Cardiovascular Genomics
Implications for Acute and Critical Care Nurses

Mary T. Quinn Griffin, PhD, RN; Deborah Klein, MSN, RN, ACNS-BC, CCRN, CHFN, FAHA; Chris Winkelman, PhD, RN, CCRN, FCCM

As genomic health care becomes commonplace, nurses will be asked to provide genomic care in all health care settings including acute care and critical care. Three common cardiac conditions are reviewed, Marfan syndrome, bicuspid aortic valve, and hypertrophic cardiomyopathy, to provide acute care and critical care nurses with an overview of these pathologies through the lens of genomics and relevant case studies. This information will help critical care nursing leaders become familiar with genetics related to common cardiac conditions and prepare acute care and critical care nurses for a new phase in patient diagnostics, with greater emphasis on early diagnosis and recognition of conditions before sudden cardiac death.

Keywords: Genomics, cardiovascular, health care, nursing

Genomics, the study of genes and their functions, is becoming increasingly routine in all clinical settings. Knowledge about genomics and diagnostic tools has great promise in individualizing diagnosis and treatment for conditions that are seen in intensive care units (ICUs). To meet the new challenges of genomic health care, the Consensus Panel on Genetic/Genomic Nursing Competencies recommends including genetics/genomics in undergraduate nursing courses to ensure that registered nurses have the required knowledge and skills in all patient care settings. These competencies have been endorsed by 47 nursing organizations, including the Council of Cardiovascular Nursing of the American Heart Association.

In addition, the Essentials of Master’s Education in Nursing, a framework for the development of a core curriculum for a master’s program, has 9 essential competencies, with 3 of the 9 addressing genetics/genomics. The Essential Genetic and Genomic Competencies for Nurse with Graduate Degrees is a document developed by a Consensus Panel supported by the American Nurses Association that lists 38 competencies on genomics and genetics for any nurse practicing with a graduate-level degree. The Consensus Panel recommends that these genetics and genomics competencies serve as core standards for any nurse functioning at the graduate level (nurse educator, advanced practice registered nurse, clinical nurse leader, nurse administrators, and nurse scientists).

Inclusion of genetics/genomics in the nursing essentials and competency recommendations heightens the urgency for all nurses to increase their knowledge in this area. As genomic health care becomes commonplace, nurses will be asked to provide genomic care in all health care settings, including acute and critical care. In this article, we reviewed 3 common cardiac conditions, Marfan syndrome, bicuspid aortic valve (BAV), and hypertrophic cardiomyopathy (HCM), to provide acute care and critical care nurses with an overview of these pathologies through the lens of genomics and relevant case studies. This information will help critical care nursing leaders become familiar with genetics related to common cardiac conditions and
prepare acute care and critical care nurses for a new phase in patient diagnostics, with greater emphasis on early diagnosis and recognition of conditions before sudden cardiac death. The cardiac conditions reviewed in this article were selected because acute care and critical care nurses are likely to care for these patients and need to understand the implications of and effects each condition has on cardiac function.

• Family Health History and Genetic Inheritance

Family health history and genetic tests are the 2 most important tools that nurses use in genomic health care to assess genetic risk. Familiarity with genomic vocabulary, research, and testing options is essential for acute care and critical care nurses to understand new information about diseases and treatments, to process patient and family requests for information, and to be sensitive and responsive to genetic conditions.

Family health history often provides the health care provider with the initial awareness that a specific condition may be inherited. A diagram of a family health history, also known as a pedigree, can aid in both diagnosis and risk assessment of genetic inheritance. Inheritance of a disorder is likely to be related to a variation in 1 or more genes, resulting in a genetic predisposition that increases the risk for development and severity of illness. For example, valvulopathy and cardiomyopathy can result directly from genetic variations. In addition, the type and number of genetic variations can affect the onset of disease, influence symptoms and progression of disease, and interact with environmental triggers for disease. There are many inherited causes of cardiac disease, including genes involved with cholesterol metabolism, clotting and thrombosis formation, and uterine development of vascular and cardiac structures. Patients with a single genetic variant who alter their environmental risk through diet or activity can mitigate their genetic risk related to onset or severity of symptoms. Some genetic variants are less amenable to lifestyle adaptations but respond well to surgical or medical intervention. For example, valve replacement surgery and medication can improve function, quality of life, and lifespan among patients with inherited valve conditions such as Marfan syndrome or BAV.

• Marfan Syndrome: Pathology Overview

Marfan syndrome is an inherited connective tissue disorder, typically presenting with cardiovascular, skeletal, and ocular derangements as well as lung, skin, and New failure of adventitia to sustain physiologic hemodynamic stress, which can lead to the expansion of blood vessels and aneurysm formation. The adventitia is a supportive layer surrounding the blood vessels that is composed of connective tissue and scaffolding around neurons. Defects in adventitia lead to a weakened vessel wall. Although manifestations are mitral valve prolapse, aortic valve regurgitation, and dilation of the ascending aorta at the level of the aortic sinus. Cardiovascular pathology in Marfan syndrome leads to complex morbidity. Premature mortality occurs with Marfan syndrome, commonly caused by aortic dissection and aortic rupture.

In 1991, a variation of the fibrillin 1 (FBNI) gene on chromosome 15 was identified in patients with Marfan syndrome. This gene encodes a structural protein that is essential for developing and maintaining elasticity in connective tissues, hence the development of valve incompetence/regurgitation and aneurysm formation. In addition to contributing to the architecture of blood vessels and valves, products of the FBNI gene interact with other molecular messengers in the extracellular matrix, such as epidermal growth factor. Since 1991, over 1000 unique variations in the FBNI gene have been reported. Gene variations can be broadly categorized as a single nucleotide polymorphism or a premature stop codon.

A single nucleotide polymorphism is a single unique nucleotide in a string of DNA. A premature stop codon is a genetic sequence of 3 nucleotides that halts the formation of a protein before a complete, functional series of amino acids is built from the affected individual’s genetic sequence. Most of the mutations in Marfan syndrome are single nucleotide substitutions, or small insertions or deletions, resulting in alternative amino acid formation and, ultimately, protein compilation. Other variations, as the result of the presence of a premature stop codon, are associated with severe skeletal and skin manifestations of disease such as elongated limbs and stretch marks unrelated to weight gain. Depending on the location of the “stop” signal, the protein can be nearly complete and functional or severely truncated and nonfunctional. Because of the multiplicity of variations, family members with Marfan syndrome who have the same alteration in the FBNI gene can show wide variation in onset and severity of cardiovascular symptoms.

Mutations in transforming growth factor β2 (TGFβ) gene on chromosome 3 also result in Marfan-like symptoms in the absence of FBNI gene mutations. Transforming growth factor β has diverse roles in cell proliferation and differentiation as well as in the formation of extracellular matrix that is essential to tissue formation. Abnormal TGFβ signaling appears to result in loss of tissue elasticity and aneurysm formation.

Genetic variants in either FBNI or TGFβ result in failure of adventitia to sustain physiologic hemodynamic stress, which can lead to the expansion of blood vessels and aneurysm formation. The adventitia is a supportive layer surrounding the blood vessels that is composed of connective tissue and scaffolding around neurons. Defects in adventitia lead to a weakened vessel wall. Although
not all possible variants in the *FBNI* or *TGFβ* genes that cause Marfan syndrome have been identified, genetic testing for Marfan syndrome is available from a wide variety of laboratories.

### BAV: PATHOLOGY OVERVIEW

The normal aortic valve has 3 leaflets (Figure 1). This configuration allows maximal opening during systole and the most efficient seal on closing to prevent leakage during diastole. In 1% to 2% of the population, the aortic valve is bicuspid with 2 leaflets (Figure 2). Bicuspid aortic valve is the most common congenital cardiac condition and can lead to narrowed or leaky valves and heart failure.12-14

A familial basis for BAV has been known since the 1970s. The prevalence of this condition among families varies, ranging from no evidence of inheritance to an identifiable autosomal dominant pattern of inheritance. Furthermore, some individuals with a recognized genetic variation do not develop BAV.5 Presence of a positive genetic variation but absence of the features of BAV is known as reduced penetrance. There is a 9% to 12% incidence of BAV among first-degree relatives of affected individuals.15,16 When 309 individuals were studied using echocardiography and a 3-generation family health history, BAV was identified in 74 individuals, indicating an even a greater degree of inheritance and confirming the familial basis of the condition.15,17 Cripe and colleagues17 suggested that BAV was almost always due to genetics, with an estimate of the genetic effect size of 0.89. The case study in Box 1 shows the benefits of examining the family health history of an individual with BAV.

### BAV Genetic and Chromosomal Markers

Several genes have been implicated in BAV development, including *NOTCH1* (chromosome 9) and *ACTA2*. The *NOTCH1* gene codes for a signaling protein that alters the structural development of the embryonic valve.15 *NOTCH1* also provides osteogenic differentiation and calcification, contributing to aortic calcification and stenosis.18,19 Mutations in the *ACTA2* gene on chromosome 10 that codes for actin, a protein component of aortic valves, has also been implicated in BAV.

A third gene, *ubiquitin fusion degradation 1-like* on chromosome 22, has also been linked to bicuspid development of the aortic valve.20 This gene codes for a signaling protein that is prevalent during the embryonic formation of cardiac outflow tracts. DiGeorge syndrome can result from the imbiguation gene abnormality. It presents with a variety of conditions, including outflow tract defects.21,22

Three additional loci associated with BAV have been identified on chromosomes 5, 13, and 18.23 In addition, BAV has been linked to Turner syndrome, a chromosomal disorder that occurs when a female child inherits only 1 X chromosome.20 Although no specific genes have been identified as causative along chromosomes 5, 13, or 18 or the sex chromosome, it is theorized that genetic chromosomal variations lead to abnormal cues during intrauterine growth and development, resulting in bicuspid rather than tricuspid leaflets of the aortic valve. There are additional genes implicated in aortic valvulopathy. These include lipoprotein metabolic pathway abnormalities, structural and functional derangements in vascular endothelial function, and macrophage characteristics that contribute to disease progression through inflammation.
The genomic contributors to aortic valve disease are not yet well validated in human subjects. Thus, genetic testing for aortic valvulopathy, including BAV, is not yet ready for clinical application. However, some clinicians and researchers may ask for a genetic sample to store for ongoing research and for offspring to be monitored.

**HCM: PATHOLOGY OVERVIEW**

Hypertrophic cardiomyopathy is the most common cause of sudden death in individuals younger than 35 years. It is characterized by a variety of disorders, including enlarged sarcomeres and left ventricular hypertrophy, malpositioned mitral valve papillary muscles that contribute to mitral regurgitation, pulmonary congestion, cardiac dysrhythmias (atrial fibrillation/flutter and ventricular tachycardia), left ventricular outflow tract obstruction, and, ultimately, diastolic heart failure.

The prevalence of HCM is about 0.2%, or 1 in 500, in the adult population, although genetic diagnosis of asymptomatic individuals might increase numbers. Typically, inherited HCM occurs in an autosomal dominant pattern, meaning an affected individual has 1 copy of a mutant gene and 1 normal gene on a pair of autosomal chromosomes. Individuals with this pattern of inheritance have a 50-50 chance of passing the mutated gene on to each of their children, affecting male and female children equally. With HCM, there is variable penetrance, meaning that the genotype is present in every generation but some family members do not show the trait even though they have the appropriate genotype. Also, the expression of the disease is variable; that is, different signs and symptoms may be present and can range from no symptoms to severe, early-onset heart failure even when the same mutation is present within members of the same family. Alcalai and colleagues reported a positive family history in 60% of individuals with HCM. About 40% of people with HCM have either unrecognized family members with the disease or have de novo mutations reflecting a genetic mutation in a family member as a result of a mutation in a germ cell (egg or sperm) of 1 of the parents or in the fertilized egg itself. In both familial and de novo cases, the chances of passing on the disorder are 50% because of the autosomal inheritance pattern. The case study in Box 2 illustrates key information about inheritable HCM.

The genomic contributors to aortic valve disease are not yet well validated in human subjects. Thus, genetic testing for aortic valvulopathy, including BAV, is not yet ready for clinical application. However, some clinicians and researchers may ask for a genetic sample to store for ongoing research and for offspring to be monitored.

**Box 1 BAV Case Study**

A 65-year-old man presented with an ejection systolic murmur over the aortic area and radiating to the neck. Echocardiogram revealed moderate aortic stenosis without regurgitation and with no significant dilatation of the ascending aorta or evidence of coarctation. Over a 5-year period, the stenosis progressed, and the man developed shortness of breath and had an aortic bioprosthesis surgically implanted. His condition subsequently improved and he remains well. Because of the man’s health history, his 3 children each were given a clinical evaluation that included an echocardiogram. His 16-year-old son had a systolic and diastolic murmur over the aortic area, but no symptoms. By echocardiogram, he had severe aortic regurgitation from a mildly stenotic BAV with 1 large prolapsed and 1 normal-sized leaflet, moderate left ventricle enlargement, and normal systolic function. The ascending aorta was 5.1 cm (up to 3.6 cm is normal) and without evidence of coarctation. He underwent aortic valve repair and replacement of the ascending aorta as per American College of Cardiology/American Heart Association guidelines where surgical repair or replacement of the ascending aorta is recommended when the aorta is greater than 5 cm in individuals with BAV, irrespective of whether the valve is severely stenotic or regurgitant. In this situation, there was 1 large and 1 normal-sized leaflet. The prolapsed large aortic valve leaflet was surgically repaired to prevent prolapse. Recovery was uncomplicated and he is now followed regularly for valve and ventricular function. A 17-year-old daughter had a soft ejection systolic murmur and a systolic ejection click. She had BAV without dilatation of the ascending aorta or aortic regurgitation, as well as minimal aortic stenosis. She requires annual echocardiography. A 21-year-old daughter had a normal trileaflet aortic valve and aorta. The children’s mother had a normal aorta and aortic valve. The family was referred to the genetic clinic for counseling regarding BAV and reproductive implications. First-degree relatives had a screening echocardiogram, and all family members were advised to have echocardiographic screening. The pedigree, which is not based on a specific patient but is representative of a positive pedigree, for inherited cardiac disease is presented in Figure 3.
Genes involved with HCM code for proteins of the cardiac sarcomere are associated with contraction of heart muscle. More than 700 mutations have been identified in 13 genes. Most mutations occur in 3 genes: MYH7 on chromosome 14, MYBPC3 on chromosome 11, and TNNT2 on chromosome 1. These genes encode the β-myosin heavy chain, myosin-binding protein C, and cardiac troponin T, respectively. Variations in cardiac actin, α-tropomyosin, cardiac troponin I, tinin, and the myosin light chains are less commonly identified in people with HCM.

Genetic variations have been linked to specific clinical manifestations of HCM. In the MYH7 gene, genetic variations result in either a single amino acid substituted for another or the presence of a premature stop codon terminating the synthesis of myosin needed for normal sarcomere contraction. These particular MYH7 variations are associated with early onset of HCM and a poor prognosis, including sudden cardiac death. Individuals with genetic mutations in the MYBPC3 gene have a late onset of HCM and a relatively good outcome because contractile proteins are relatively intact. Mutations in the TNNT2 gene are associated with a high incidence of sudden cardiac death, even in mild forms of HCM. However, the precise relationship between phenotype and genotype is limited, as many of these mutations occur infrequently.

Tanjore and colleagues examined HCM in Mumbai, India, and patients were divided into subtypes based on a pattern of hypertrophy. In 127 patients with HCM, heterogeneity of hypertrophy was found, suggesting that genes and mutations involved in subtypes were different. In addition, age of onset differed by more than 10 years in familial versus nonfamilial cases. The preponderance of male to female participants in the Mumbai India sample is more than 3.7:1, a ratio that is greater than reported in previous studies of Western and Japanese patients. Of individuals with HCM, 31% had a familial history, similar to other studies. Therefore, inheritance patterns other than autosomal dominance are implicated in subsets of HCM.

Approximately 5% of patients with unexplained HCM have genetic variations that do not encode for a sarcomere protein. Nonsarcomeric protein mutations have been identified in 2 genes, PKRAG2, which encodes a γ-2 regulatory subunit of adenosine monophosphate–activated protein kinase, and LAMP2, encoding a lysosome-associated membrane protein-2. These 2 genes were involved in glycosgen accumulation in cardiac muscle cells, suggesting a metabolic variation in HCM. Metabolic HCM was linked to a high incidence of atrial fibrillation and ventricular preexcitation. Mutations for metabolic HCM were implicated in about 1% of all HCM cases but as much as 50% of HCM with ventricular preexcitation. In cases where metabolic HCM is suspected, DNA sequence analysis for PRKAG2 and LAMP2 mutations can be conducted.

Clinical genetic testing is available for many genetic variations associated with HCM. Genetic testing should be considered when there is a family history of HCM in 2 or more closely related family members and HCM is diagnosed before the age of 40 years. A referral to a genetic clinic will facilitate the selection of the correct genetic test, subsequent interpretation of test results, and counseling about test findings. It is important to note that, because of the overwhelming number of genetic mutations in HCM, the first genetic test should be completed in a symptomatic first-degree relative to identify the most probable gene mutation.
DNA sequence analysis can be completed for the 3 most common genes, the MYH7, MYBPC3, and TNNT2 genes. Testing can be subdivided. For example, MYH7 sequencing can be completed first in cases of severe hypertrophy, whereas TNNT2 can be completed first if hypertrophy is mild.²⁷ A patient may have DNA analysis completed for all 3 genes, as it is possible to inherit multiple genetic variations causing HCM pathology (Table).

**IMPLICATIONS FOR CRITICAL CARE NURSES: FAMILY HEALTH HISTORY AND PEDIGREE**

A family health history is the only individualized, inexpensive genetic tool available to all health care providers. Family health histories reflect not only patterns of inheritance but also genetic susceptibilities, shared exposures to environmental risks, and common behaviors. As a screening tool, family health history is powerful in identifying both disease and responses to treatment. It takes about 15 to 20 minutes to build a basic family health history.

When obtaining a cardiac history for a pedigree, family health information must be collected routinely and include 3 generations. The pedigree illustrates both the number and the degree of relationship among family members who have a related disorder. Disorders with a genetic cause may not follow a typical autosomal dominant or recessive pattern yet still indicate a need for a genetic referral. In addition, a pedigree can be used to recognize the range of symptoms in conditions that have reduced or variable penetrance. For example, aortic valve disease may occur in multiple generations, with variable severity. Only when a pedigree is constructed is the inheritable component of aortic valve disease clearly evident. In HCM, clinical features can vary widely from mild symptoms to severe involvement of the heart despite the same genetic variation leading to protein malformation. Pedigrees for the BAV and HCM case studies are illustrated in Figures 1 and 2, respectively.

The Surgeon General’s Family History Initiative can be used by nurses to help patients gather family information (www.hhs.gov/familyhistory/) and update it periodically.³¹ After information is entered at the site, it can be displayed as both a report (ie, a list of relatives and their health information) and a pedigree that can be used to determine risks related to cardiac diseases. The electronic record is not saved at the government Web site but can be saved to a personal computer or data storage device and shared with health care providers.

Nurses must be able to create a pedigree from the collected health history information using standardized symbols (Figure 1).³² They should have an understanding of patterns of inheritance and be able to recognize these on the pedigree. One advantage of constructing a pedigree is that it can help visualize risk related to cardiac disease. When family health history indicates 2 or more first-degree relatives with a cardiac disorder, there is an increased probability of a genetic component to the disease, and a referral to a genetic clinic for evaluation and testing may be warranted.

Nurses should recognize pedigrees with patterns of inheritance. For example, multiple generations affected by a disorder indicates autosomal dominant inheritance. A pedigree with many siblings who have a similar condition is a hallmark of autosomal recessive inheritance. In addition, a pedigree with family members affected with a disease at an early age is a red flag for potential genomic contributions. When the pattern of inheritance is complex, nurses can refer or consult with a genetic specialist or clinic.
to better assist patients in obtaining informed and individualized care.

**RISK STRATIFICATION AND GENETIC CONSULTATION**

Family history risk stratification guidelines have been developed for common chronic diseases to stratify genetic risk into high, moderate, or average risk categories. These guidelines use the number of affected relatives and their age at disease onset to calculate risk. The overall goal of risk identification is to recognize individuals among whom lifestyle choices can prevent or mitigate genomic expression and reduce risk or severity of inherited disorders such as BAV or HCM. Although there is no specific tool for BAV or HCM disease genetic risk stratification based on family health history, several related tools exist.

One tool designed for acute myocardial infarction genetic risk uses both the number of relatives with a similar diagnosis and the degree of relationship between relatives. If 2 first-degree relatives were affected, the patient is stratified as high risk. If instead 2 second-degree relatives from the same lineage were affected, the patient is stratified in the moderate risk group. If no relatives were affected, the patient would be stratified in the average risk group. The myocardial infarction risk stratification tool may underestimate inheritable risk when there are no affected relatives or no information on family health history, as the default risk level is average risk. Furthermore, the tool was validated in white women and may underestimate the risk in African American, Hispanic, or other ethnicities of women and men. Nonetheless, use of a risk stratification tool can inform patients and families about inheritance risk and guide the clinician in decisions to refer affected family members to genetic specialists.

A detailed family health history involves gathering information from multiple family members. Hinton developed a series of cardiovascular system questions to collect information on all family members, affected and unaffected, to draw a pedigree. Evaluation of the pedigree and detailed family health history may indicate a need for a genetic specialist consultation. Genetic professionals and clinics can be located easily online at GeneTests (http://www.geneclinics.org) through a list of national and international genetic centers.

Tailoring genetic messages to reflect cultural, literacy, and religious preferences for patients is critical in providing genomic care. Patients want genetic information, and the Genetic Information Nondiscrimination Act (GINA) of 2008 protects US citizens against employment and health insurance discrimination based on genetic information.

Genetic information is defined by GINA as genetic test results, genetic results of family members including fourth-degree relatives, family health history, and any request for genetic services such as genetic testing, counseling, or education by an individual or family member. In GINA, a genetic test is defined as an “analysis of human DNA, RNA, chromosomes, proteins, or metabolites that detects genotypes, mutations, or chromosomal changes.” Although GINA does not mandate coverage for any test or treatment, it prohibits health insurers and employers...
from requesting genetic information, with the exception of employers with fewer than 15 employees.36

**CONCLUSION**

Genomic information increases understanding of pathogenesis of cardiac valve disease and may be a targeted diagnostic test or used to individualize treatment regimens. Nurses should become familiar with genomic advances and engage patients and families in discussions about genetic testing. Understanding the contributions of both a screening and detailed family health history and interpreting a pedigree are important skills for acute care and critical care nurses to identify potentially life-threatening illnesses.

Essential nursing competencies and curricular guidelines for genetics and genomics have been adopted by almost 50 nursing organizations1 to establish the minimum educational level to prepare nurses in competent genetic and genomic-focused nursing care. Advance practice nurses should be able to construct a 3-generation family health history, and all nurses should be able to evaluate a family health history. Understanding genomics and the genetic contribution to critical illness can promote optimal care by acute care and critical care nurses.

**References**


ABOUT THE AUTHORS

Mary T. Quinn Griffin, PhD, RN, is an associate professor at Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, Ohio. Dr Quinn Griffin has attended the Summer Institute in Genetics at the National Institute of Nursing Research, National Institute of Health, Washington, DC. She has also attended the Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, Web-Based Genetics Institute (218 contact hours). She teaches genetics to graduate nurses.

Deborah Klein, MSN, RN, ACNS-BC, CCRN, CHFN, FAHA, is a clinical nurse specialist at the coronary intensive care unit, heart failure intensive care unit, and cardiac short stay/post anesthesia care unit at the Cleveland Clinic, Ohio.

Chris Winkelman, PhD, RN, CCRN, FCCM, is an associate professor at Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, Ohio. Dr Winkelman has attended the Summer Institute in Genetics at the National Institute of Nursing Research, National Institute of Health, Washington, DC, and incorporates genomic knowledge in her master of science in nursing nurse practitioner courses.

The authors have disclosed that they have no significant relationship with, or financial interest in, any commercial companies pertaining to this article.

Address correspondence and reprint requests to: Mary T. Quinn Griffin, PhD, RN, 10900 Euclid Avenue, Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, OH 44106-4904 (mary.quinngriffin@case.edu).