Published in final edited form as:

Prog Cardiovasc Nurs. 2009 September ; 24(3): 80–85. doi:10.1111/j.1751-7117.2009.00039.x.

Cardiovascular Nursing on Human Genomics: What do cardiovascular nurses need to know about congestive heart failure?

Lorraine Frazier, R.N., Ph.D., M.S., F.A.A.N.,

Nancy B. Willerson Distinguished Professor in Nursing, The University of Texas Health Science Center at Houston School of Nursing, Houston, Texas

Shu-Fen Wung, PhD, RN, ACNP, FAAN,

Associate Professor, University of Arizona

Elizabeth Sparks, RN, MS, CS, APNG, and

Senior Research Specialist, Seidman Laboratory, Harvard Medical School, Boston MA

Cathy Eastwood, BN, MN

Advanced Clinical Nurse for Heart Failure and MI, St. Luke's Episcopal Hospital, Houston, Texas

Abstract

This paper presents the main causes of heart failure (HF) and an update on the genetics studies on each cause. The review includes a delineation of the etiology and fundamental pathophysiology of HF and provides rationale for treatment for the patient and family. Various cardiomyopathies are discussed, including primary cardiomyopathies, mixed cardiomyopathies, cardiomyopathies that involve altered cardiac muscle along with generalized multi-organ disorders, and various cardiovascular conditions, such as coronary artery disease (ischemic cardiomyopathy) and hypertension (hypertensive cardiomyopathy).¹ A brief review of pharmacogenetics and HF is presented. The application of the genetic components of cardiomyopathy and pharmacogenetics is included to enhance cardiovascular nursing care.

Keywords

Congestive heart failure; genetics; genetic testing; cardiomyopathy

Introduction

Heart failure (HF) is a chronic and progressive decline in the heart's ability to fill with or eject enough blood to the body tissues. The decline in function is accompanied by cardiac remodeling as the body attempts to maintain cardiac function during short-term cardiac stress.² HF is most often accompanied by a decline in quality of life and functional capacity. The fatigue and dyspnea symptoms of HF are caused by peripheral and/or pulmonary congestion.³ Unfortunately, HF continues to increase in incidence in North America.

Cardiomyopathy is second to coronary artery disease as the most common direct cause of sudden death in the United States.⁴ As defined in the most recent consensus on classification, cardiomyopathies are a heterogeneous group of myocardial diseases associated with mechanical and/or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilatation. Cardiomyopathies are due to a variety of causes, frequently genetic.⁵ The contemporary view taken by the consensus team of the American Heart Association Council on Clinical Cardiology, Heart Failure and Transplantation

Committee was that genetics play a significant role in HF development. This genetic link was determined from the study of inherited familial genetic patterns or mutations in protein encoding genes for cell ion transport. Cardiac remodeling, or changes in myocyte shape and number, occurs in one of two patterns-hypertrophy or dilation. Hypertrophic cardiomyopathy is marked by myocyte enlargement, interstitial fibrosis, myocyte disarray with impaired relaxation, and predominantly diastolic dysfunction. In contrast, ventricular dilation and diminished contractile (systolic) function are the predominant features in dilated cardiomyopathy. 6 Clinical manifestations, or phenotypes, and cardiac morphologic remodeling respond to sarcomere mutations, genes that regulate the renin-angiotensin system, and matrix metalloproteases. The considerable phenotypic overlap has made it difficult to distinguish hypertrophic from restrictive cardiomyopathy (RCM), and subsequently more difficult to identify genetic causes of RCM. 7

Cardiomyopathies have been grouped as primary, meaning limited to the heart muscle (including genetic, mixed genetic and nongenetic causes), and acquired or secondary. Secondary forms include a large list of conditions that alter cardiac muscle along with generalized multi-organ disorders. It is becoming clearer that some patients with HF have a familial predisposition to HF due to a primary cardiomyopathy, caused by a single gene defect. 1 Pedigrees of families with autosomal dominant disorders demonstrated equal distribution of affected males and females, and affected individuals in every generation (linear inheritance). In contrast, affected siblings (horizontal inheritance) characterizes pedigrees of families with recessive disorders. In recessive disorders, inheritance of two copies of the mutated gene, one from each parent, are necessary for expression of the abnormal trait or disease. Clear delineation of the etiologies of HF provides nurses with the fundamental pathophysiology that shapes clinical decision-making and rationale for treatment and patient/family interventions.

Primary Cardiomyopathies

Primary cardiomyopathies encompass hypertrophic (obstructive) cardiomyopathy (HOCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) and ion channelopathies. HOCM is defined as unexplained ventricular hypertrophy with normal ventricular chamber dimensions on cardiac imaging studies, and the absence of chronic systemic hypertension or aortic valve stenosis. HOCM is the most common cause of sudden cardiac death in young people, and is likely the most commonly occurring cardiomyopathy. A “variety of mutations encoding contractile proteins of the cardiac sarcomere occur with this autosomal dominant genetic disease” .5

The ion channelopathies are the most recently delineated cluster of electrolyte movement irregularities resulting in serious dysrhythmias. 5 In arrhythmogenic right ventricular cardiomyopathy/dysplasia, ARVC/D, the myocardium becomes arrhythmogenic as a result of diffuse or segmental thinning of the right ventricle that is replaced by fibro-fatty tissue. The longer one lives with the right ventricular dysfunction, the more likely the left ventricle will enlarge. ARVC/D is less common but prevalent in isolated populations such as the island of Newfoundland in Canada. 8 ARVC/D most often appears in young people or athletes. Ventricular tachycardia results in symptoms of syncope, and sudden cardiac death. 9 The ion channelopathies are rarer and can be associated with dysrhythmias. These dysrhythmias result from inherited and congenital long or short QT arrhythmia syndromes, caused by mutations in genes encoding sodium-potassium ion transporter proteins in the cell membrane. These regulator proteins maintain homeostasis at the cellular level.

Mixed Cardiomyopathies (genetic and nongenetic)

Dilated cardiomyopathy (DCM) is classified under the category of mixed cardiomyopathies. Although ischemic heart disease and hypertension are the most common causes of HF, dilated cardiomyopathy is the third most common cause, with as many as 30% of patients having a genetic cause. When familial, DCM is usually caused by autosomal dominant transmission. Secondary DCM results from systemic causes: infectious agents; toxic chemical ingestion or exposure; or from autoimmune disorders. Patients with DCM present with left ventricular dilation, reduced systolic function, and normal wall thickness on echocardiogram.⁶

A genetic association with familial cardiomyopathy was postulated in the early 1980s, with the identification of alpha actin (ACTC) as the first disease-causing DCM gene in 1998.¹⁰ Familial screening with echocardiography and genetic studies has been instrumental in identifying sarcomere mutations in 25% to 30% of asymptomatic affected relatives of individuals with dilated cardiomyopathy.^{11, 12} Moreover, up to 50% of all idiopathic cardiomyopathy cases are inherited or familial. Currently, the number of disease-causing DCM genes approaches 20. (Table 1)

Restrictive cardiomyopathy is another rare mixed cardiomyopathy, and can be idiopathic or familial. RCM is marked by normal left ventricular cavity dimension, biatrial enlargement, impaired ventricular filling, and may or may not be associated with increased left ventricular wall thickness (hypertrophy).⁷ Secondary RCM is poorly understood, and occurs secondary to infiltration (amyloidosis), toxins (drugs, heavy metals, and chemotherapy agents), inflammation (sarcoidosis), endocrine disorders (diabetes mellitus and thyroid dysfunction) or other neurological and autoimmune disorders. These are but a few examples illustrating the breadth of disorders that can lead to cardiomyopathy. Historically, it has been difficult to assign clinical status in younger patients with heritable cardiomyopathy because the signs and symptoms of disease (phenotypes) may not emerge until adulthood.

Heart Failure Secondary to Cardiovascular Comorbidities

In addition to primary and secondary genetic causes, cardiomyopathy and HF can also result from cardiovascular comorbidities, such as valvular heart disease, systemic hypertension or myocardial ischemia/infarction. These cardiovascular conditions account for the majority of patients with HF symptoms. In the Western World, systolic dysfunction resulting from myocardial ischemic injury/infarction due to underlying coronary artery disease is the most common cause of HF. Currently, the genetic contribution to ischemic cardiomyopathy is limited, due to the multifactorial nature of this disease.¹ The second most common cause of secondary HF is chronically increased intracardiac pressure due to uncontrolled hypertension. Elevated intracardiac pressure impedes myocardial filling during diastole, or diastolic dysfunction.¹³ Diastolic dysfunction is frequently identified in elderly women with HF symptoms (fatigue and dyspnea) whose echocardiograms demonstrate left ventricular ejection fractions greater than 50% and abnormal diastolic indices.

Genetic Testing and Cardiomyopathy

Research findings over the past two decades have led to the option of clinical DCM testing.¹⁴ To be informative, novel genetic changes should be correlated with clinical findings and family history, since some genetic changes are neutral variants that do not correlate with disease. The genetic status of clearly affected and unaffected individuals is extremely helpful in resolving the significance of genetic findings. As well, testing both subgroupshelps to reduce test uncertainty and improve confidence in the genetic test.

For members of families with heritable cardiomyopathy, genetic testing informs patients about their likelihood of developing cardiomyopathy. Knowing one carries a disease-causing mutation empowers the patient by guiding medical and lifestyle decisions. Conversely, “negative” results are usually “uninformative”. For example, it is quite possible that there remain cardiomyopathy genes which have not been discovered. Alternatively, it is also possible that the cause of cardiomyopathy in some families is caused by the interaction of several genes (polygenic), or from the interaction of genes and the environment (multifactorial). The etiology of these unidentified causes of cardiomyopathy awaits resolution. “Uninformative” samples should undergo reanalysis as novel genetic discoveries emerge. Coupled with the expense of genetic testing, uninformative/uncertain genetic test results create considerable angst for the patient and family.¹⁵

In addition to empowering individuals, genetic discoveries promote our understanding of molecular and cellular mechanisms that drive pathophysiology. More importantly, these discoveries provide the foundation for gene-targeted therapies. Studies in genetically engineered mice demonstrated that cellular calcium dysregulation precedes the earliest observable cardiac phenotype-left ventricular hypertrophy. Genotypically affected mice were randomized to placebo or to the calcium channel blocking medication, diltiazem. The placebo-treated mice developed HF and myocardial changes consistent with hypertrophic cardiomyopathy, whereas ventricular hypertrophic changes were mitigated or prevented in the diltiazem-treated mice.¹⁶ Based on these findings in the genetically engineered mice, a randomized double-blind diltiazem versus placebo human study is currently under way. This study will compare left ventricular hypertrophy, diastolic performance, extent and severity of myocardial fibrosis and plasma biomarkers in children and young adults harboring the genetic substrate for hypertrophic cardiomyopathy.

The renin-angiotensin system, the sympathetic-adrenergic system, cytokines and growth factors, endothelin and related receptors, endothelial release factor system, matrix metalloproteases and related inhibitors, cardiac natriuretic peptides, adenosine/adenosine monophosphate, and oxidative stress have all been shown to contribute to the initiation and progression of HF. Therefore, most genetic research in HF patients has been conducted by studying genes encoding these pathophysiologic pathways. This is known as the candidate gene approach, and is widely used to study genetic polymorphisms (variations) and genetic defects directly involved in the pathophysiology of HF (susceptibility genes) or modification of HF phenotypic expression (modifier genes).

In the last five years, the effects of a common variation in the DNA sequence, single nucleotide polymorphisms (SNPs) in candidate genes in HF have been reviewed and summarized by several authors.^{17·18·19·20·21} These reviews suggest that there is evidence that genes play a role in the pathophysiology of HF. Most studies report that many SNPs may have a modest effect on HF outcomes. Overall, genetic study results in HF have been inconsistent. These contradictory outcomes have been attributed to the small sample size (lack of power) to detect the typically small effects in genetic association studies of multifactorial traits, such as with HF.²² Therefore, results of several research investigations are integrated, referred to as meta-analysis. A recent meta-analysis²³ examined five polymorphisms: 1) insertion/deletion polymorphism in the gene encoding angiotensin-converting enzyme [ACE I/D], 2) β_1 -adrenergic receptor gene [ADRB₁] Arg389Gly, 3) β_2 -adrenergic receptor gene [ADRB₂] Arg16Gly, 4) ADRB2 Gln27Glu, and 5) tumor necrosis factor gene G308A). These study results indicate that there was no significant association between these genetic markers and ischemic HF, except for polymorphism ADRB2 Arg16Gly. Results of another recent meta-analysis¹⁷ of three studies looking at the effect of the ADRB₁ Arg389Gly on left ventricular remodeling in patients taking β -blockers indicated that Arg389 homozygotes (individuals with the same copy of each gene) had a

significant improvement of left ventricular ejection fraction - 5% more than Gly389 carriers (individuals with one copy of the Gly 389 gene).

β -adrenergic receptor signaling is critical in the progression of HF because increased sympathetic activity is inversely correlated with survival in HF. Blockage of the β_1 -adrenergic receptor has been shown to produce a clinical improvement in patients with HF. However, despite extensive research, the importance of common variants in the β -adrenergic receptor genes in HF has not been settled. The recent review by Muthumala and colleagues³ suggested that functional ADRB polymorphisms are probably not causative in human HF, but are likely to be disease modifiers. These genetic variations seem to influence softer clinical outcomes, such as exercise capacity and arrhythmia. Although the results have been inconsistent, ADRB polymorphisms have also been shown to interact with different β -blockers to influence hemodynamics and survival in patients with HF.

Pharmacogenetics

Pharmacogenetics is the study of genetic modifications that give rise to variations in pharmacological response. The clinical potential of pharmacogenetics is to optimize therapy by identifying or predicting the individuals who will respond well or poorly to, or are at high risk for adverse events from a given pharmacological agent. Thus far, the majority of pharmacogenetic studies in HF have focused on the genetic contributions of β -adrenergic receptor genes, ADRB1, and ADRB2. International guidelines recommended patients with systolic HF and lack contraindications to be treated with β -blocker regimen. However, standardized pharmacologic treatment leads to marked variability in clinical outcome.^{19, 24} Recently, pharmacogenetic data for β -blockers in patients with HF and potential implications of β -blocker pharmacogenetics for HF patients have also been summarized by several authors.^{25, 26} It is suggested that the ADRB1 Arg389Gly polymorphism might predict responsiveness to β_1 -adrenergic receptor agonists and blockers: individuals homozygous for the Arg389 polymorphism may be good responders, while those homozygous for Gly389 may be poor or non-responders.¹³

Nursing Roles with Genetics in General

Currently, nurses' education and competence related to genetics lags behind the testing and information available to healthcare consumers. To fully contribute on healthcare teams of the future, nurses will need to recognize disease patterns that have a genetic link, collect family histories, understand pharmacogenetics, and be versed with the ethical, legal and social implications of genetic testing.²⁷ Nurses will need the knowledge and skill to understand and interpret test results and guide the patient towards the best resources.

Nursing Roles with Inheritable Cardiomyopathies

Nurses must be able to identify hereditary patterns and characteristics that predispose patients to inheritable cardiomyopathies.²⁸ Once patients are identified, Jenkins, Grady and Collins (2005) suggest that nurses must be able to promote behaviors and surveillance that will reduce disease risk. Genetic testing may reveal that a young person will develop heart failure symptoms with the presence of an inheritable cardiomyopathy. Nurses must be prepared to assist with interventions that promote the best outcomes in cases of early diagnosis of cardiomyopathy. Interventions will include patient education about the disease process and its management, specifically adherence to the medications, a low sodium diet aimed at symptom prevention, and nursing support for the psychosocial implications.

Nursing Roles with Pharmacogenetics

Molecular advances in inheritable cardiomyopathies may result in progression in disease treatment, and a prognosis for HF that is more closely tied to the underlying genetic cause or to pharmacogenetics. Nurses need to stay alert for patient's responses to medications that vary with phenotypes (eg. age, gender, type of cardiomyopathy). Variation in response may provide clues that of genotypic variation (with specific genetic structures like SNPs) that may respond differently to certain therapies. The presence or absence of these SNPs in individuals has been linked to how patients respond to drugs.

As stated earlier, exploration of specific genotypes reveals that there are several SNPs that regulate receptors within the renin angiotensin-aldosterone and sympathetic nervous systems. Of particular interest (and on the verge of FDA approval) is bucindolol, a non-selective beta-blocker with mild alpha blocking properties. The Beta-blocker Evaluation of Survival Trial (BEST) that included 2708 patients, contained a prospectively designed 1040 patient DNA substudy. This DNA substudy showed that treatment effects with bucindolol are enhanced by the B₁Arg/Arg plus the α_{2c} -wild type or -deletion genotype combination. In fact, patients with this genotype (n=493) showed a statistically significant 38% and 48% reduction in all cause mortality and cardiovascular mortality, respectively. Further, HF hospitalizations were significantly reduced by 44%.²⁹ No other FDA approved beta-blockers have shown an improvement in mortality in patients with the aforementioned B₁ adrenergic polymorphisms. Bucindolol and the genetic test to identify this subgroup (genotype) are both currently under review by the FDA.

Nurses Roles in Genetic Testing

Genetic testing of patients in clinical trials and in clinical practice may provide improved predictability of treatment response, ultimately leading to better clinical outcomes. Nurses are currently contributing to the discussions with physicians and biopharmaceutical companies to determine who should be tested. Should all people eligible for beta blocker therapy be genetically tested prior to their starting dose to determine if they may have the ADRB₁ Arg389Gly polymorphism or SNP? Or, should patients only be tested once considered a "non-responder" when they experience no improvement or worsening symptoms on standard beta blocker therapy? Nurses and nurse practitioners in outpatient HF clinics, particularly, will be determining with their team how to best utilize genetic tests.

Nurses Roles in Personalized Medicine

Sue Wingate, RN, DNSc, CRNP, President of American Association of Heart Failure Nurses, expanded a panel discussion in 2008 on heart failure and genetics to include the possibility that genetics will guide personalized or individualized medicine. As with cancer medications, the knowledge of the presence of specific polymorphisms affecting the body's ability to metabolize drugs has allowed for better drug selection and reduced the occurrence of serious complications in people unable to tolerate certain chemotherapy drugs. Relevant to cardiology nurses, warfarin titration has the potential to become much more predictable and safe with the recent ability to identify who has the polymorphisms (CYP2C9 and VKORC1) that have been shown to regulate warfarin metabolism. Issues arise related to cost and timing of testing and as well as the potential anxiety that may occur when genetic testing is proposed. Genetic testing for heart failure patients is a promising means for improving the selection of therapies for each individual and improving the probability of a good response. Concurrently, we may see a reduction in the personal and health care costs related to adverse drug responses.

Conclusion

Genetic studies involving patients with common forms of HF has grown significantly in the past decade. However, it may be disappointing that the knowledge gained has not yet lead to substantial changes in daily clinical practice for physicians or nurses.¹ A clinical geneticist's evaluation and testing for various genetic polymorphisms to predict the occurrence of HF is indicated for individuals with single gene mutations associated with the familial cardiomyopathies. A genetic evaluation is not warranted at this time for those with HF that is multifactorial in nature.¹ Currently, no clinical guideline recommends genetic testing before the initiation of pharmacotherapy in HF. To address the complexity of common HF, future research involving advanced genetic technology, larger sample size, various stages of HF, advanced analysis to determine gene-gene and gene-environmental interactions are needed. The advanced genetic technology may include a functional genomic approach and genome-wide scans that may help to identify novel genes that will fill gaps in our knowledge of HF development, progression, and drug response.³⁰

To prepare for the changes in clinical practice brought on by genetic discoveries, clinicians should update their education on genetics and genetic testing. The cardiovascular nurse clinician of the future should be able to collect and assess the medical and family history, physical examination, and diagnostic test results, including genotype, for incongruencies that would suggest phenotypic variation in HF.³¹ They should be able to critique genetic literature for evidence based interventions that allow them to begin to understand and ask questions about gene-environment interactions. Genetic knowledge of HF will result in an understanding the disease and treatment on a molecular level necessary for more advanced clinical judgments and interventions that will result in better patient outcomes.

Acknowledgments

I would like to acknowledge the following RO1 support in the paper, "Depressive Symptoms and Genetic Influences on Cardiac Outcomes. 1R01NR010235-01A1 funded by the NIH, National Institute of Nursing Research".

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Table 1**Genes that Cause Dilated Cardiomyopathy**

Protein Type	Protein Name	Gene	Phenotype	*Year
Cytoskeleton	Dystrophin	<i>DMD</i>	D/M	1991
	Delta Sarcoglycan	<i>SGCD</i>	D/M	1997
Sarcomere	Beta Myosin heavy chain	<i>MYH7</i>	H/D	1989
	Alpha Actin	<i>ACTC</i>	H/D	1998
	Troponin T	<i>TNNT2</i>	H/D	1995
	Alpha Tropomyosin	<i>TMP1</i>	H/D	1994
	Troponin I	<i>TNNI3</i>	H/D/R	1997
	Troponin C	<i>TNNC1</i>	H/D	2004
	Myosin binding protein C	<i>MyBPC3</i>	H/D/R	1995
Sarcomere/Z-disc proteins	Titin	<i>TTN</i>	H/D	1999
	Titin-cap/telethonin	<i>TEL</i>	H/D/M	2002
	Muscle LIM protein	<i>CRP3</i>	H/D	2002
	Metavinculin	<i>VCL1</i>	D	2002
	Cypher/ZASP	<i>LDB3</i>	D/LVNC	2003
Channel proteins	Cardiac sodium channel	<i>SCN5A</i>	D/A	1995
	ATP-sensitive potassium	<i>SUR2A/ABCC9</i>	D/A	2004
	Phospholambin	<i>PLN</i>	D	2003
Intermediate filament proteins	Desmin	<i>DES</i>	D/R/M	1999
	Lamin A/C	<i>LMNA</i>	D/M/L	1999
Mitochondria	Tafazzin	<i>G4.5/TAZ</i>	D/LVNC	1997

* Year in which the gene was first associated with cardiac phenotype/cardiomyopathy.

H-hypertrophic cardiomyopathy; D-dilated cardiomyopathy; R-restrictive cardiomyopathy; M-muscular dystrophy; L-lipodystrophy; LVNC-left ventricular noncompaction; A-arrhythmias.