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The Genetic Challenges and Opportunities in Advanced Heart Failure

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Abstract

The causes of heart failure are diverse. Inherited causes represent an important clinical entity and can be divided into 2 major categories: familial and metabolic cardiomyopathies. The distinct features that might be present in early disease states can become broadly overlapping with other diseases, such as in the case of inherited cardiomyopathies (ie, familial hypertrophic cardiomyopathy or mitochondrial diseases). In this review article, we focus on genetic issues related to advanced heart failure. Because of the emerging importance of this topic and its breadth, we sought to focus our discussion on the known genetic forms of heart failure syndromes, genetic testing, and newer data on pharmacogenetics and therapeutics in the treatment of heart failure, to primarily encourage clinicians to place a priority on the diagnosis and treatment of these potentially treatable conditions.

In the United States, heart failure (HF) with reduced ejection fraction is newly diagnosed in more than 500,000 individuals each year, costs approximately $37 billion, and has an estimated death rate of 50,000 individuals per year.[1] The approximate lifetime cost of HF for each individual patient is $100,000 per year.[2] Although survival after diagnosis of HF has improved in the past quarter century, the 5-year mortality is still as high as many cancers.[3] Based on the Framingham Heart Study, after a new diagnosis of HF, 30-day mortality is approximately 10%, 1-year mortality is 20%–30%, and 5-year mortality is 45%–60%.[4]

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The causes of HF are diverse,[5] and the diagnosis and treatment of advanced HF might be challenging for clinicians. The prevalence of inherited cardiomyopathy is underappreciated in advanced HF.[6,7] Recent advances in genetic analysis, understanding of the effects of modifier genes, and appreciation for the effect of an individual's genetic fingerprint on response to therapy provide the basis for greater application of genetics in the diagnosis and treatment of advanced HF. In this review, we seek to provide an up to date framework for understanding the current and future effect of the genetic factors that underpin the etiology and treatment of HF.

Inherited Cardiomyopathies That Might Lead to HF

Inherited forms of cardiomyopathies can be broadly classified into: (1) familial cardiomyopathies (hypertrophic cardiomyopathy [HCM], familial dilated cardiomyopathy [FDCM], arrhythmogenic right ventricular cardiomyopathy [ARVC]), left ventricular (LV) noncompaction (LVNC), and restrictive cardiomyopathy (RCM); and (2) metabolic cardiomyopathies (disorders of fat metabolism (FAOD), mitochondrial function, carbohydrate metabolism, and lysosomes) (Table 1).[8]

Familial Cardiomyopathies

The first cardiomyopathy-associated gene was discovered in 1989,[30] using linkage analysis, and sparked a rapid expansion in cardiogenetics. Genetic testing has uncovered numerous cardiomyopathy-associated genes (Table 2; refer to Table 3 for nonstandard abbreviations, acronyms, and definitions) that encode proteins underlying the normal structure and function of cardiomyocytes (Fig. 1). The genetic mutation alone cannot yet sufficiently explain the clinical phenotype, and gene-based disease classification of cardiomyopathies remains a hope for the future.[8,33] Therefore, the discussion that follows is divided according to clinical phenotype.

HCM

HCM is the most common cause of sudden cardiac death (SCD) in otherwise young healthy individuals, and has a prevalence of approximately 1 in 500 (0.2%) worldwide.[9] HCM is diagnosed by the observation of unexplained hypertrophy on cardiac imaging (eg, echocardiography) coupled with typical electrocardiographic abnormalities.[11] Distribution of hypertrophy is variable with 2 dominant phenotypes characterized by either apical or asymmetric septal hypertrophy.[11] Evolution to end-stage HF occurs in a small but significant cohort.[52] Disease progression is linked to progressive fibrosis, but the underlying biological pathways are incompletely understood.[11] Unfortunately, there is no specific medical therapy that can interrupt this process, and symptom management ultimately followed by heart transplantation is frequently the only option in advanced disease.

HCM is caused by autosomal dominant (AD) mutations in structural genes (Fig. 1, Table 2). Although there are approximately 1400 mutations (largely missense) associated with familial HCM,[10,36] no specific genotype has been broadly associated with progression to advanced HF. Approximately 70% of individuals with HCM have mutations in 1 of 2 genes, myosin-7 (β-myosin heavy chain) and cardiac myosin-binding protein C (50% penetrance

by age 50 in men; Table 2),[33,53] and cardiac muscle troponin T and other genes each account for < 5% of cases (Table 2).[54] Approximately 8% of individuals have mutations in more than 1 sarcomere gene, leading to a more severe phenotype and greater likelihood of HF.[10]

The presence of HF in a patient with unexplained hypertrophy, or HF symptoms out of proportion with degree of hypertrophy, should trigger consideration of inherited phenocopies of HCM like Friedreich ataxia and Fabry disease (FD), and familial transthyretin amyloid cardiomyopathy and senile familial transthyretin cardiomyopathy.[55] Genetic testing can be useful to differentiate these entities.[56] For example, the *FXN* gene, which causes Friedreich ataxia, is estimated to affect 1 in 40,000 people and can manifest with adult-onset HCM that begins after age 25 and might present with hypokinetic-dilated cardiomyopathy or LV hypertrophy.[56] Overall, the yield of genetic testing in index patients with a family history of HCM is 40%–70%, and in sporadic cases is closer to 34%.[33,57–59]

The treatment of HCM requires a multidisciplinary approach for control of HF and anginal symptoms, LV outflow tract obstruction, and arrhythmias. Pharmacotherapy with β-blockers (first-line agents), calcium channel blockers, and disopyramide is the backbone of therapy for obstruction.[60] Active research on various agents, including statins[61] and N-acetylcysteine (ClinicalTrials.gov Identifier: NCT01537926) might expand the therapeutic options in the future. Survival of patients whose disease progresses to require cardiac transplantation is comparable with patients who receive a transplant for non-HCM diseases.[62]

ARVC

ARVC is characterized by enlargement, aneurysm, and/or dysfunction of the right and/or left ventricle with associated depolarization and repolarization abnormalities and important arrhythmic risk.[12] Histological evaluation might reveal characteristic fibrosis, myocyte necrosis, and fatty replacement.[12] With an estimated prevalence of 1 in 2000, ARVC is a leading cause of ventricular arrhythmia in young otherwise healthy individuals.[12] Asymptomatic patients with ARVC have low rates of disease progression to right ventricular dilation and HF.[63] However, when patients have disease that progresses to clinical HF, management can be complicated by right ventricular failure (RVF), which limits treatment options in advanced disease. Aggressive use of ventricular tachycardia ablation might contribute to a decline in ventricular function and progression of disease.[64] Frequent intense aerobic exercise might lead to more rapid disease progression,[65,66] so aerobic conditioning for ARVC patients should be limited.[67]

Early challenges in genetic diagnosis were overcome by recognition of severe autosomal recessive (AR) forms associated with palmoplantar keratosis and woolly hair.[13] Several genes most commonly transmitted as AD are known to cause ARVC (Table 2), although there are rare AR forms.[34] Although nondesmosomal gene mutations (eg, lamin A/C [*LMNA*] and cardiac sodium channel; Table 2), have been seen, desmosomal proteins account for most cases that meet clinical diagnostic criteria (30%–70% of cases; desmocollin-2, desmoplakin, plakophilin-2, etc; Table 2).[33,34] Unfortunately, the signal to noise ratio for ARVC genetic testing is relatively poor, which has created challenges in interpretation of genetic test results.[35] Compound or digenic heterozygosity of desmosomal

mutations are frequently seen among symptomatic adults,[68] implicating multiple genetic factors.

The management of advanced HF in ARVC remains a challenge. With predominantly RVF, use of LV assist device therapy, as a bridge to transplantation, remains impossible for most of these patients.[69] Caution should be used in applying ablation therapy, which might speed progression to RVF. The 1-year survival after transplantation is 94%, and 88% are alive at an average follow-up of 6.2 ± 4.8 years after transplantation.[69]

RCM

Inherited RCM is probably more appropriately considered a subtype of HCM.[15] Multiple sporadic forms of RCM exist and are associated with infiltrative processes (eg, hemochromatosis[31]), and environmental exposures (chemotherapy, radiation).[14] Phenotypically, the disease presents with atrial arrhythmias, increased right- and left-sided filling pressures with clinical signs and symptoms of RVF, and ventricular arrhythmias.[14] RCM is nearly universally associated with substantial and progressive HF, and transplantation outcomes vary significantly among subgroups.[70]

Hereditary amyloidoses are a heterogeneous group of AD disorders characterized by the extracellular deposition of insoluble protein fibrils.[42] Clinical manifestation ranges from polyneuropathy to cardiomyopathy[55]; the latter is notable with 3 mutations in the transthyretin gene, and is more common among middle-aged black individuals in the United States.[43] One mutation (val122-to-ile substitution) associated with late-onset RCM is particularly frequent and under-diagnosed in black individuals, with an estimated allele frequency of 3.9%.[44] Because RNA interference (RNAi) against transthyretin shows promise in clinical trials, the importance of this diagnosis cannot be overstated.[71]

The management of RCM is challenging. RVF leads to congestive hepatopathy[72] and cardiorenal syndrome.[73] An LV assist device can be applied in only a limited fashion and earlier referral in patients with symptoms of HF is reasonable.[74] Only patients with idiopathic RCM have favourable outcomes with cardiac transplantation.[70]

FDCM

FDCM is characterized by dilatation and impaired LV systolic function with enlargement of ventricular mass and variable penetrance.[16] The genetics of FDCM is complex and can follow any inheritance pattern, including AD (most common), mitochondrial DNA (mtDNA), and X-linked.[16] The most frequently reported gene mutations are *LMNA* and *TTN* (Fig. 1, Table 2), accounting for up to 7% and 25% of patients with FDCM, respectively.[16,32] Patients with the *LMNA* variant are at greater risk of malignant events, especially men or patients with nonmissense mutations (eg, mutations that affect splicing).[45] Larger LV size and systolic and diastolic dysfunction predict disease progression in children.[75] In adults, asymptomatic FDCM was identified in 4.6% of asymptomatic relatives, and only LV enlargement independently predicted disease progression.[76] When FDCM is associated with cardiac conduction disease, increased creatine kinase level, or family history, the yield from genetic testing is highest (15%–25%).[33,54] In patients who

undergo cardiac transplantation, the 10-year survival rate is 57% in women and 45% in men.[77]

LVNC

A developmental failure in trabecular compaction causes a 2-layered appearance of the myocardial wall in LVNC.[17] Changes in cardiac imaging and oversensitive criteria have led to an epidemic in the diagnosis of LVNC,[78] and caution is needed in assignment of this diagnosis. LVNC might be sporadic or familial, with AD, AR, and X-linked inheritance reported.[17] Mutations in sarcomere protein genes have been found in up to 50% of patients, with most in the myosin-7 (β-myosin heavy chain) gene, and > 50% that overlap with HCM (Table 2).[17] Unfortunately, existing diagnostic criteria lack specificity.[18] It might be that LVNC represents a common morphologic trait that overlaps between normal individuals and those with adverse remodelling due to other cardiomyopathic processes.[19]

Metabolic Cardiomyopathies

There are 4 main groups of inborn errors of metabolism (IEM) with prominent cardiac involvement: FAOD, mitochondrial function, carbohydrate metabolism (muscle glycogenoses), and lysosomes. Cardiac involvement can also occur with other disorders of intermediary metabolism (like organic acidemias, inherited defects of glycosylation, urea cycle defects, etc).[79]

With the exception of FD (see section on *Disorders of Lysosomes*), the cardiac features of IEM that cause cardiomyopathy are nonspecific and clinical clues to IEM lie in the pattern of extracardiac organ involvement, including diabetes mellitus, diplopia, hearing loss, skin lesions, neuropathic pain, kidney disease, or a history suggestive of rhabdomyolysis.[22,80] Although most IEM that cause cardiomyopathy are very rare (with the exception of medium-chain acyl coenzyme A [CoA] dehydrogenase [MCAD] and FD), there is disease-specific therapy available for most (eg, FD cardiomyopathy).[81]

FAOD

FAOD are multisystem and clinically heterogeneous FAOD inherited in an AR pattern.[21,22] The most common cause of exercise-induced rhabdomyolysis are FAOD[80]; other clinical features might include neuropathy, hypoglycemia, and cardiomyopathy.[22] Cardiomyopathy often results from FAOD that affect the metabolism of long-chain fats like very long-chain acyl-CoA dehydrogenase deficiency and long-chain acyl-CoA dehydrogenase deficiency, but can also occur in more common FAOD.[21,82–84] The prevalence of cardiomyopathy in patients with FAOD ranges from 12% to 55% depending on the age of onset.[85]

MCAD deficiency, an IEM that can present with SCD, was the first FAOD to be included in newborn screening panels.[20] Many patients with MCAD are asymptomatic as children and present as adults when their condition decompensates because of intercurrent illness or alcohol use.[85] Cardiomyopathy can be the presenting syndrome in adults, with high mortality rates (29%), so the index of suspicion should be high even in previously asymptomatic adults.[20] Acylcarnitine profile with tandem-mass spectrometry can identify >

20 different metabolic defects of fatty acid and organic acid metabolism.[22] The diagnosis is confirmed with mutation analysis and fibroblast cultures of enzyme activity.

Disorders of mitochondrial function

Mitochondrial disorders are caused by defects in nuclear or mtDNA genes that lead to abnormal cellular bioenergetics.[86] Any pattern of inheritance is possible.[24,87] Mitochondrial disorders are common (estimated prevalence: approximately 1 in 11,000 adults and approximately 1 in 6000 children).[23]

There are a number of well described syndromic presentations of mitochondrial disorders. For example, the most common clinical syndrome in adults is chronic progressive external ophthalmoplegia plus, usually associated with multiple mtDNA deletions,[49] and manifests with bilateral ptosis and ophthalmoparesis due to myopathy that affects the extraocular muscles.[49] The second most common syndrome is the mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode associated with the m.3243A>G mutation.[87] This syndrome causes stroke-like episodes and seizures (each affecting more than 60% of patients), diabetes mellitus (40%), proximal muscle weakness and fatigue (each affecting > 30% of patients).[24,46] More common than these syndromic presentations are patients with nonspecific clinical features, in whom gene panels including hundreds or thousands of genes are required to make the diagnosis.[88] The cardiac manifestations can be very diverse and include HCM or dilated cardiomyopathy, LVNC, and arrhythmia.[47] Patients can even present with HF as adults.[48] The diagnosis should be suspected with symptoms (hearing loss, endocrinopathies, exertional myalgia, seizures) and signs (nerve involvement, ataxia, myopathy) of disease involvement outside the cardiovascular system.[88]

Disorders of carbohydrate metabolism

Muscle glycogen storage diseases (GSD, most AR) are due to defects in glucose metabolism that lead to organomegaly, hypoglycemia and myopathy.[26,50] The most common adult form is McArdle disease (due to a *PYGM* mutation that affects myophosphorylase) with an estimated prevalence of between 1 in 7650 and 1 in 42,355 in Caucasian individuals.[25] Severe cardiomyopathy can be a feature of GSD III and IV.[89,90] In patients with myopathic GSD, a unique “second wind phenomenon” (an improvement in exercise tolerance 10–30 minutes into exercise, as muscle metabolism switches from carbohydrates to fat) might occur.[91] Creatine kinase level is usually increased with myopathic GSD, which can help to distinguish between GSD and FAOD.[50]

Two disorders classified as either GSD or lysosomal disorders are Pompe disease and Danon disease. Pompe disease cardiomyopathy is much more common and serious in the infantile-onset form.[92,93] Danon disease (X-linked dominant condition due to deficiency of lysosome-associated membrane glycoprotein 2) with glycogen accumulation within cardiomyocytes, skeletal myopathy, and cognitive impairment.[37] A third disorder, caused by mutations in the 5′ adenosine monophosphate (AMP)-activated protein kinase subunit γ2 (*PRKAG2*; encoding the enzyme that modulates glucose uptake and glycolysis) is associated with familial HCM,[26] with glycogen-associated granule accumulation leading to ventricular hypertrophy, pre-excitation, and conduction system defects (particularly Wolff-Parkinson-

White syndrome).[94] The glycogen deposition distinguishes familial HCM caused by sarcomere mutations from *PRKAG2* cardiomyopathy.[95] A *PRKAG2* mutation mouse model showed reversibility in cardiac dysfunction and electrophysiological disorders, suggesting that glycogen storage cardiomyopathy can be modulated by a decrease of glycogen content in the heart.[96]

Disorders of lysosomes

FD is caused by X-linked pattern mutations in the α-galactosidase A gene, which causes a deficiency in α-galactosidase.[28] FD is most commonly diagnosed in adults, with average age of death of approximately 60 years in untreated men.[97] FD is said to affect an estimated 1 in 40,000 to 60,000 men.[27,98] More recent data showed FD mutations in 1 in 1600 men with newborn screening.[99] FD screening in patients with HCM show a prevalence from 1% to 10%, therefore FD should be considered in every patient with HCM.[38–40]

In FD, the buildup of globotriaosylceramide causes acroparesthesias, angiokeratomas (dark red spots on the skin), hypohydrosis, hearing loss, chronic kidney disease, and cardiomyopathy.[27] Although this is an X-linked disorder, women can be affected with severe FD manifestations including cardiomyopathy (eg, late enhancement on gadolinium imaging before LV hypertrophy[29]) and stroke.[28]

FD can be screened using a simple dried blood spot test.[38] Enzyme activity can be normal in affected women, and requires genetic testing for diagnosis.[40] FD cardiomyopathy is amenable to enzyme replacement therapy and all patients should be referred to an expert centre for further evaluation.[81]

Genetic Modifiers of HF

Myocardial stress alters the expression of numerous genes leading to myocardial hypertrophy, dilatation, and interstitial fibrosis.[100] These genes, often a re-expression of a fetal gene program, are dynamically regulated in HF.

One large-scale study of more than 20,000 subjects showed 2 single nucleotide polymorphisms (SNPs) (odds ratio [OR], approximately 1.5) to be associated with HF.[101] An SNP in the K_a renal chloride channel gene is associated with HF risk (OR, 1.27 per allele copy),[102] which might have a considerable effect at the population level.[100,102,103] Other predisposing genetic factors, including epigenetic mechanisms like DNA methylation, histone modifications, adenosine triphosphate-dependent chromatin remodelling, and noncoding RNAs are related to the acquisition of HF, however, their discussion is beyond the scope of this article.[103]

Genetic Testing

Since the Human Genome Project was completed in 2003,[104] sequencing has become faster and less expensive. Whole-exome sequencing (WES) offers a more complete genetic picture with a cost that is equal to or less expensive than gene panels.[105] Genetic ascertainment of suspected familial cardiomyopathy using WES[54,106] presents several challenges: (1) clinical

diagnosis attained in an unclear percentage of index cases; (2) identification of novel and functionally deleterious variants for which significance is unclear; (3) confusion in interpretation of genetic testing results; (4) burden on clinical resources including staff and cost; and (5) effect on relatives, including anxiety and commitment to future screening.

WES can be particularly helpful in determining the genetic factors responsible for familial cardiomyopathy, however, there is a documented lack of genotype-phenotype correlation (Table 2), which makes the use of genetic panels challenging.[105] It also offers the potential of new gene discovery.[105] Genetic testing should always be performed in a skilled, high-volume setting with expertise in genetic counselling.

Current guidelines recommend genetic testing for any patient with a clinical diagnosis of familial cardiomyopathy, and mutation-specific testing for family members of a genotype-positive proband.[33,53] Two of the most compelling reasons for genetic testing in clinical practice are: (1) the identification of family members with no structural abnormalities at potential risk; and (2) clarification of diagnosis in patients with IEM for whom clinical presentation and pattern is similar to familial cardiomyopathies but with differing outcomes (Table 2). Table 4 shows the recommended interval surveillance of adult patients with gene-positive cardiomyopathy. Large studies are needed to assess the effect of genetic diagnosis on response to drug therapies and outcomes.

Genetic Approaches to Therapy: Pharmacogenetics and Future Approaches

Pharmacogenomics

The treatment of chronic HF improved markedly with the adoption of 3 drug classes; angiotensin converting enzyme (ACE) inhibitors (ACEi)/angiotensin-II receptor blockers, β-blockers, and aldosterone antagonists, along with implanted cardioverter defibrillators and cardiac resynchronization therapy.

However, there is vast interindividual variation in response to those treatments and a significant amount of the variability is likely due to individual genetic variation.[107] Various cytochrome P450, family 2, subfamily D, polypeptide 6 (*CYP2D6*) alleles in metoprolol users increase the drug's plasma concentration in patients with *0/*0 genotypes and intermediate genotypes compared with those with 2 fully functional alleles ($n = 31$; $P < 0.01$).[108] This pronounced effect of the *CYP2D6* genotype causes increased blood levels of metoprolol by several fold, which might have an effect on its cardioselectivity. Another study found no association between the various *CYP2D6* genotypes and metoprolol-induced adverse effects or efficacy in hypertensive patients[109]; a subsequent study that examined carvedilol's pharmacokinetic effects showed similar results.[110] In the largest study to examine this association, Bijl et al. showed a lower diastolic blood pressure (approximately 5.4 mm Hg lower) in poor β-blocker metaolizers by *CYP2D6* compared with extensive metabolizers who harboured similar polymorphisms.[111] However, the results from such studies are rather inconsistent because of small population size and limitations in the study methodology. Therefore, although this pharmacogenetic effect is likely to have theoretical

risks on the clinical benefits of β-blocker treatment and adverse drug reactions, investigations of this type might lead to personalized medication regimens and improved clinical outcomes in the future.

Adrenergic receptors variants and β-blockers

In response to decreased cardiac output in chronic HF, several neurohormonal systems, including the sympathetic nervous system, are activated in an effort to maintain adequate circulation. Sympathetic hyperactivation in HF results in five-to sixfold increased circulating levels of norepinephrine compared with healthy control subjects,[112] and is increased in direct proportion to the degree of LV dysfunction.[113] Chronic stimulation of the adrenergic receptor in HF by the circulating catecholamines norepinephrine and epinephrine result in cardiac dysfunction.

β-Blockers have been the backbone of HF therapy since 1997 when the US Food and Drug Administration approved carvedilol for the treatment of HF.[114,115] Nevertheless, there have been several studies that documented a variation in response to β-blocker therapy with some HF patients benefiting more than others.[114,116,117] Genetic polymorphisms in the β1-adrenergic receptor (ADRB1) have been examined. One of the most studied polymorphisms in the *ADRB1* gene is the Arg389Gly variant, which is highly conserved among species with conflicting results in various studies. The **B**eta-Blocker **E**valuation of **S**urvival **T**rial (BEST) (ClinicalTrials.gov Identifier: NCT00000560) was a large, randomized clinical trial in which the efficacy of bucindolol in HF was evaluated. The trial was terminated prematurely because of a lack of mortality benefit in the overall trial population; however, mortality benefit was significantly improved in the nonblack subset of patients. In a genetic substudy of BEST, Arg-389 homozygotes treated with bucindolol had a statistically significant age-, sex-, and race-adjusted reduction in mortality (38%) and reduction in mortality or hospitalization (34%) vs placebo.[118] In contrast, Gly-389 carriers had no clinical response to bucindolol compared with placebo.[118] However, there are conflicting data with regard to other β-blocker therapies. No significant difference in mortality, hospitalization, or drug effect was found in other randomized trials in which the effect of the Arg389Gly variant in patients who took long-acting metoprolol and carvedilol was assessed.[117,119]

Another variant that has been studied in *ADRB1* is a Ser to Gly change at codon 49. Patients with idiopathic dilated cardiomyopathy who were homozygous for Ser49 had poorer prognoses, as measured by occurrence of death or cardiac transplant, compared with Gly49 carriers.[120] In a follow-up study, the response to β-blocker therapy was evaluated based on genotype. In patients who took low-dose β-blocker therapy, the 5-year mortality rate was lower among Gly49 carriers than in Ser49 homozygotes.[121] In patients who took high-dose β-blockers, there was no significant difference in outcome between genotypes, with better outcomes for Ser49 homozygotes.[121]

Polymorphisms in the β2-adrenergic receptor (ADRB2) gene have also been extensively studied. In a large prospective cohort study of β-blocker therapy after acute coronary syndrome, Lanfear et al. showed a differential 3-year survival in β-blocker users on the basis of Gly16Arg (46 GA) and Gln27Glu (79 CG) genotypes in *ADRB2*.[122] In another study on the response to carvedilol in HF patients, subjects who were homozygous for Gln27

displayed a lower response rate of improvement of LV function (≥10%) or fractional shortening (≥ 5%) than patients who were homozygous or heterozygous for Glu27 (26% vs 63%; $P = 0.003$).[123] In a further report on the effect of genetic polymorphisms in the sympathetic nervous and the renin-angiotensin-aldosterone system on prognosis in HF, patients carrying 2 copies of the *ADRB2* Arg16Gln27 haplotype had increased risk for adverse outcomes (hazard ratio, 1.91; 95% confidence interval, 1.09–3.36).[124] Other studies have shown that polymorphisms in *ADRB1* and adrenoceptor alpha 2C gene (*ADRA2C*) synergistically influence the ejection fraction response to β-blocker therapy of HF patients,[125,126] and have been associated with the development of hypertension.[127] More clinical studies are warranted before genetic testing for predicted response to β-blocker therapy is applied in the clinical setting. Particularly, there is a need to assess multiple adrenergic receptor variants simultaneously to get an accurate picture of the overall effect on pharmacological therapy.

Renin-angiotensin-aldosterone system

Multiple clinical trials have established the survival benefit of ACEi therapy, resulting in their central prominence in modern day HF pharmacotherapy.[115,128,129] An insertion/deletion (D) polymorphism in *ACE* has been shown to explain approximately half of the variance in systemic ACE levels (the D allele associated with increased ACE levels) and is associated with HF incidence and severity.[129–132] Because the *ACE* D allele results in higher ACE levels, it has been theorized that HF patients who carry the D allele might require a higher dose of ACEi to achieve a response similar to individuals who do not carry the D allele. Most studies that assessed intermediate phenotypes of this (ie, serum ACE activity, aldosterone escape, and mean arterial pressure) support this theory.[133–136] The relationship between the *ACE* polymorphism and survival benefit in HF requires further evaluation in larger studies.

In the most extensive pharmacogenetic study of HF patients to assess the *ACE* polymorphism, a dose-dependent relationship between the *ACE* D allele and transplant-free survival was observed.[137] After a mean follow-up of 33 months, patients who received low-dose ACEi therapy had poorer transplant-free survival associated with the D allele (relative risk of 2.07 for DD homozygotes).[137] The relative risk in DD homozygotes was 2.75 for those who did not receive β-blocker therapy.[137] As might be expected, there was no significant difference between the effects of the D allele in patients who received high-dose ACEi therapy. So, although the D allele was associated with poorer transplant-free survival, these were the patients who benefited most from ACEi and β-blocker therapy.

Diuretics, Aldosterone Antagonists, and Digoxin Therapy

The clinical implication of pharmacogenetics on other cardiovascular-related drugs have been reported albeit the data are limited. One study that examined individuals receiving a thiazide diuretic who were carriers of 1 or 2 copies of the Trp460 variant allele showed greater protection from the combined outcome of myocardial infarction and stroke (OR, 0.49; 95% confidence interval, 0.32–0.77) than patients with Gly460.[138] Verstuyft et al. examined the multidrug resistance gene (*MDR1*) C3435T SNP on digoxin plasma

concentration and showed that individuals who were homozygous TT had the highest digoxin concentrations.[139] In another study in African Americans with resistant hypertension who were randomized to treatment with placebo, spironolactone, amiloride, or combination, the spironolactone arm with rs3890011 GG and GC (variants of cytochrome P450, family 4, subfamily A, polypeptide 11 [*CYP4A11*]) but not in CC homozygotes ($P = 0.002$), had reduced blood pressure when compared with the other drugs.[140] Collectively, there is currently no role for pharmacogenetic testing in the clinical use of these medications and further studies are needed to replicate these results, which would then have important therapeutic implications in the management of cardiovascular disease.[140]

Future Approaches to Genetic Therapies

It has been the goal of the Clinical Pharmacogenetics Implementation Consortium of the National Institutes of Health's Pharmacogenomics Research Network (http://www.pgrn.org) and the Pharmacogenomics Knowledge Base (PharmGKB; http://www.pharmgkb.org) to provide guidelines for gene therapy to facilitate the translation and clinical use of pharmacogenomics.[141] One of these approaches includes promotion of high volume laboratories to construct a genomic profile that can preemptively be tested in patients who take certain drugs and aid with individualized therapy.

There has been some progress in gene therapy as a futuristic option to treat HF. For example, one study that involved the transfer of the sarcoplasmic reticulum Ca^{2+} ATPase gene, with the help of a vector, into the cardiac myocardium to rescue HF,[142] showed potential beneficial effects on the cardiomyocyte.[143] However, there are unprecedented challenges in translating gene therapy to human patients and clinical practice, such as inefficient delivery methods and host immune responses, to technological limitations in health care systems and provider awareness about genomics.

Several microRNA experiments have provided some hope for the therapeutic application of microRNA in heart disease. Carè et al. showed that in vivo inhibition of microRNA 133 by a single infusion of an antagomir caused marked and sustained cardiac hypertrophy.[144] A recent study in a mouse model revealed that increased expression of endogenous microRNA 25 contributed to declining cardiac function during HF and can be halted by injection of an antisense oligonucleotide against microRNA 25, and thereby improve cardiac function and survival relative to control.[145]

Collectively, more studies are warranted to help determine the individual's genomic profile, which might be of value in the tailoring of therapy in patients with HF and the understanding of precision medicine.

Conclusions

The causes of advanced HF are diverse. Inherited etiologies represent an important and potentially treatable group of disorders with which clinicians should become very familiar. Genetic technology has revolutionized cardiovascular genetics, and as we continue to discover novel disease-causing genes on an unprecedented scale, new methods and technologies to rapidly assess the functional significance of variants singly, or in

combination, will evolve. In this review, we focused on the various inherited phenotypes of cardiomyopathy, treatment challenges, and future genetic therapies.

In summary, we recommend a careful 3-generation pedigree search for history of acquired or inherited cardiometabolic diseases, including SCD, and a thorough review of systems to help ascertain the etiology; a careful assessment for potentially reversible causes of cardiomyopathy (eg, FD, hemochromatosis, HCM etc); a tailored approach to early referral for consideration of various therapies, including those for advanced HF, however, we would not recommend genetic testing for SNPs in patients at this point in time; and judicious collaboration with a centre of expertise in cardiovascular genetics for counselling and testing in all patients with possible advanced HF not due to typical ischemic etiologies.

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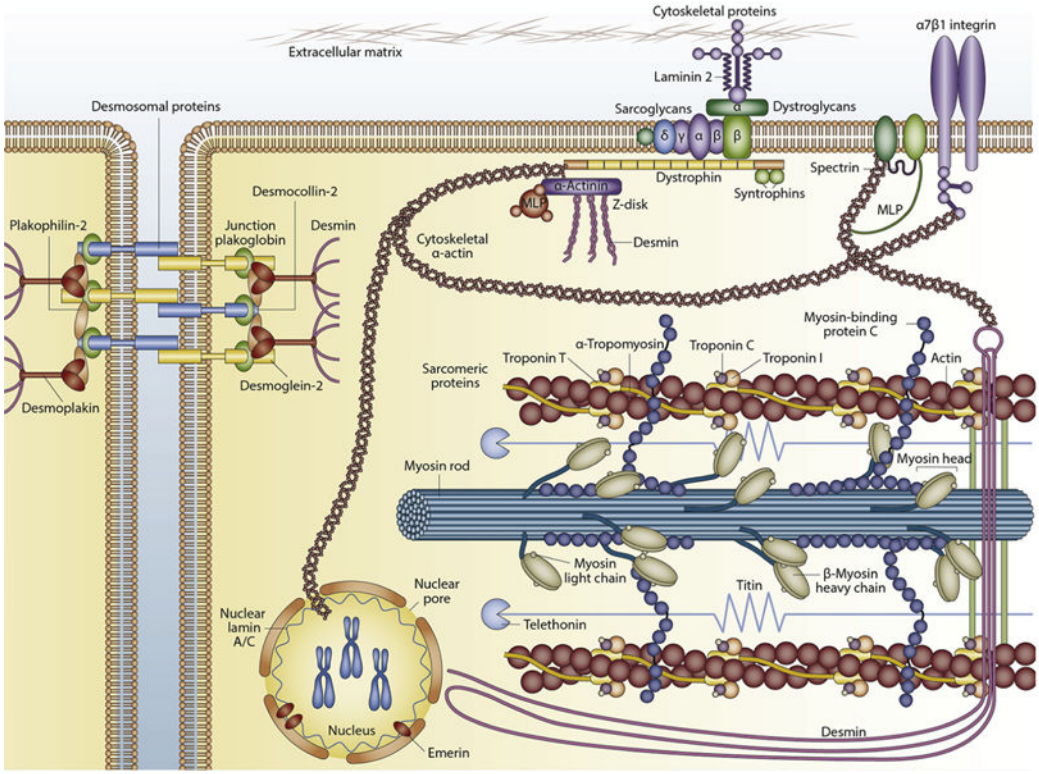

Figure 1.

Main types of proteins involved in familial cardiomyopathy. MLP, muscle protein. Reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews Cardiology*.[51] Copyright © 2013.

Table 1

Characteristics of inherited causes of heart failure

Disease	Prevalence	Inheritance pattern	Investigations
Familial cardiomyopathy			
1. HCM	Approximately 1 in 500[9]	Most: AD[10] >50% familial[10]	Unexplained hypertrophy on cardiac imaging, typical ECG abnormalities and genetic testing[11]
2. ARVC	Approximately 1 in 2000[12]	Most: AD with incomplete penetrance[13] Rare AR forms[13] 30–50% familial[13]	Enlargement, aneurysm, and fatty infiltration of the ventricles, ECG changes, and genetic testing[12]
3. RCM	1 in 1000–5000[14]	Most: AD[15] Usually not familial[15]	Generally, atrial arrhythmias, right and left sided filling pressures with clinical signs and symptoms of RVF, and ventricular arrhythmias, with and without genetic testing[14]
4. FDCM	Approximately 1 in 2500[16]	Any pattern: AD (most common), mtDNA, and X-linked[16] Variable penetrance[16] 35% familial[16]	Ventricular dilatation, impaired systolic function, and overall enlargement of ventricular mass[16]
5. LVNC	Not well known[17]	AD, AR, and X-linked[17]	Existing diagnostic criteria might be oversensitive[18] Diagnosis is controversial[19]
Metabolic cardiomyopathy			
1. FAOD	MCAD: approximately 1 in 10,000[20] Others: less common[21]	Most: AR[21]	Screening: acylcarnitine profile Confirmation: mutation analysis or fibroblast culture[22]
2. Mitochondrial disorders	Adults: approximately 1 in 11,000; children: approximately 1 in 6000[23]	Any pattern: maternal (through mtDNA) or nuclear DNA in AD, AR or X-linked[24]	Muscle biopsy with analysis for defects in mtDNA and/or nuclear DNA[24]
3. Glycogen storage diseases	Varies with type[25] McArdle disease: approximately 1 in 7650–42,355[25]	Most: AR[26]	Muscle biopsy: increased glycogen stores[26] Subtyping: enzyme or DNA analysis[26]
3. Disorders of lysosomes	Varies with type[27] FD: approximately 1 in 40,000 men[27]	FD is X-linked[27] Other patterns reported[28]	Levels of α galactosidase can be tested in WBC and are diagnostic in men but might be normal in clinically affected women Mutational analysis (*GLA* gene in FD)[29]

AD, autosomal dominant; ARVC, arrhythmogenic right ventricular cardiomyopathy; ECG, electrocardiogram; FAOD, disorders of fat metabolism; FD, Fabry disease; FDCM, familial dilated cardiomyopathy; *GLA*, α-galactosidase A; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction cardiomyopathy; MCAD, medium chain acyl coenzyme A dehydrogenase; mtDNA, mitochondrial DNA; RCM, restrictive cardiomyopathy; RVF, right ventricular failure; WBC, white blood cells.

Table 2

Selective genes associated with inherited cardiomyopathies

Gene (location)	Protein	Disease	Reference(s)
Membrane and or cytoplasm			
HFE (6p21.3)	Hereditary hemochromatosis protein	DCM*	31
FKTN (9q31.2)	Fukutin	DCM	16,32
TMEM43 (3p25.1)	Transmembrane protein 43	ARVC	33–35
LAMP2 (Xq24)	Lysosome-associated membrane glycoprotein 2	Danon disease: DCM* HCM*	10,33,36,37
GLA (Xq22)	α-Galactosidase A	FD* HCM*	38–41
PRKAG2 (7q36.1)	5′–AMP-activated protein kinase subunit γ2	GSD: HCM*	26
PSEN1 (14q24.3)	Presenilin-1	DCM	33–35
TTR (18q12.1)	Transthyretin	Amyloidosis: RCM	42–44
Ion channels			
SCN5A (3p21)	Cardiac sodium channel	DCM	33–35
DTNA (18q12.1)	α-Dystrobrevin	LVNC	17,18
ABCC9 (12p12.1)	SUR2A subunit, K_{ATP} channel	DCM	33–35
ILK (11p15.4)	Integrin-linked kinase	DCM	33–35
CHRM2 (7q33)	M2-muscarinic acetylcholine receptor	DCM	33–35
PLN (6q22.1)	Cardiac phospholamban	HCM, ARVC, DCM	10,33–36
CASQ2 (1p13.1)	Calsequestrin 2	DCM, LVNC	33–35
RYR2 (1q43)	Ryanodine receptor 2	ARVC	33–35
Cytoskeleton			
CRYAB (11q22.3–q23.1)	α-Crystallin B chain	HCM, DCM	10,33–36
DMD (Xp21.2)	Dystrophin	DCM	16,32
DES (2q35)	Desmin	ARVC, RCM, DCM,	10,33–36,45
LAMA4 (6q21)	Laminin subunit α4	DCM	33–35
FKTN (9q31-q33)	Fukutin	DCM	33–35
FXN (*FRDA*) (9q21.11)	Frataxin, mitochondrial	HCM	10,33
Nuclear			
LMNA (1q22)	Lamin A/C	ARVC, DCM	10,33–36
PRDM16 (1p36.32)	PR domain-containing 16	DCM	33–35
NKX2-5 (5q35.1)	Homeodomain transcription factor	DCM, LVNC	10,33,35,36
EMD (Xq28)	Emerin	DCM	33–35
Desmosomal			
DSP (6p24)	Desmoplakin	ARVC, DCM, LVNC	33–36
FHL1 (Xq26)	Four and a half domains protein 1	HCM	10,33
FHL2 (2q12.2)	Four and a half domains protein 2	DCM	33,35
JUP (17q21)	Junction plakoglobin	ARVC	33–36
PKP2 (12p11)	Plakophilin-2	ARVC, DCM	10,33–36
DSG2 (18q12.1)	Desmoglein-2	ARVC, DCM	10,33–36

Gene (location)	Protein	Disease	Reference(s)
DSC2 (18q12.1)	Desmocollin-2	ARVC, DCM	10,33–36
Sarcomere			
TTN (2q31)	Titin	HCM, ARVC, DCM	10,33–36
MYH7 (14q12)	Myosin-7 (β-myosin heavy chain)	HCM, RCM, DCM, LVNC	10,33–36
MYH6 (14q12)	Myosin-6 (α-myosin heavy chain)	HCM, DCM	10,33,35,36
MYL2 (12q24.11)	Myosin regulatory light chain 2	HCM, RCM	10,33,36
MYL3 (3p21.3-p21.2)	Myosin light chain 3	HCM, RCM	10,33,36
MYLK2 (20q11.21)	Myosin light chain kinase 2	HCM	10,33
MYBPC3 (11p11.2)	Cardiac myosin-binding protein C	HCM, DCM, LVNC	10,33–36
TNNT2 (1q32)	Cardiac muscle troponin T	HCM, RCM, DCM, LVNC	10,33–36
TNNI3 (19q13.4)	Cardiac muscle troponin I	HCM, RCM, DCM, LVNC	10,33–36
TPM1 (15q22.1)	Tropomyosin α1 chain	HCM, RCM, DCM, LVNC	10,33–36
ACTC1 (15q14)	Cardiac actin	HCM, RCM, DCM, LVNC	10,33–36
TNNC1 (3p21.1)	Cardiac muscle troponin C	HCM, DCM	10,33,35,36
Z-disc			
LDB3 (10q22.2-q23.2)	LIM domain-binding protein 3	HCM, DCM, LVNC	10,33–36
MURC (9q31.1)	Muscle-restricted coiled-coil	DCM	35
TCAP (17q12)	Telethonin	HCM, DCM	10,33,35,36
ANKRD1 (10q23.31)	Ankyrin repeat domain-containing protein 1	HCM, DCM	10,33,35,36
MYPN (10q21.3)	Myopalladin	HCM, DCM	10,33,35,36
ACTN2 (1q42-q43)	α-Actinin-2	HCM, DCM	10,33,35,36
Mitochondrial disorder			
MT-TL1 location (mitochondrially located)	Transfer RNA	MELAS, MIDD, CPEO+, MERRF	46–48
COX15 (10q24.2)	Cytochrome *c* oxidase assembly protein	Leigh syndrome, complex IV deficiency	46,49,50
TAZ (Xq28)	Zinc finger and domain-containing protein 18	Barth syndrome: DCM, LVNC	46,49,50
SDHA (5p15)	Succinate dehydrogenase	DCM	46,49,50

AMP, adenosine monophosphate; ARVC, arrhythmogenic right ventricular cardiomyopathy; ATP, adenosine triphosphate; CPEO+, chronic progressive external ophthalmoplegia plus; DCM, dilated cardiomyopathy; FD, fabry disease; GSD, glycogen storage diseases; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction cardiomyopathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode; MERRF, myoclonic epilepsy with ragged-red fibers; MIDD, maternally inherited diabetes and deafness; RCM, restrictive cardiomyopathy.

*Potentially reversible.

Table 3

Nonstandard abbreviations, acronyms, and definitions

ADRB: β-adrenergic receptor
Alleles: alternative forms of a gene
ARVC: arrhythmogenic right ventricular cardiomyopathy
CPEO+: chronic progressive external ophthalmoplegia syndrome plus
FA: Friedreich ataxia
FAOD: disorders of fat metabolism
FD: Fabry disease
FDCM: familial dilated cardiomyopathy
Genes: units of inheritance at specific locations (loci) on a chromosome
GSD: glycogen storage diseases
HCM: hypertrophic cardiomyopathy
Heterozygous: a genotype with 2 different alleles of a gene for a particular trait
Homozygous: a genotype with the same allele of a gene for a particular trait
IEM: inborn errors of metabolism
LCHAD: long chain acyl coenzyme A dehydrogenase deficiency
LVNC: left ventricular noncompaction cardiomyopathy
MCAD: medium chain acyl coenzyme A dehydrogenase
MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome
MERRF: myoclonic epilepsy with ragged red fibre syndrome
MIDD: maternally inherited diabetes and deafness
mtDNA: mitochondrial DNA
Mutations: alteration of genetic material producing a new variation
Phenotype: detectable expression of a genotype
RCM: restrictive cardiomyopathy
SCD: sudden cardiac death
TRR: familial transthyretin
VLCAD: very long chain acyl coenzyme A dehydrogenase deficiency
X-linked: a gene that is carried by the X (sex) chromosome

Table 4

Evaluation of relatives of patients with cardiomyopathy

Cardiomyopathy	Interval	Screening
Gene positive	12 months	Symptom assessment SCD risk stratification Medication reconciliation Exercise counselling Physical examination ECG and echocardiography
	3–5 years (if stable without clinical progression or related complications)	As above
Gene negative	12–18 months (in those with ventricular enlargement or depressed fractional shortening)	As above
	3–5 years (if stable without clinical progression or related complications)	As above

ECG, electrocardiogram; SCD, sudden cardiac death.

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