

Review

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.

RÉSUMÉ

L'étiologie de l'insuffisance cardiaque est variée. Les causes génétiques représentent une entité clinique importante et peuvent être divisées en deux grandes catégories : les myocardiopathies familiales et métaboliques. Les caractéristiques distinctives pouvant se manifester aux stades précoces de la maladie s'apparentent souvent aux caractéristiques d'autres maladies, comme dans le cas des myocardiopathies génétiques (c.-à-d. myocardiopathie familiale hypertrophique ou maladie mitochondriale). Dans le cadre de cet article de synthèse, l'accent sera mis sur les troubles génétiques associés à l'insuffisance cardiaque de stade avancé. En raison de l'importance émergente de ce sujet et de son ampleur, nous désirons concentrer la discussion sur les formes génétiques connues des syndromes d'insuffisance cardiaque, le dépistage génétique, et les nouvelles données sur la pharmacogénétique et les agents thérapeutiques utilisés dans le traitement de l'insuffisance cardiaque, principalement pour encourager les cliniciens à prioriser le diagnostic et le traitement de ces affections pouvant être traitées.

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

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.

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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 (<i>GLA</i> 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.

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

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