite their molecular differences, mutations in SCN5A and HERG have similar cellular consequences. Inappropriately timed reopening of sodium channels or reduced potassium channel function both lead to delayed myocellular repolarization and increased cellular excitability (Fig. 1). The ion channels that cause LQT are expressed at varying levels in different regions of the heart, so the effect of LQT-associated ion channel dysfunction has regional variability. Aberrant cardiac repolarization creates a substrate for arrhythmia. The trigger for arrhythmia in this setting is unknown, but in vitro evidence suggests a role for spontaneous secondary depolarizations during the repolarization phase of cardiac action potentials. Once triggered, the arrhythmia is maintained by a regenerative circuit of electrical activity around relatively inexcitable tissue, a phenomenon known as reentry. The development of multiple reentrant circuits within the heart causes ventricular fibrillation, an arrhythmia that causes sudden death.

Abnormal cardiac repolarization and susceptibility to arrhythmia can also be acquired. The most common form of acquired LQT is a side effect of treatment with medications, particularly certain anti-arrhythmics, antihistamines, and antibiotics. Most of these medications block HERG channels, leading to reduced repolarizing HERG current and delayed myocellular repolarization (Fig. 1). Thus, the observation that one form of LQT results from loss-of-function mutations in HERG provides a mechanistic link between an inherited and an acquired cardiac arrhythmia.

Improved mechanistic understanding of

Table 1. Postulated mechanisms of inherited cardiovascular disease. Acyl-CoA, acyl–coenzyme A; LDL, low density lipoprotein; TGF-β, transforming growth factor–β.

Disorder	Aberrant protein	Mechanism
Arrhythmias		
LQT disease	HERG K^+ channel	Dominant negative loss of K^+ channel function → delayed myocellular repolarization and increased excitability
	Cardiac Na^+ channel	Gain of Na^+ channel function through destabilization of inactivation gate → delayed myocellular repolarization, and increased excitability
	KVLQT1	?
Cardiomyopathies		
Familial hypertrophic cardiomyopathy	β Cardiac myosin heavy chain	Loss of function → reduced myocellular contractility, cellular hypertrophy, and myofibrillar disarray
	α Tropomyosin	?
	Troponin T	?
	Cardiac myosin binding protein C	?
Duchenne and Becker muscular dystrophy	Dystrophin	Loss of dystrophin → myocellular injury and dilated cardiomyopathy
Barth syndrome	Taffazzins	?
Acyl-CoA dehydrogenase deficiencies	Acyl-CoA dehydrogenase	Loss of function in fatty acid β oxidation pathway → reduced energy metabolism, myocellular injury, and dilated cardiomyopathy
Mitochondrial disorders	Mitochondrial proteins	Impaired oxidative phosphorylation → reduced myocellular energy metabolism, myocellular injury, and dilated cardiomyopathy
Vascular diseases		
Familial hypercholesterolemia	LDL receptor	Reduced LDL receptor function → increased cholesterol synthesis and risk of atherosclerosis
Hypobetalipoproteinemia	Apolipoprotein B	Reduced apolipoprotein binding affinity → increased cholesterol synthesis and risk of atherosclerosis
Homocystinuria	Cystathionine synthase	Reduced condensation of homocysteine and serine to cystathione → increased risk of thrombosis and atherosclerosis
Type III hyperlipoproteinemia	Apolipoprotein E	Reduced binding to lipoprotein receptors → elevated levels of cholesterol and triglycerides and increased risk of atherosclerosis
Supravalvular aortic stenosis	Elastin	Reduced elastin content during vascular development → relatively inelastic vasculature that is susceptible to recurrent injury
Ehlers-Danlos syndrome IV	Type III procollagen	Reduced collagen synthesis in the vascular adventitia → aneurysms
Marfan syndrome	Fibrillin-1	Dominant negative loss of fibrillin function → predisposition for vascular dilation and dissection
Hereditary hemorrhagic telangiectasia	Endoglin	Loss of endoglin function → reduced ability of the endothelium to respond to TGF-β, resulting in microvascular disease

LQT has facilitated new therapeutic strategies. Individuals with mutations in the cardiac sodium channel, for example, respond to medications that block the sodium channel (9). Unfortunately, this therapy will not be effective for individuals with HERG mutations because the molecular mechanisms are different. An unusual property of HERG, however, has provided an opportunity for more general therapy. HERG channels are paradoxically activated by modest increases in extracellular potassium concentration, effecting increased repolarizing potassium current (6). Preliminary data indicate that potassium supplementation alone can correct the repolarization abnormality observed in individuals with HERG mutations (*10*). This therapy will likely be effective in all inherited and acquired forms of LQT and may prove useful for the prevention of arrhythmia in some cardiomyopathies associated with QT prolongation.

Familial Cardiomyopathies

Nearly 25,000 people die from cardiomyopathy in the United States every year (*11*). Most cardiomyopathies are secondary, resulting from hypertension and valvular heart disease, but genetic factors are also clearly important. A number of rare inherited metabolic disorders increase the risk of cardiomyopathy and valvular dysfunction (*12*), but in this discussion we focus on the two main forms of cardiomyopathy, hypertrophic and dilated. Familial hypertrophic cardiomyopathy (FHC) is a heterogeneous autosomal dominant disorder characterized by thickening of the ventricular walls, impaired relaxation, and reduced ability of the heart to fill. The disorder manifests itself in many different ways; it can be clinically silent and produce mild symptoms such as decreased exercise tolerance and shortness of breath, or in the extreme, it can induce cardiac arrhythmias and sudden death. The prevalence of FHC in the United States is estimated to be between 20 and 200 cases per 100,000 people (*13*).

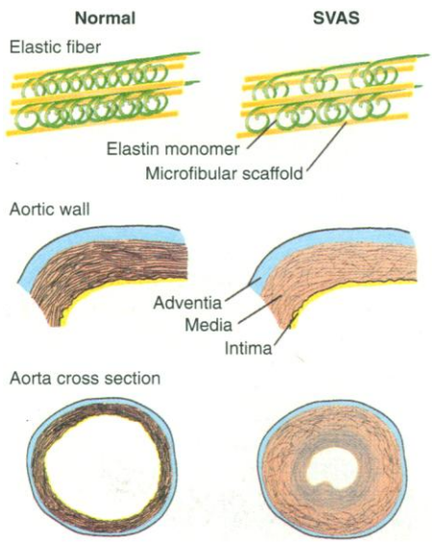

Fig. 2. A molecular mechanism for obstructive vascular disease. Elastic fibers (top) are constructed of elastin monomers (green) that are laid down on a microfibrillar scaffold (yellow) during development of the vascular lamina and media. These fibers provide the vascular elasticity that is essential for dampening changes in blood pressure caused by cardiac contraction and relaxation. In supravalvular aortic stenosis (SVAS), which has been attributed to mutations in the elastin gene, the reduced elastin content leads to disarray of elastic fibers in the media (middle) and intimal proliferation of smooth muscle cells and fibroblasts (bottom). These changes may in turn reduce the elasticity of the aortic media and cause increased susceptibility to hemodynamic and other vascular stresses.

Four genes have been implicated in FHC. All four encode cardiac contractile proteins: β cardiac myosin heavy chain, α tropomyosin, troponin T, and cardiac binding protein C (*14*). An in vitro biochemical assay demonstrated reduced translocation of actin filaments by mutant myosin molecules, which is consistent with the hypothesis that reduced contractility is a primary defect in this disorder (*15*). The molecular consequences of mutations in the other contractile proteins are not yet known. The cellular mechanisms underlying FHC are also not fully defined. However, one likely mechanism involving β cardiac myosin heavy chain is that a reduction in myocellular contractility, caused by inefficient actin-myosin cross-bridge cycling, leads to a secondary myofibrillar disarray and hypertrophy (*14*). The resultant ventricular hypertrophy and architectural defects may lead to abnormalities in diastolic filling and systolic ejection and increased risk of arrhythmia. The challenge now is to define mechanisms that link the primary defect in contractile proteins with the secondary development of hypertrophy, because it is these mechanisms that are most likely important for the development of common forms of cardiac hypertrophy. A murine model of FHC based on a missense mutation in β cardiac myosin heavy chain should facilitate these mechanistic studies (*16*).

Dilated cardiomyopathy (DCM) is characterized by enlargement of the cardiac chambers, thinning of the ventricular wall, reduced contractility, heart failure, and death. The prevalence of DCM is 37 cases per 100,000 people in the United States, and this disorder is the primary indication for cardiac transplantation. It is estimated that genetic factors are key to the pathogenesis of 20 to 25% of cases of idiopathic DCM (*17*).

Recent genetic linkage studies have indicated that the disease is heterogeneous in origin. Mutations in genes encoding enzymes involved in β-oxidation of fatty acids, including acyl–coenzyme A dehydrogenases and carnitine palmitoyltransferase II, can cause rare recessive forms of DCM (*18*). Deletions in the mitochondrial genome can also contribute to rare cardiomyopathies that show maternal inheritance patterns (*19*). An X-linked cardiomyopathy has been associated with deletions in dystrophin, the gene responsible for skeletal and cardiac myopathies in Duchenne and Becker muscular dystrophies (*20*). Heart failure in X-linked DCM occurs rapidly after onset of symptoms during the late teens to early 20s in males but is delayed in onset and progresses slowly in females. In all cases studied, dystrophin mutations lead to a loss of protein function. Finally, recent studies have implicated a novel gene, G4.5, in the pathogenesis of X-linked DCM in Barth syndrome (*21*). The function of the protein encoded by this gene (tafazzin) is unknown. Four loci associated with autosomal dominant nonsyndromic DCM have been mapped: two on chromosome 1, one on chromosome 3, and one on chromosome 9 (*22*). These DCM genes remain to be identified.

Inherited Vascular Diseases

Atherosclerotic vascular disease is very common, leading to about 490,000 deaths from coronary artery disease and 150,000 deaths from stroke every year in the United States (*11*). The inheritance pattern for most cases of atherosclerosis is not clear, making genetic linkage studies difficult. Epidemiologic and biochemical studies have led to the hypothesis that the pathogenesis of atherosclerosis is complex, resulting from the interplay of multiple heritable and environmental factors. Nevertheless, studies of rare but clearly inherited vascular disease have begun to shed light on the mechanisms underlying atherosclerosis and other vascular diseases. Familial hypercholesterolemia, hypobetalipoproteinemia, homocystinuria, and type III hyperlipoproteinemia are four inherited disorders of cholesterol metabolism that predispose individuals to atherosclerosis. These disorders and other complex traits that contribute to the risk of vascular disease (for example, hypertension, diabetes, and other metabolic disorders) have been extensively reviewed (*12*) and will not be discussed here. More recently, molecular genetic studies have focused on vascular disorders that appear to result from primary defects in vascular development and function. These disorders can be characterized as leading to obstructive, dilating, or microvascular disease.

Supravalvular aortic stenosis (SVAS) is an inherited disorder that causes generalized obstructive vascular disease. The incidence of this disorder is approximately 5 cases in 100,000 people (*23*). Although SVAS can affect any artery, the most severe disease often occurs in the ascending aorta. SVAS often leads to heart failure and death, and the only current treatment option is surgical palliation. SVAS can be inherited as an isolated, autosomal dominant trait or as part of a pleiotropic disorder, Williams syndrome. In addition to vascular disease, patients with Williams syndrome show cognitive defects, facial abnormalities, and infantile hypercalcemia. SVAS is caused by mutations in the elastin gene on chromosome 7, and Williams syndrome results from submicroscopic deletions of chromosome 7q11.23 that encompass an elastin allele (*24*).

Elastin gene mutations in SVAS and Williams syndrome suggest a possible mechanism of vascular pathogenesis. Functional elastogenesis begins in the third trimester of fetal development and ends during childhood; no functional vascular elastic fibers are synthesized during adult life. Because individuals with SVAS have abnormally low levels of elastin during vascular development, their arterial walls may be relatively inelastic and more susceptible to hemodynamic stress. Recurrent hemodynamic injury to the endothelium may lead to intimal proliferation of smooth muscle cells and fibroblasts, causing fibrosis (Fig. 2). Medial elastic fibers are often disrupted in advanced atherosclerosis, which suggests that secondary vascular inelasticity may contribute to the pathogenesis of common vascular disease. An animal model for SVAS is required to test these mechanistic hypotheses.

Vascular dilation and aortic rupture account for about 1 to 2% of all deaths in industrialized society (*25*). Atherosclerosis is a common cause of vascular dilation, or aneurysm, but molecular genetic studies have also implicated systemic disorders of type III procollagen. Ehlers-Danlos syndrome type IV is an autosomal dominant disorder of type III procollagen characterized by translucent skin, susceptibility to bruising, mitral valve prolapse, and spontaneous rupture of large arteries. Mutations in other collagen genes cause additional forms of Ehlers-Danlos syndrome and osteogenesis imperfecta and are associated with mitral valve prolapse (*12*).

Ehlers-Danlos syndrome type IV is caused by mutations in *COL3A1*, the gene on chromosome 2 encoding type III procollagen (*26*). Mutations of *COL3A1* have also been associated with nonsyndromic forms of aortic aneurysm. *COL3A1* mutations lead to reduced collagen formation, and in the case of Ehlers-Danlos syndrome, the effect is severe. Collagen has a key role in the structural integrity of the vascular adventitia. Because one function of the adventitia is to maintain the vascular diameter, reduced adventitial collagen leads to increased risk of aneurysm.

Marfan syndrome, another vascular dilation disorder, also affects the skeletal and ocular systems. The incidence of this autosomal dominant disorder in the United States is approximately 10 cases per 100,000 people (*12*). Individuals with Marfan syndrome have increased risks of vascular dilation, vascular dissection, and mitral valve prolapse. The most commonly affected artery is the ascending aorta. Dilation of the aortic root frequently leads to aortic regurgitation and congestive heart failure but can cause sudden death from acute aortic rupture. Marfan syndrome is caused by mutations in the gene encoding fibrillin-1 on chromosome 15 (*27*). Disease-associated mutations are predominantly missense mutations that have a dominant negative effect on microfibrillar assembly.

A less severe disease, characterized by aortic root enlargement and ascending aortic aneurysm but without the other phenotypic features of Marfan syndrome, has been associated with a missense mutation in an epidermal growth factor–like domain of fibrillin-1 (*28*). In this disorder, fibrillin-1 synthesis appears normal, but deposition into the extracellular matrix is reduced. Fibrillin-1 is an important component of the microfibrillar scaffold that is essential for elastogenesis. Elastic fiber abnormalities are a prominent feature of Marfan syndrome, but elastic fiber defects do not explain the vascular pathology of this disorder. Unlike elastin, fibrillin-1 is highly expressed in the vascular adventitia, and reduction of this protein in the adventitia is the likely mechanism for increased risk of aneurysm.

Hereditary hemorrhagic telangiectasia (HHT), a microvascular disorder, is characterized by arteriovenous malformations, vascular dilation, and recurrent bleeding. Vascular malformations occur at many different sites, including the nose, skin, lung, brain, and gastrointestinal tract. HHT is inherited as an autosomal dominant trait and has an incidence of 2 cases per 100,000 people in the United States (*29*). Several loci have been implicated in this disorder, and one HHT gene has been identified, the endoglin gene on chromosome 9 (*30*). This gene encodes a receptor for transforming growth factor–β and is expressed on vascular endothelial cells. An initiating event, such as inflammation, is required to generate the discrete lesions typical of this disorder. It is not yet clear whether endoglin mutations increase the risk of developing microvascular abnormalities or whether they reduce the ability of the vasculature to repair spontaneous malformations.

Presymptomatic Diagnosis and Prognosis

Molecular genetic technologies provide an important opportunity for presymptomatic diagnosis of cardiovascular disease. This is particularly important for disorders that cause sudden death, like FHC and LQT. These disorders frequently affect young, otherwise healthy individuals who can be entirely asymptomatic until the life-terminating event. Even if these individuals have early symptoms, diagnosis with standard clinical tests like electrocardiography and echocardiography is neither sensitive nor specific (*31*). Because therapies for LQT and for FHC are available now, presymptomatic diagnosis is clearly desirable. Genetic testing is also useful for other, less acute cardiovascular disorders, because these tests facilitate early and specific diagnosis, thus enabling prevention of irreversible pathology. For example, genetic testing can distinguish between Marfan syndrome and other connective tissue disorders that are not associated with cardiovascular disease, such as scoliosis, joint hypermobility, myopia, and mitral valve prolapse. In Marfan syndrome, early treatment with medications that block the β-adrenergic receptor slows the progression of vascular dilation and lessens the risk of aortic rupture (*12*).

In some cases, great advances have been made in the genetic diagnosis of cardiovascular disease. Genetic testing by fluorescence in situ hybridization with elastin gene probes has revolutionized diagnosis of Williams syndrome, providing diagnostic acumen that was not previously possible. Diagnosis of this disorder was previously made by physical examination and was accurate only when the examination was performed by an expert clinical geneticist. Now, the diagnosis can be made at any medical center with an inexpensive test that has 99% sensitivity and specificity. Genetic testing for other disorders is also possible for members of families in which a genetic mutation has already been identified. This is the case for an increasing number of families with LQT, FHC, SVAS, Marfan syndrome, and HHT. The presence or absence of the disease-associated mutation can be detected in additional family members with many different techniques, most of which involve amplification of genomic DNA using polymerase chain reaction and subsequent hybridization and restriction or DNA sequence analyses. Finally, genetic linkage analyses using polymorphisms located within disease genes can be used to accurately

assess risk in familial cases where the specific mutation is not yet known.

Unfortunately, sensitive genetic testing of genetically heterogeneous disorders is not yet practical for patients who are not members of families with a defined mutation. For example, mutations in at least five different genes can cause LQT, yet only three of these genes have been identified. Moreover, 40 mutations have already been defined in the three known genes. Analysis of risk in an individual who is not part of an LQT family would require mutational analysis of all LQT-causing genes. Advances in the sensitivity and efficiency of genetic testing, coupled with continued molecular genetic discoveries, will enable more reliable and cost-effective analysis of risk for cardiovascular disorders in the general population.

Risk stratification is another important application of molecular genetics. In FHC, for example, certain mutations of the gene encoding β cardiac myosin heavy chain carry substantially greater risk of sudden death (*32*). Substitution of Glu for Gly at position 256 is associated with a disease penetrance of only 56% and a benign prognosis, whereas substitution of a Gln for Arg at position 403 is associated with 100% disease penetrance and a high risk of sudden death (*33*). Similarly, physiologic studies of LQT-associated mutations in HERG indicate a spectrum of HERG K^+ channel dysfunction, which ranges from a partial loss of function to complete dominant negative suppression. Although the power of a single piece of genetic information can be limited by modification of genetic and environmental factors, this prognostic information can nevertheless be quite useful in inherited cardiovascular disorders. This is particularly true when one can select from a spectrum of therapies that are increasingly aggressive, such as medical therapy versus implantation of an internal defibrillator for FHC or LQT.

Thus, in less than a decade, the techniques of molecular genetics have contributed dramatically to our understanding of cardiovascular disease pathogenesis. Many genes that have a major effect on cardiovascular risk have already been identified, and genetic diagnosis, prognosis, and mechanism-based therapy are available in some cases. Continued genetic discoveries and technological advances are likely to make genetic testing and genotype-based therapy a routine part of clinical care in the future.

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Mouse Models of Atherosclerosis

Jan L. Breslow

As a species the mouse is highly resistant to atherosclerosis. However, through induced mutations it has been possible to develop lines of mice that are susceptible to this disease. For example, mice that are deficient in apolipoprotein E, a ligand important in lipoprotein clearance, develop atherosclerotic lesions resembling those observed in humans. These lesions are exacerbated when the mice are fed a high-cholesterol, high-fat, Western-type diet. Other promising models are mice that are deficient in the low density lipoprotein receptor and transgenic mice that express human apolipoprotein B and transdominant mutant forms of apolipoprotein E. These models are now being used to study the pathogenesis of atherosclerotic lesions, as well as the influence of genetics, environment, hormones, and drugs on lesion development.

Atherosclerotic cardiovascular disease is the major cause of morbidity and mortality in much of the world. Atherogenesis is a complex process in which the lumen of a blood vessel becomes narrowed by cellular and extracellular substances to the point of obstruction. Lesions tend to form at the branch points of arterial blood vessels and progress through three stages (Fig. 1). The first stage is the fatty streak lesion, which is characterized by the presence of lipid-filled macrophages (foam cells) in the subendothelial space. The second stage is the fibrous plaque, which consists of a central acellular area of lipid, derived from necrotic foam cells, covered by a fibrous cap containing smooth muscle cells and collagen. The final stage is the complex lesion, which shows evidence of thrombus formation with deposition of fibrin and platelets.

Researchers in vascular biology are

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