



CARDIOLOGY AND GENOMICS

The Fifth Pair of Articles in a Series about the Significance of Genetic Science for Catholic Health Care

A MEDICAL VIEW

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It is well known that cardiovascular disease is the number one killer in the United States.¹ Cardiovascular disease accounted for 1 of every 2.6 deaths in the United States in 2002. It has been estimated that in 2005 the direct and indirect cost of cardiovascular disease was \$393.5 billion. The disease affects people of all ages, and it ranks as the number two cause of death for children under age 15. Because most of such children are born with a congenital cardiovascular defect, it is clearly important to understand the mechanisms of cardiovascular disease and to use this information to develop treatment and prevention strategies.

The majority of cardiovascular diseases follow a pattern of multifactorial inheritance—a combination of environmental factors and genetic predisposition contribute to an individual's risk for developing disease. Research is ongoing to identify specific genes and pathways involved in cardiovascular development. Medical researchers hope that this knowledge—combined with our current understanding of such environmental risk factors as obesity and smoking—will aid cardiologists in the clinical management of their patients.

A few cardiovascular diseases are single-gene disorders that typically have other clinical features in addition to cardiovascular issues. The recent trend is a move from research on single-gene disorders to research of the whole genome and how the function and interaction of genes affect cardiovascular development and tendency towards disease. The following examples demonstrate how genomic advances have affected the diagnosis and management of congenital heart

disease, cardiac arrhythmias, cardiomyopathies, and coronary artery disease.

GENOMICS AND CONGENITAL HEART DISEASE

Congenital heart disease (CHD) is the result of an abnormal formation of the heart or its blood vessels. There are at least 15 distinct types of heart defects with subtle anatomic variations within each type.² The types of defects range from tiny holes in the heart that close on their own to major malformations that may require multiple surgeries.

CHD can be an isolated clinical issue or part of a known genetic syndrome that might have a variety of other features, in addition to the heart defect. Although there are still many unknowns, genomic advances have shaped our understanding of both isolated and syndromic CHD.

Research is ongoing to understand the potential genetic basis of isolated heart defects. Researchers hope that this understanding can help physicians answer questions from parents, such as “Why did this happen to my child?” and “What are the chances it could happen again to future children?” Scientists would also like to understand the pathways that lead to proper cardiac development and function. Cardiovascular genetic registries are being created to gather clinical and genetic information and are an invaluable resource for research in this area. A “candidate gene approach” is a common way for researchers to study heart development. The theory is that if researchers can identify genes involved in normal heart development, they can determine if certain alterations in these genes cause the heart to form differently than expected, resulting in a heart

defect in an infant. This information could then be used to determine recurrence risks and, possibly, to develop unique interventions. It may also be possible to use the knowledge of the genetic pathways involved in heart development to prevent some types of heart defects.

CHD is a common feature in many genetic syndromes. Other features of the syndrome may be quite subtle, so the first opportunity for diagnosis may occur in the cardiology clinic. There are a variety of reasons why it is important to recognize a genetic diagnosis in an individual as early as possible. For example, an individual may be at risk for other health complications in addition to heart issues. Understanding the diagnosis and inheritance pattern can also help to identify other at-risk family members before serious complications arise. There is an important role for genetics in cardiology in identifying syndromic patients early and initiating appropriate referrals, interventions, and testing of family members.

GENOMICS AND CARDIAC ARRHYTHMIAS

Normal cardiac rhythm depends on the correct movement of ions that send electrical impulses to the different heart chambers and cause a coordinated contraction.³ If there is an abnormality in an ion channel, an abnormal heart rhythm (arrhythmia) can result. Arrhythmias can lead to serious consequences in individuals, such as palpitations, fainting, cardiac arrest, or sudden death. Arrhythmias can be detected using an electrocardiogram (ECG) that measures the rate and regularity of heart beats.

In the last decade, researchers have recognized that alterations in a variety of ion channel genes are responsible for several cardiac arrhythmia syndromes. For example, the long QT syndrome is a repolarization disorder characterized by prolongation of the QT interval on the ECG. The clinical picture for individuals with long QT syndrome is quite variable, both in age of presentation and symptoms. Symptoms such as fainting episodes are frequently present in childhood. Without treatment, individuals are at risk for potentially lethal arrhythmias.

Knowledge of the specific gene responsible for long QT syndrome in an individual is invaluable. Depending on the gene involved, there may be a different clinical picture seen on an ECG and variable clinical features, such as triggers for cardiac events (emotional stress or physical activity). Given this knowledge, physicians can tailor treat-

ment to the individual based on the specific gene involved. If, moreover, there is a genetic explanation for the clinical symptoms in an individual, this information can be used to test and identify other at-risk family members who may currently be asymptomatic.

The long QT syndrome is an example of how genetic testing is likely to become an important part of the clinical workup for patients with cardiac arrhythmias. This insight may aid researchers in understanding the basis for other types of arrhythmias.

GENETIC SCREENING AND HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) occurs in 1 in 500 people in the general population, making it the most common genetic cardiovascular disease.⁴ Many such individuals remain asymptomatic and therefore undiagnosed. Symptomatic patients may have heart failure, exercise intolerance, and chest pain, and are at an increased risk for sudden death from lethal arrhythmias.

HCM is a familial cardiac disease that is clinically variable, meaning that affected individuals within the same family can have very different severity. Prospective screening of HCM family members is done to ascertain who is affected and who is unaffected. This typically involves serial two-dimensional echocardiography and ECG. Currently, physicians must rely on patient compliance over potentially long periods of time to identify and treat life-threatening symptoms early. This places a large burden on medical resources and may produce anxiety in at-risk individuals because of the diagnostic uncertainty.

It is now known that HCM is caused by mutations in genes responsible for encoding protein components of the cardiac sarcomere (the basic unit of cardiac muscle contraction in the heart).⁵ It is possible to diagnose some individuals, even in the absence of clinical symptoms of the disease, using a laboratory-based DNA test.

Why is genetic testing for familial HCM valuable? In certain families, a genetic test can identify those members who are at risk for developing

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HCM and, therefore, need additional clinical monitoring and possibly intervention. Conversely, in some families a negative test will negate the need for intense clinical follow-up.

CORONARY ARTERY DISEASE: ARE GENES TO BLAME?

Coronary heart disease affects 13 million Americans, approximately 7 million of whom experience a myocardial infarction.⁶ The financial and social impact of coronary heart disease is considerable, making the need for improved prevention and treatment strategies paramount.

Coronary artery disease (CAD) is believed to be caused by a combination of environmental and genetic factors.⁷ Examples of known environmental factors that increase an individual's risk for developing CAD include cigarette smoking, dietary fat consumption, hypertension, and physical inactivity. National prevention strategies exist to increase awareness of these risks and to encourage Americans to live healthier lifestyles.

However, cardiologists know that a strong family history of CAD is as important, if not more important, than these environmental hazards.

It is estimated that the genetic contribution to the development of CAD is between 20 percent and 60 percent.⁸ In some families, CAD results from a single-gene disorder, such as familial hypercholesterolemia. Affected individuals have markedly elevated low-density lipoprotein cholesterol levels, beginning in childhood. The result is an increased risk for myocardial infarction at an early age. However, these single-gene disorders are only part of the genetic explanation.

In general, it is likely that there are several genes that predispose a person to an increased risk for developing CAD. People with this genetic background have a lower risk threshold which, when combined with environmental triggers such as cigarette smoking, result in higher risk for CAD and myocardial infarction than the general population risk.

Currently, investigators are using a candidate-gene approach to identify CAD predisposition genes. These candidate genes include those involved in inflammation, general metabolism, vascular homeostasis, hemostasis, and lipid metabolism, particularly cholesterol homeostasis. Once genes are identified, screening tests can be developed and used to predict which individuals are at risk for developing the disease. Intervention and prevention strategies can then be

developed and implemented based on this genetic knowledge. Cardiologists and geneticists will be able to discuss specific risks as they pertain to individual families.

THE FUTURE OF CARDIOVASCULAR GENOMICS

These examples demonstrate the important relationship between cardiology and genomics. Rapid genomic advances will affect many areas of cardiovascular disease, placing an additional burden on cardiologists to incorporate these advances into the clinical care of their patients. There may be an increasing need for genetics professionals, both geneticists and genetic counselors, to be involved directly in cardiology departments.

Several cardiovascular genetics clinics already exist to provide comprehensive care to patients and families. This is an effective way to allow each physician to share his or her expertise without the burden falling on either the professional or the patient receiving suboptimal clinical care. Many clinics are structured so that the geneticist or genetic counselor coordinates the patient's care to ensure that appropriate referrals are made and follow-up tests are completed, both within the cardiology clinic as well as other specialties.

Genomic research will continue to help us understand how mutations affect the complex process of heart failure. This knowledge can be used in the development of novel therapeutic targets for both genetic and nongenetic causes of heart failure.

POTENTIAL CHALLENGES

Genomic advances in cardiology are not without potential social and ethical challenges. There is a real possibility of genetic discrimination, meaning that an individual's genetic test results could be used to deny that individual a job or insurance. Recently, a professional basketball player was told to undergo genetic testing for cardiovascular disease before the managers would sign him to the team. The player refused to have the test, and the ensuing controversy led to his trade to another team.

It is conceivable that, in the near future, genetic tests will be routinely used to help us predict who is at risk for developing cardiovascular disease. The challenge lies in the interpretation of these tests. Can we predict that people who have a positive genetic test will absolutely develop heart disease, or will there be a gray area? If a person has a negative test, does that mean he or she is not at increased risk, or could there be another gene to blame that has not yet been discovered? Once we know that someone is at an increased risk, what options can we offer for prevention and treatment?

The challenge lies in the interpretation of genetic tests.

As new tests are developed, it will be important to have discussions with families about the implications of genetic testing for cardiovascular disease. Families should be made aware of the benefits and limitations of testing before they proceed. There must be appropriate follow-up mechanisms for those who have positive test results to ensure that both they and their family members are managed appropriately. ■

NOTES

1. American Heart Association, *Heart Disease and Stroke Statistics—2005 Update*, American Heart

- Association, Dallas, 2005, p. 3.
2. American Heart Association, p. 24.
3. A. A. Wilde and C. R. Bezzina, "Genetics of Cardiac Arrhythmias," *Heart*, vol. 91, no. 10, October 2005, pp. 1,352-1,358.
4. B. J. Maron, J. G. Seidman, and C. E. Seidman, "Proposal for Contemporary Screening Strategies in Families With Hypertrophic Cardiomyopathy," *Journal of the American College of Cardiology*, vol. 44, no. 11, December 2004, pp. 2,125-2,132.
5. Maron, Seidman, and Seidman, p. 2,126.
6. American Heart Association, p. 10.
7. M. A. Nordlie, L. E. Wold, and R. A. Kloner, "Genetic Contributors toward Increased Risk for Ischemic Heart Disease," *Journal of Molecular and Cellular Cardiology*, vol. 39, no. 4, October, 2005, pp. 667-679.
8. Nordlie, Wold, and Kloner, p. 668.

CARDIOLOGY AND GENOMICS

AN ETHICAL VIEW

Jessie Hastings's article summarizes the increasing role that genetic research is playing in the diagnosis, treatment, and prevention of cardiovascular disease. In our own article, we discuss some of the ethical implications of this research, concentrating primarily on issues that patients and their families may confront. The wider, societal implications and the implications for access to health care are not discussed.

FRAMING THE PROBLEM

As the Human Genome Project (HGP) officially got under way in 1990, observers realized even then that the project was going to give rise to a wide array of ethical concerns. These concerns, it was thought, would arise primarily as a result of two predicted consequences of the project, namely, a rapidly growing "therapeutic gap" between the project's diagnostic findings and its therapeutic capabilities, on one hand, and, on the other, an "information overload" problem having to do with managing the enormous amounts of information generated by the project.

The "therapeutic gap" refers to that stage of the research and development process in which large numbers of diagnostic tests and screens would become available to detect and predict genetic diseases, while at the same time there would be few, if any, genetically based therapies available to treat those diseases. With some important qualifications that will be discussed below, it is safe to say that medical science is cur-

rently in this stage. We are discovering numerous genetic markers but have yet to develop any significant genetic therapies.*

The "information overload" problem refers to the sheer volume of information being generated by research efforts in genetics—by the HGP itself and then by ongoing research spun off by the project in public and private laboratories around the world—and to the rapidity with which this information is being moved from the research setting into the clinical setting. It is, in particular, the interaction of the therapeutic gap and the information overload problem that gives rise to most of the ethical implications around genetic testing and screening. Clinicians can at present and for the foreseeable future test for many, many more diseases than they can meaningfully treat.

Testing is not without merit, however, and cardiovascular disease may represent a possible exception to the generalization above, since many of its symptoms can be treated conventionally with surgery or drugs. Nevertheless, because of the multifactorial patterns of inheritance behind most cardiovascular diseases, it will probably be a

*Early observers hoped that this therapeutic gap would be short-lived, but it is likely to be with us for quite a while, for at least two reasons. First, genetic therapies per se have proven to be elusive. Second, the HGP's discovery that humans have far fewer genes than originally thought means that disease processes must be tracked to the interaction of genes and to gene projects, which is a far more complex undertaking than tracking single-gene defects.

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