Congestive heart failure (CHF) resulting from cardiomyopathy is a serious malady and a principal cause of death and disability in children and adults. This disorder is the most common disease that leads to heart transplant, with an associated healthcare cost in the United States of roughly US$200 million per year\(^1\). Cardiomyopathies are classified into four forms: dilated, hypertrophic, restrictive and arrhythmogenic right ventricular dysplasia/cardiomyopathy. Restrictive cardiomyopathy is the rarest form, accounting for only 5% of the total\(^2\), but has the worst prognosis and poorest therapeutic options of all the cardiomyopathies\(^3\). Arrhythmogenic right ventricular dysplasia is a complex arrhythmogenic disorder associated with cardiomyopathy and characterized by gradual loss of myocytes and replacement by fatty and fibrous tissue\(^4\). In Italy the prevalence has been reported as 1:5,000 people, accounting for 20% of sudden deaths in young adults\(^5\) and 25% of cardiac sudden deaths among athletes\(^6\); the incidence and prevalence are unknown in the United States. In this review we will discuss the identification of genes responsible for cardiomyopathies, as well as some of the animal models now being developed to further characterize the pathogenesis of these disorders.

**Dilated cardiomyopathy**

Dilated cardiomyopathy (DCM) is the most common cause of CHF, affecting 40 people in every 100,000 of the population\(^7\). Depending on the diagnostic criteria used, the annual incidence varies from 5 to 8 cases in a population of 100,000 (refs 7–9); the true incidence is probably underestimated by these numbers, as many asymptomatic cases go unrecognized.

Idiopathic DCM (IDCM) is characterized by an increased ventricular chamber size and reduced pumping of the heart (that is, reduced contractility; ref. 9 and Fig. 1) in the absence of coronary artery disease, valvular abnormalities or pericardial disease\(^10\). Backflow through the mitral valves and abnormal heart rhythms are common. Clinical features include common symptoms of CHF such as shortness of breath, easy fatigability, inability to tolerate physical exertion, fainting, light headedness, sweating at rest, and sudden death. Other signs are increased heart rate and an enlarged liver.

Most commonly, DCM presents between 18 and 50 years of age, but children of all ages and the elderly can be affected. It occurs more frequently in men than in women (2.5:1), and in African–Americans than in Caucasians (2.5:1), but the causes of these differences are not understood\(^11\). The clinical course of DCM, almost regardless of the underlying cause, may be progressive, with roughly 50% of individuals reported to die within 5 years of diagnosis without transplantation\(^8,10\). The cause of death is divided evenly between sudden death and pump failure. Longer survival has been accomplished recently with improved medical therapies (such as angiotensin-converting enzyme inhibitors).
inhibitors and β-blockers) and interventions (such as implantable defibrillators and ventricular assist devices).

**Genetics of dilated cardiomyopathy**

About 30–40% of individuals with DCM have a familial form of the disease (FDCM). Autosomal dominant inheritance is the predominant pattern of transmission; X-linked, autosomal recessive and mitochondrial inheritance are less common. Mitochondrial inheritance is seen most often in childhood forms of FDCM, whereas X-linked and autosomal recessive forms seem to be evenly distributed between childhood and adult forms of disease.

Over the past decade, progress has been made in understanding the genetic aetiology of FDCM. Initial advances were made a decade ago through studies of families with X-linked forms, and in the past few years the autosomal dominant forms have become better understood. In the case of X-linked forms of DCM, two disorders have been well characterized: X-linked dilated cardiomyopathy (XLCM), which presents in adolescence and young adults; and Barth syndrome, which is well characterized: X-linked cardiomyopathy (XLCM), which presents in infancy. The more common autosomal dominant form of FDCM also has two main forms: ‘pure’ DCM, and DCM associated with cardiac conduction system disease (CDDC).

**Autosomal dominant dilated cardiomyopathy**

Individuals who succumb to DCM with CDDC do so typically in their twenties, and what begins as mild conduction system disease can progress to complete heart block over decades. Dilated cardiomyopathy usually presents late in the course of disease but is out-of-proportion to the degree of conduction disorder. In many patients, mild conduction system disease occurs with subsequent development of severe DCM.

There is genetic heterogeneity of autosomal dominant DCM, with ten genetic loci mapped for pure DCM and five loci mapped for CDDC. In the case of pure DCM, the genetic loci identified so far include chromosomes 1q32, 2q31, 2q35, 4q12, 5q33, 9q13–22, 10q21–23, 14q11, 15q2 and 15q14 (refs 13–22). As listed in Table 1, seven of these genes are now known: actin (chromosome 15q14), desmin (chromosome 2q35), α-sarcoglycan (chromosome 5q33), β-sarcoglycan (chromosome 4q12), cardiac troponin T (chromosome 1q32), β-myosin heavy chain (chromosome 14q11) and α-tropomyosin (chromosome 15q2).

Cardiac actin, a sarcomeric protein, is a member of the sarcolemma, a thin filament that interacts with tropomyosin and the troponin complex (Fig. 2). Actin is significant because it links the sarcomere to the sarcolemma by binding to the amino terminus of dystrophin (at the sarcolemma) and to β-myosin heavy chain (β-MHC) in the sarcomere. Notably, DCM-related mutations of actin may affect directly its binding to dystrophin; by contrast, mutations in the sarcomeric end of actin result in hypertrophic cardiomyopathy (HCM).

The DCM-causing mutations, first described by Olson et al., are thought to result in disease by causing force transmission abnormalities. The mutations in cardiac β-MHC and cardiac troponin T are thought to cause reduced force generation by the sarcomere. In the case of β-MHC, the location of the mutations seems to disrupt either stereospecific interactions between myosin and actin that are essential for initiating the power stroke of contraction, or a hinge region of myosin that transmits movement. By contrast, mutations in cardiac troponin T may reduce ionic interactions that form a tight binary complex of cardiac troponin T and cardiac troponin C, again reducing the power stroke of contraction. In individuals with

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**Figure 2** Proteins and pathways involved in the development of cardiomyopathies. Identified genes that result in dilated cardiomyopathy include the cytoskeletal protein-encoding genes β- and α-sarcoglycan in the sarcolemma, dystrophin and the intermediate filament protein-encoding genes desmin and lamin A/C. Sarcomeric protein-encoding genes actin, β- and α-myosin heavy chain, α-tropomyosin and cardiac troponin T cause either dilated cardiomyopathy or hypertrophic cardiomyopathy, whereas cardiac troponin I and the myosin light chains cause hypertrophic cardiomyopathy. Mutations in α-dystrobrevin cause the intermediate phenotype, left ventricular noncompaction. MLP, muscle LIM protein; nNOS, neuronal nitric oxide synthase.
DCM, mutations in α-tropomyosin are thought to affect the surface charge of the protein; these mutations may compromise the integrity of the thin filament, resulting in defects in force transmission. In individuals with HCM, however, α-tropomyosin mutations show different characteristics.

Desmin is a cytoskeletal protein that forms intermediate filaments specific for muscle. It is found at the Z lines and intercalated disc of muscle, and its role in muscle function seems to involve the N-terminal actin-binding region of dystrophin. Experimental evidence shows that mutations in this gene cause abnormalities of force and signal transmission in cardiomyocytes, supporting the idea that this group of proteins is important to the normal function of the myocytes that are involved in the function of the DGC, which interacts with α-dystroglycan, a dystrophin-associated membrane-bound protein that is involved in the function of the DGC, which includes α-dystroglycan, the sarcoglycan subcomplex (α-, β-, γ-, δ-), syntrophins and dystrobrevins. Dystrophin is a cytoskeletal protein that provides structural support to myocytes by creating a lattice-like network to the sarcolemma. In addition, dystrophin has a principal role in linking the sarcomeric contractile apparatus to the sarcolemma and in transducing signals from the extracellular matrix through the DGC. The mechanisms responsible for the development of DCM and conduction system abnormalities are currently unknown.

X-linked dilated cardiomyopathy

First described in 1987 as a form of DCM occurring in males with X-linked dilated cardiomyopathy (XLCM), XLCM is distinguished by elevated amounts of serum creatine kinase muscle isoforms — a sign of underlying skeletal muscle disease. Female carriers tend to develop mild to moderate DCM in their fifties, and the disease is slowly progressive. Towbin et al. identified the disease-causing gene, dystrophin, and showed that it is responsible for the clinical abnormalities owing to a severe reduction or absence of dystrophin protein in the heart of these individuals (Table 1). These findings were later confirmed, with most mutations clustering in the 5'-portion of the gene and affecting the N-terminal actin-binding region of dystrophin.

Table 1 Genetic causes of cardiomyopathies

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Inheritance pattern</th>
<th>Chromosomal locus</th>
<th>Gene</th>
<th>Protein</th>
<th>Skeletal myopathy</th>
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<td>G4.5</td>
<td>Tatffin</td>
<td>Barth syndrome</td>
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<td>α-dystrobrevin</td>
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In addition to the dysfunction of dystrophin, mutations in dystrophin secondarily affect proteins that interact with dystrophin. As mentioned above, the N terminus of dystrophin binds to the sarcomeric protein actin, a member of the thin filament of the contractile apparatus. The carboxy terminus of dystrophin interacts with α-dystroglycan, a dystrophin-associated membrane-bound protein that is involved in the function of the DGC, which includes α-dystroglycan, the sarcoglycan subcomplex (α-, β-, γ-, δ-sarcoglycan), syntrophins and dystrobrevins. Dystrophin is a cytoskeletal protein that provides structural support to myocytes by creating a lattice-like network to the sarcolemma. In addition, dystrophin has a principal role in linking the sarcomeric contractile apparatus to the sarcolemma and in transducing signals from the extracellular matrix through the DGC. The mechanisms responsible for the development of DCM and conduction system abnormalities are currently unknown.
primary disease of the cytoskeleton/sarcolemma, which leads to sarcomeric dysfunction.

Barth syndrome

Initially described as X-linked cardioskeletal myopathy with abnormal mitochondria and neutropenia (low white blood count), Barth syndrome typically presents in male infants as CHF associated with neutropenia (cyclic) and 3-methylglutaconic aciduria. Mitochondrial dysfunction is detected by electron microscopy and electron transport chain biochemical analysis. Echocardiograms show that these infants typically have left ventricular dysfunction with left ventricular dilation, endocardial fibroelastosis or a dilated hypertrophic left ventricle. In some cases they succumb to CHF/sudden death or sepsis caused by dysfunction of white blood cells. Most of these children survive infancy and do well clinically, although DCM usually persists.

The genetic basis of Barth syndrome was first described by Bione et al., who cloned the disease-causing gene (Table 1). This gene encodes the protein tafazzin, whose function is not known. But mutations in G4.5 result in many clinical disorders, including apparent classical DCM, hypertrophic DCM, endocardial fibroelastosis and left ventricular noncompaction (LVNC), with or without other features of Barth syndrome.

Animal models of dilated cardiomyopathy

So many of the genes identified for inherited DCM are also known to cause skeletal myopathies (Table 1), which suggests that skeletal and cardiac muscle share a ‘final common pathway’. Further support for this concept comes from studies of animal models. Mutations in β-sarcoglycan in hamsters result in cardiomyopathy, whereas mutations in any of the sarcoglycan subcomplex genes in mice cause skeletal and cardiac muscle disease. Mutations in other DGC genes, as well as in dystrophin, also consistently show abnormalities of skeletal and cardiac muscle function in murine models.

Arber et al. have produced a mouse that is deficient in muscle LIM protein — a structural protein that links the actin cytoskeleton to the contractile apparatus. These mice develop severe DCM and CHF, and have disrupted cardiac myocyte cytoskeletal architecture. Badorff et al. have shown that the DCM that develops after viral myocarditis may have a mechanism similar to the inherited forms. Using coxsackievirus B3 (CVB3) infection of mice, they showed that the CVB3-encoded protease 2A (enteroviral protease 2A) cleaves dystrophin, resulting in sarcolemmal disruption and possibly defects in force transmission, and DCM. A similar dystrophin mutation that affects individuals with XLCM shows a consistent mechanism of DCM development, namely, abnormalities of the cytoskeleton/sarcolemma.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a complex cardiac disease with unique pathophysiological characteristics and many morphological, functional and clinical features. In affected individuals the heart is thick; in particular, the interventricular septum and left ventricular posterior wall are thickened (usually asymmetric septal hypertrophy), and exaggerated pump function (that is, hypercontractile systolic function) is noted along with poor relaxation of the heart (diastolic dysfunction). The disease process in young children is thought to differ from that in older children and adults, with different apparent causes. Because HCM is a principal cause of sudden death in young, healthy individuals and athletes, it affects any population. In addition, a significant proportion of individuals develop CHF, caused either by diastolic dysfunction or by the development of left ventricular dilation and systolic dysfunction.

Genetics of familial hypertrophic cardiomyopathy

The first gene for HFC was mapped to chromosome 14q11.2–q12 using genome-wide linkage analysis in a large Canadian family. Soon afterwards, HFC locus heterogeneity was identified and several genes were mapped including chromosome 1q3, chromosome 15q2 and chromosome 11p11.2 (ref. 58). Five other loci were subsequently reported, located on chromosomes 7q3, 3p21.2–3p21.3, 12q23–q24.3, 15q14 and 2q31 (refs 23,58; and Table 1). Several other families are not linked with any known HFC loci, indicating the existence of additional HFC-causing genes.

The genes involved in HFC encode proteins that are part of the sarcomere — a complex structure with an exact stoichiometry and several sites of protein–protein interactions. The sarcomere proteins affected.
by FHC include three myofilament proteins, β-MyHC, ventricular myosin essential light chain 1 (MLC-1s/v) and ventricular myosin regulatory light chain 2 (MLC-2s/v); four thin filament proteins, cardiac actin, cardiac troponin T, cardiac troponin I and α-tropomyosin (α-TM); one myosin-binding protein, the cardiac myosin-binding protein C (CMYBPC); and titin (ref. 58 and Table 1). Each of these proteins is encoded by multigene families that show tissue-specific, developmental and physiologically regulated patterns of expression.

The gene responsible for cardiac hypertrophy and Wolff–Parkinson–White syndrome, previously linked to chromosome 7q3 (ref. 58), has been identified as that encoding the α2 subunit of AMP-activated protein kinase (AMP-PK), a gene that is important in energy use (refs 60, 61, and Table 1). Affected individuals may develop disease in early life or as adults, and may succumb to CHF or sudden death. It is likely that these symptoms develop as a secondary result of sarcomeric dysfunction, and mutations in mitochondrial DNA result in dysfunction of respiratory chain enzymes of the mitochondrial energy-producing compartment and also lead to hypertrophic cardiomyopathy, especially in young children (Table 1). In some cases, hypertrophic dilated or frank dilated cardiomyopathy can develop. Hence, energy production and use, which is required for sarcomeric function and membrane integrity, are also important causes of these disorders.

**Left ventricular noncompaction**

Left ventricular noncompaction is characterized by deep trabeculations in the left ventricular epicardium (Fig. 4), in association with left ventricular hypertrophy, dilatation or hypertrophy/dilatation. In some individuals the left ventricle is hypercontractile, but systolic dysfunction predominates in others. Two forms of LVNC have been described, an isolated form and a form associated with congenital heart disease. In the latter case, this non-isolated LVNC may be found in combination with septal defects, pulmonic stenosis or hypoplastic left ventricle. The two forms of LVNC are found in all age groups, although an infantile presentation seems to be most common; survival seems to be good.

The inheritance patterns of LVNC include X-linked inheritance in males with isolated LVNC, and an autosomal dominant pattern in some isolated and non-isolated cases. In the X-linked form, mutations in the gene G4.5 (Table 1), which encodes tafazzin, were initially identified by Bleyl and co-workers. This gene is identified by Bione and colleagues as causative for Barth syndrome (see above); in fact, some individuals with LVNC also have clinical features of Barth syndrome. Recently, we and our co-workers identified a gene for non-isolated LVNC in a family with broad clinical features ranging from apparent isolated LVNC to LVNC with septal defects alone, to LVNC associated with hypoplastic left ventricle. This gene, α-dystrobrevin, encodes a dystrophin-associated protein (Fig. 2) that maps to chromosome 18q12 (refs 44, 45; and Table 1). α-Dystrobrevin helps to maintain structural integrity of the muscle membrane, but also has signalling functions through the nicotinic oxide synthase pathway and is a substrate for tyrosine kinases. Deletion of this gene causes cardiomyopathy in mutant mice, supporting α-dystrobrevin as the cause of ventricular dysfunction. Again, skeletal myopathy is a feature to be noted. It is possible that the cardiac muscle abnormality is caused by disturbance of structural integrity and the congenital heart disease is due to perturbation of these signalling pathways in humans.

**Animal models**

Many animal models of HCM and LVNC have been generated. In the case of HCM, most of the known causative genes have been examined in mutant mice. The HCM phenotype first studied was that represented by the severe β-MyHC mutation Arg403→Gln, a mutation known to cause early death and severe hypertrophy in humans. Because MyHC mutations have also been generated, and typically the mutant protein is predominant in mice (and not β-MyHC), the α-myosin heavy chain gene was mutated in the animal models and an Arg403→Gln mouse mutant was generated using a gene targeting strategy. Homozygous animals were found to die shortly after birth, whereas sedentary heterozygotes survived, but showed abnormal cardiac structural and functional abnormalities typical of human HCM. Histopathological and physiological abnormalities included myocytodisarray, hypertrophy and fibrosis, which increased with age. Functional consequences included an acceleration in actin-activated cycling, increased rate of pressure rise and force development. Other MyHC mutations have also been generated, and typically the mutant mice show physiological abnormalities similar to those seen in humans carrying the corresponding mutations.

Murine models have also been developed for myosin light chain, myosin-binding protein C, α-tropomyosin, cardiac troponin T and troponin I, with variable similarities to the corresponding human mutations. Mariant et al. have developed an transgenic rabbit model caused by a common β-MyHC point mutation. As the predominant MyHC in rabbits is β-MyHC, mutant animals are more comparable to humans. In this model, wild-type and mutant human β-MyHC complementary DNAs were cloned 3′ to a 7-kilobases murine...
β-MyHC promoter. Purified transgenes were injected into fertilized zygotes to generate two lines each of the wild-type and mutant transgenic rabbits. Animals carrying the mutant transgene showed substantial myocyte disarray, increased interstitial collagen expression in the myocardium, and hypertrophy of the interventricular septum and posterior wall of the left ventricle, mimicking the classical symptoms of human HCM. In addition, the incidence of premature death was increased. Therefore, this model is potentially more useful than mouse models for future studies to define mechanisms of human HCM and to develop new treatments.

Kittleson et al. 67 have reported a feline experiment of nature. A colony of Maine coon cats was found to have cardiomyopathy features characterized by moderate to severe papillary muscle and left ventricular concentric hypertrophy. In addition, the histopathology of the hearts of these animals has striking resemblance to human HCM, as does the natural history of the disease. Genetically, these cats have autosomal dominant inheritance with 100% penetrance. Crossbreeding the affected animals was lethal in these homozygotes. Heterozygous animals developed HCM after six months of age, usually with an increasingly severe phenotype with age; classical features of HCM were seen typically during adolescence and young adulthood. Sudden death occurred in 20% of animals, and CHF was seen in 15% of cases. The gene responsible for this naturally occurring disease is not yet known.

Models of LVNC have been rarely described. So far, the only clearly defined model has been reported by Shou et al. 68, who used embryonic stem cells to generate mutant mice lacking exon 3 of the dystrophin gene. These mice developed cardiomyopathy and the authors did not describe features of LVNC. In this model, exon 3-targeted deletion was used to generate the mutant mice; this is the exon that is mutated in individuals with LVNC. It is likely that mutation of this gene not only disrupts the DGC, but also impairs signalling through the nitric oxide pathway. Whether there is any relationship between α-dystrophin and FKBP12 is not known.

A common thread

Clearly, HCM of adults is a disease of the sarcomere. Similarly, FDCM is caused by mutations in genes encoding cytoskeletal proteins. Hence, the final common pathways of these disorders include cytoskeletal proteins (DCM) and the sarcomere (HCM) (ref. 48; and Fig. 5). Similar pathways have been identified for ventricular arrhythmias (ion channels) and congenital heart disease (transcription factors). 69 In addition, it seems that whereas cascade pathways are involved directly in some cases (that is, mitochondrial abnormalities in HCM and DCM), secondary influences are likely to result in the various clinical symptoms seen in individuals with similar mutations.

In both DCM and HCM, mitochondrial and metabolic influences are also likely to be important. In addition, molecular interactions with such molecules as calcineurin, sex hormones, growth factors and other signalling pathways may be involved in the development of clinical signs, symptoms and age of presentation. In the future we expect these factors to be uncovered, allowing the development of new therapeutic strategies. Moreover, using these pathways for molecular screening is likely to uncover disease-causing genes in individuals with falling hearts.

The future for failure

With so much known about the genetic defects that underlie the cardiomyopathies, one obvious direction for the future treatment of this condition is gene therapy (see the review by Isner in this issue, pages 234–239). Although dystrophin is the best studied of the known DCM-causing genes, correcting the dystrophin defects associated with X-linked cardiomyopathy has not been attempted as yet. However, many groups have reported approaches for the phenotypic correction of the potentially lethal skeletal muscle disorder Duchenne muscular dystrophy. Adenovirus vectors encoding dystrophin have been used in mdx mice, resulting in efficient transduction of muscle fibres following intramuscular injection. Restoration of dystrophin-associated glycoprotein complex proteins to the sarcolemma and a decrease in centrally located nuclei, a characteristic of dystrophin-deficient skeletal muscle, was observed. 68, 70, 71 As yet there have been no studies in the heart.

Although gene therapy may be many decades away, our increasing knowledge of the aetiological basis and mechanisms causing CHF is now starting to encourage different therapeutic approaches. 72, 73 In recent years it has become clear that therapies focused on improving cardiac function with inotropic agents improve the indices of contraction, as measured by echocardiography, but give no survival advantage. By contrast, β-blocker therapy, 74, which reduces heart rate and is a negative inotropic agent, improves survival and leads to...
reverse remodelling (that is, normalization of ventricular size and function). In addition, left ventricular assist devices can also lead to reverse remodelling. These findings suggest that reducing myocardial mechanical stress can improve cardiac function, possibly through remodelling of the sarcomere-sarcolemma-extracellular matrix linkage. For example, dystrophin loss is reversed after 4–6 weeks of assist device therapy. In cases in which the dystrophin link is intact, administration of calcium channel blockers has been shown to be beneficial in mouse models. The benefit is thought to stem from protection from myocardial ischaemia but might result from calcium blockage or vasodilatation. However, the identification of genetic aetiologies combined with tailored gene-specific therapeutic approaches may offer significant improvements in disease prognosis and management in patients with congestive heart failure.