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Genetic Epidemiology of Coronary Artery Disease

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INTRODUCTION

Coronary artery disease is responsible for almost 500,000 deaths each year making it the number one killer of women and men in the United States (1). As many as 1.5 million individuals have a myocardial infarction each year, and at least 250,000 die of their myocardial infarction within 1 hour of symptoms. Over 13 million Americans have a history of symptomatic coronary artery disease. Coronary artery disease is responsible for more than $90 billion annually in economic costs (1).

Coronary atherosclerosis is the major cause of coronary artery disease (2). The atherosclerotic process is an organized, active, lifelong process involving elements of chronic inflammation followed by repair in the artery wall (3). The endothelium and many growth factors, cytokines, and vasoregulatory molecules are involved in the process (3). Atherosclerosis begins with the appearance of fatty streaks in the intima (4). The fatty streaks may evolve into fibrous plaques by accumulation of lipid, smooth muscle, and connective tissue. These plaques undergo vascularization, intraplaque hemorrhage, rupture, ulceration, and calcification and can impede blood flow through an artery. A thrombosis superimposed on a lesion can lead to myocardial infarction or sudden death (4).

Comprehensive studies to date have identified risk factors for coronary artery disease endpoints including sudden death, myocardial infarction, or angina pectoris (see table 1). These established risk factors include older age, male sex, elevated total cholesterol levels, elevated low-density lipoprotein cholesterol levels, reduced high-density lipoprotein cholesterol levels, hypertension, diabetes mellitus, smoking, obesity, physical inactivity, and family history of premature coronary artery disease (5, 6) (see table 1). These factors, however, fail to identify a large proportion of coronary artery disease endpoints (7, 8), and the disease process is not fully understood (7).

Coronary artery disease does not segregate as a simple Mendelian trait attributable to a single gene with large effects. Familial aggregation of coronary artery disease, however, has been recognized for almost 100 years (9). Studies support the hypothesis that coronary artery disease aggregates in families even after controlling for established risk factors (10, 11). In a recent twin study, the risk of death from coronary artery disease, after controlling for risk factors, was increased 8–15 times in monozygotic twins when their cotwin died prematurely from this disease (12). In this study, age at which one twin died of coronary artery disease was the primary independent variable to predict risk of death from the same disease in the other twin. In multivariable analyses, other risk factors for an individual, along with the age of twin's death from coronary artery disease, were the independent variables. The estimated increased risks of death from coronary artery disease when a cotwin died prematurely were little influenced by inclusion of information about the other risk factors. While many established risk factors have been shown to have at least some genetic basis (13–19), the increased risk of coronary artery disease associated with a family history of this disease after controlling for these risk factors suggests that some genetic mechanisms for susceptibility are yet to be identified.

Many genes and many environmental exposures contribute to coronary artery disease susceptibility. Thus, coronary artery disease and many of its risk factors are considered to be complex traits. The complexity arises because many genes may be involved in determining a particular phenotype (e.g., a specific total cholesterol level) and many phenotypes (e.g., a range of total cholesterol levels) are associated with a particular genotype (20). This complexity is attributed to 1) the large number of genes that influence coronary artery disease susceptibility in the population, 2) different subsets of genes that influence susceptibility in different families, 3) the influence of factors, such as age, sex, diet, and smoking, on the relation between genes and coronary artery disease susceptibility, and...
TABLE 1. Selected coronary artery disease endpoints and selected risk factors used in epidemiologic and genetic studies*

<table>
<thead>
<tr>
<th>Selected coronary artery disease endpoints</th>
<th>Established coronary artery disease risk factors</th>
<th>Proposed coronary artery disease risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td>Older age</td>
<td>Apolipoprotein E isoforms</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Male sex</td>
<td>Lipoprotein(a)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>Family history of premature coronary artery disease</td>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td>Angiographically detected stenosis</td>
<td>Cigarette smoking</td>
<td>Reduced apolipoprotein A1 levels</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>Obesity</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Percutaneous transluminal coronary angioplasty</td>
<td>Hypertension</td>
<td>Lipoprotein particle oxidation</td>
</tr>
<tr>
<td>Carotid artery atherosclerosis</td>
<td>Physical Inactivity</td>
<td>Lipoprotein particle subspecies</td>
</tr>
<tr>
<td>Coronary artery calcification</td>
<td>Diabetes mellitus</td>
<td>Low-density lipoprotein receptor</td>
</tr>
<tr>
<td></td>
<td>Elevated total cholesterol levels</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td></td>
<td>Elevated low-density lipoprotein cholesterol levels</td>
<td>Factor VII</td>
</tr>
<tr>
<td></td>
<td>Reduced high-density lipoprotein cholesterol levels</td>
<td>Plasminogen</td>
</tr>
</tbody>
</table>

* Adapted from the National Cholesterol Education Program (5) and Hoeg (6).

4) the large number of quantitative biochemical and physiologic traits that intervene between discrete allelic variations in genetic loci and individual variation in coronary artery disease susceptibility (20).

It is not the intent of this presentation to review the genetic basis of every risk factor for coronary artery disease, the postmortem studies, the animal studies, or the studies of monogenic disorders thought to account for a small proportion (approximately 15 percent) of individuals with premature myocardial infarction (9); the reader is referred to other reviews of studies of the genetic basis of coronary artery disease and its risk factors (13, 14, 20–31). This review has three goals: 1) to provide an overview of questions, strategies, and accumulated evidence from past studies of the genetic basis of coronary artery disease and its risk factors; 2) to review recent epidemiologic and genetic studies that use noninvasive measures of atherosclerosis; and 3) to speculate about future studies to understand the role of genes in the development and progression of preclinical coronary artery disease.

GENETIC BASIS OF CORONARY ARTERY DISEASE AND ITS RISK FACTORS—THE PAST

Questions

The major goal of many studies has been to determine if there is evidence that genes are involved in the variation in either coronary artery disease endpoints or risk factors. The coronary artery disease endpoints studied include, but are not limited to, sudden death due to coronary artery disease, myocardial infarction, and angiographic evidence of stenosis (see table 1). Almost all risk factors have been considered both as discrete and as quantitative variables. Discrete risk factors studied include hyperlipidemia, hypertension, diabetes, and smoking behavior. Quantitative risk factors studied include measures of lipids, lipoproteins, apolipoproteins, lipoprotein(a), blood pressure, fibrinogen, insulin, glucose, homocysteine, and body mass index. If there is evidence that genes are involved, then questions focus on: How many genes are involved? What are the number of alleles for each gene and what are their relative frequencies? What is the relation of each allele to coronary artery disease risk, discrete risk factors, or quantitative risk factors? Are genes acting through the pathways of measurable risk factors (e.g., lipids and blood pressure) or through novel pathways that have not been or cannot be directly measured in vivo? Is there evidence for gene by gene interactions and/or gene by environment interactions (20)? Ultimately, the answers to these questions will provide the minimum set of genes, along with other measures representing biologic factors and/or environmental exposures, that are needed for more accurate prediction of coronary artery disease risk. The genes and risk factors that predict coronary artery disease risk are expected to vary among individuals, among families, and/or among populations (20, 25).

Strategies

There are two general strategies to address the above questions (32). The first is an unmeasured genotype strategy that uses biometric analysis to determine whether there is evidence that unmeasured genes influence variation in coronary artery disease risk or a risk factor. The unmeasured genotype strategy can
only be applied to samples of related individuals. Since the genotypes of individuals are unknown, they must be inferred by using information on the distribution of coronary artery disease or its risk factors and the genetic relations among individuals in the sample. The second is the measured genotype strategy. It takes advantage of the availability of candidate genes or gene products to determine the ability of these genes to explain interindividual variation in coronary artery disease or its risk factors. This strategy can also use the large number of anonymous markers throughout the genome (33). The measured genotype strategy can be applied to samples of unrelated individuals as well as to samples of related individuals. While the focus in this strategy is on the measured genes, assumptions are made about the role of unmeasured genes in some applications (i.e., classic linkage analysis). Both the unmeasured and the measured genotype strategies have been applied to many of the same coronary artery disease risk factors, although not usually in the same study.

Unmeasured genotype strategy

The models used in this strategy assume that the observed distribution of a trait is a consequence of the independent contributions from combinations of the following: 1) a single, unmeasured gene with a large effect; 2) the effects of a large number of unmeasured, independent polygenes each with a small additive effect; 3) the effects of unmeasured environmental exposures shared by members of the same household; and 4) unmeasured individual-specific environmental influences (including measurement error). Reviews of the methods of this strategy are extensive (29, 34–38).

Selected findings from the unmeasured genotype strategy

Evidence for polygenes for selected risk factors. Almost 20 years ago, the contribution from polygenes (i.e., heritability) for early onset for coronary artery disease was estimated to be 56 percent (39). Based on recent studies, comparing the disease status in monozygotic twins to the disease status in dizygotic twins, there is evidence for unmeasured polygenes contributing to coronary artery disease mortality (12), smoking behavior (16), non-insulin-dependent diabetes mellitus (40), and hypertension (41).

A recent study of quantitative risk factors among Mexican-Americans included over 1,000 members of 42 randomly ascertained extended families (19). This study included measures of covariates, including dietary and physical activity patterns, medication use, smoking habits, alcohol consumption, and other lifestyle behaviors, as well as age and sex. The percent of variance attributed to measured covariates, polygenes, shared household effects, and individual-specific environmental effects are shown in table 2 for selected coronary artery disease risk factors including total cholesterol, high-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, apolipoprotein E, lipoprotein(a), fasting glucose, fasting insulin, systolic blood pressure, and body mass index (weight divided by height squared (kilograms/meters 2)).

For the risk factors shown in table 2, age, sex, and other measured covariates explained as little as 1.4 percent of the total phenotypic variance for lipoprotein(a), and as much as 30.8 percent of the total phenotypic variance for systolic blood pressure. For every trait, the contribution from the polygenes (range of 17.8–69.0 percent) was substantially higher than the other measured covariates.
various methods exist for incorporating measured candidate genes or anonymous DNA markers into studies of related individuals. First, methods of classic linkage analysis are applicable to both discrete and quantitative risk factors to study cosegregation of measured candidate genes or anonymous DNA markers with putative risk factor alleles within a pedigree, and to estimate recombination (29, 38, 64). This type of linkage analysis makes assumptions about the role of unmeasured genes and depends on the presence of a single unmeasured gene with a large effect on the discrete or quantitative risk factor. Classic linkage analysis is usually not applied to coronary artery disease endpoints given their failure to show evidence of Mendelian transmission (9). Second, model-free methods of linkage analysis that do not require a priori evidence of a single unmeasured gene with a large effect exist for both pedigree data and samples of siblings (65–69). There are models for both discrete and quantitative outcomes. Lastly, models have been developed for family data to partition the genetic variation in a quantitative risk factor into the proportion attributable to specific measured genes and the proportion due to the segregation of unmeasured polygenes (69).

Selected findings from the measured genotype strategies

Coronary artery disease and selected discrete risk factors. Many case-control studies of associations between measured genotypes (usually structural genes for apolipoproteins) and coronary artery disease have reported conflicting results (70). One of the most studied apolipoprotein genes is apo E (71). There are three major apo E isoforms, with amino acid and functional differences, which are the products of three alleles of a single gene on chromosome 19 (72). At the population level, the apo E polymorphism is thought to explain 12 percent of myocardial infarction cases (73). Findings, however, with respect to associations between apo E isoforms and various coronary artery disease endpoints have not been consistent among studies (74–77). Likewise, the association between a deletion variant of the gene for angiotensin-converting enzyme and increased risk of myocardial infarction has been inconsistent among studies (78).

Several genes for discrete coronary artery disease risk factors have been identified in individual studies. The gene encoding angiotensinogen has been linked to hypertension in a study of hypertensive sibling pairs and has been associated with hypertension in case-control studies (79). A recent population-based study, however, could not confirm the association between variation in this gene and hypertension (80). An anony-
ymous DNA marker on chromosome 2, designated NIDDM1, showed evidence of linkage to non-insulin-dependent diabetes mellitus in 330 affected sibling pairs from Mexican-American families (81). While this finding was confirmed in a second sample from the same population (81), it is yet to be confirmed in other populations.

Selected quantitative risk factors. Recent studies have identified specific anonymous DNA markers influencing quantitative measures of human obesity (82, 83). In Mexican-Americans, a DNA marker on chromosome 2 influences serum leptin levels and fat mass (82), while in Pima Indians, a DNA marker on chromosome 11 influences percent body fat (83). While neither study identified a specific candidate gene for human obesity, both identified regions of the genome that may contain important human obesity genes.

Many studies have investigated the relation between structural genes and quantitative measures of lipids, lipoproteins, and apolipoproteins (13, 29, 61–63, 84–87). The most impressive measured gene finding in quantitative coronary artery disease risk factors comes from a study reporting that the apo(a) gene accounts for more than 90 percent of the variation in quantitative lipoprotein(a) levels in a sample of siblings (87). The most consistent findings are for the relation between apo E isoforms and plasma levels of apolipoprotein E. In one population-based sample, the apo E isoforms explained almost 12 percent of the variation in quantitative lipoprotein(a) levels in a sample of siblings (87). While variation in apo E isoforms explains some variation in plasma apolipoprotein E, other genes may explain additional variation.

Several studies using measured genotypes have reported gene by environment interactions and gene by gene interactions (88). In one study, there was an interaction between apo E isoforms and the cholesterol-lowering drug pravastatin on the changes in cholesterol levels in heterozygous familial hypercholesterolemic individuals (89). Individuals with at least one e4 allele had larger reductions in cholesterol levels compared with e3/3 individuals. The investigators hypothesized that the E4 isoform and the cholesterol lowering drug might act synergistically to promote enhanced cholesterol catabolism.

In general, measured genotypes often explain less than 10 percent of the variation in various measures of lipids, lipoproteins, and apolipoproteins (85, 86). Whether candidate genes that are not structural genes for apolipoproteins will explain more or less of the variation than is explained by these structural genes remains unknown. It has been suggested that measured genotypes with low effects will most likely be revealed by association studies, rather than classic linkage studies, and using related, rather than unrelated, individuals (90).

Limitations of studies using the unmeasured and measured genotype strategies

Limitations of genetic studies have been well described (38, 59). Differences among studies in estimates of the contributions from unmeasured or measured genotypes are due, in part, to variation among studies in 1) specific genetic relations in the sample, 2) the ascertainment of study participants, 3) the ages of study participants, 4) measurement technique(s) for the risk factor or coronary artery disease endpoint, 5) distribution of the risk factor or coronary artery disease endpoint in the sample, 6) methods to adjust for measured covariates, 7) the genetic background of the sample, 8) the diversity in environmental exposures in the sample, 9) the alternative hypotheses considered, 10) the sample size, 11) the effects of unmeasured confounders, and 12) in how well assumptions of the model are met.

NEWER STUDIES OF NONINVASIVE MEASURES OF THE Atherosclerotic PROCESS

Motivation

A major limitation of previous genetic studies, as well as a possible explanation for inconsistent findings among studies, is use of specific clinical coronary artery disease endpoints such as sudden death, myocardial infarction, and angina pectoris. These endpoints cannot identify all individuals with atherosclerosis because many lack symptoms, yet individuals with asymptomatic disease do not necessarily experience lower risk of death than individuals with symptoms (91). The risk factors for coronary artery disease, including genes, probably act on several components of the disease process that lead to these clinical coronary artery disease endpoints (92). Thus, studies of subclinical atherosclerosis are expected to extend knowledge concerning etiology, prevention, and treatment of coronary atherosclerosis.

Noninvasive imaging modalities

Noninvasive imaging modalities exist that allow us to visualize abnormalities at the vessel wall and measure subclinical atherosclerosis. A measure for epidemiologic and genetic studies should be low cost, accurate, reproducible, and acceptable. To assess accuracy, potential noninvasive measures have been compared to coronary angiography. Coronary angiography is invasive and expensive (cost ~ $4,800), has
associated risks (93), and is used primarily in individuals with symptoms of coronary artery disease (94). Based on angiography, the presence of coronary artery disease is usually defined as the presence of at least a 50 percent luminal narrowing in an epicardial artery.

Two noninvasive measures of atherosclerosis that have similar, relatively low costs (~ $400) are B-mode ultrasonography of the carotid arteries and electron-beam computed tomography of the coronary arteries. B-mode ultrasonography measures intima-media thickening in the carotid arteries to identify carotid atherosclerosis (table 1), which is used as a surrogate measure of coronary atherosclerosis. Electron-beam computed tomography measures quantity of coronary artery calcification as a marker of coronary atherosclerosis (table 1).

The sensitivity and specificity of a B-mode summary score to detect angiographically-defined coronary artery disease are 73 percent and 78 percent, respectively, in women over 50 years of age (95). The sensitivity and specificity are similar in men over 50 years of age when low-density lipoprotein cholesterol is also taken into the classification scheme (95). In women or men under 50 years of age, however, the B-mode score is not significantly associated with the presence of angiographically-defined coronary artery disease after controlling for coronary artery disease risk factors (95). Sensitivity and specificity were derived from recursive partitioning and the classification and regression tree algorithm (95). The intima-media thickening measure is reproducible (96). The procedure is safe and is not associated with a radiation dose. Its use in several studies provides evidence of its acceptability (97-99).

The sensitivity and specificity of electron-beam computed tomography measures of coronary artery calcification to detect angiographically-defined coronary artery disease are 90 percent and 62 percent, respectively, in women and men aged 20 to 59 years (100). The sensitivities and specificities are consistent across many studies (101). The measure of the quantity of coronary artery calcification is reproducible (100, 102). The radiation dose to the skin for an electron-beam computed tomography examination is 10 mGy (1 rad) (equivalent to that received from an abdominal x-ray). Electron-beam computed tomography is highly acceptable as evidenced by a high participation rate (i.e., 91 percent) in a recent community-based study (102).

Selected epidemiologic studies of variation in carotid artery wall thickness

Atherosclerosis in the carotid arteries detected ultrasonographically has been shown to predict the future risk of myocardial infarction (103). In cases and controls from the Atherosclerosis Risk in Communities study, those with evidence of carotid intima-media thickening (i.e., the cases) had higher levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, blood pressure, and pack-years of smoking, and lower levels of high-density lipoprotein cholesterol compared with those without carotid intima-media thickening (104). Older age, being male, and other coronary artery disease risk factors explained 40 percent of the variation in extent of carotid artery atherosclerosis in patients hospitalized for elective angiography (105).

Selected genetic studies of variation in carotid artery wall thickness

The unmeasured genotype strategy has recently been applied to measures of the intima-media thickening of the common and internal carotid arteries in a sample of adult siblings living in Mexico City (106). For intima-media thickening in the common carotid artery, the covariates accounted for an estimated 27.7 percent of the variance, the polygenes accounted for 66.0 percent, and individual-specific environmental effects accounted for the remaining 6.3 percent. For intima-media thickening in the internal carotid artery, 11.5 percent of the variance was attributed to covariates, 74.9 percent to polygenes, and 13.6 percent to individual-specific environmental effects (106). The findings from this study have not yet been replicated by others.

In a study using a measured genotype strategy in a sample of Caucasian women and men aged 45–64 years from the Atherosclerosis Risk in Communities cohort, the apo E genotype e2/3 was associated with having significant carotid artery atherosclerotic disease compared with the e3/3 genotype after controlling for age, body mass index, smoking behavior, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol (107). Carotid artery atherosclerosis was based on carotid wall thickness measured by B-mode ultrasonography. The estimated odds ratio for the association between significant carotid artery atherosclerosis and having the e2/3 genotype was greater than 2.0 (107).

Selected epidemiologic studies of variation in coronary artery calcification

Coronary artery calcification has been shown to predict future coronary artery disease clinical endpoints such as sudden death, myocardial infarction, coronary artery bypass surgery, and percutaneous transluminal coronary angioplasty in both symptom-
atic and asymptomatic adults (108, 109). The quantity of coronary artery calcification is associated with many risk factors for coronary artery disease (101, 102, 110). In a community-based sample of 740 asymptomatic adults (378 women), men had a higher quantity of coronary artery calcification than women (102). Within each sex, age, the ratio of total cholesterol to high-density lipoprotein cholesterol, systolic blood pressure, body mass index, and having a history of smoking were associated with quantity of coronary artery calcification. These factors explained less than 40 percent of the variation in quantity of coronary artery calcification among women and men (102).

Selected genetic studies of variation in coronary artery calcification

One study found evidence that quantity of coronary artery calcification clusters in families independently of other risk factors (111). This finding of familial aggregation parallels the discovery that coronary artery calcification is determined, in part, by genetic factors among inbred mouse strains (112). When different mouse strains were crossed with one another, there was evidence of incomplete penetrance as well as multiple genetic factors influencing calcification.

In a study of asymptomatic women and men aged 20 to 59 years, apo E genotype did not predict the presence of coronary artery calcification after coronary artery disease risk factors were considered as predictors (113). Apo E genotype did, however, influence the relation between coronary artery calcification and risk factors. In men, there was positive association between having coronary artery calcification and cholesterol levels for those with e2/3 and e3/3 genotypes. Among men with the e3/4 genotype, the probability of having coronary artery calcification was independent of cholesterol levels (113).

SUMMARY

Evidence for unmeasured genes for established coronary artery disease risk factors, including smoking, obesity, blood pressure levels, measures of lipid metabolism, and diabetes, has been reported by many investigators studying diverse populations. In addition, many studies have also found evidence for unmeasured genes for several of the proposed risk factors (see table 1) including apolipoprotein AI, lipoprotein(a), insulin levels, and fibrinogen. Evidence for specific candidate genes or anonymous DNA markers being associated with risk factors is accumulating rapidly. Within a few years, most of the risk factors, both established and proposed, will be found to be associated with specific measured genes. Except for apo E, no specific candidate gene or anonymous marker has been consistently associated with coronary artery disease endpoints. Few studies relating candidate genes to coronary artery disease endpoints have been replicated, and few have considered risk factors simultaneously with candidate genes. The next few years should provide us with many new genes for coronary artery disease endpoints as well as an opportunity to begin to understand how these genotypes modify disease susceptibility in the presence or absence of specific risk factors.

THE FUTURE

Advancements in technology, especially in molecular genetics, and statistical approaches, along with the existence of large population-based studies, should enable us to identify genes for coronary artery disease susceptibility. New noninvasive technologies to examine the coronary arteries are currently under development. Using contrast-agent and electron-beam computed tomography, researchers have detected stenoses of the coronary arteries (114). Recent advances in magnetic resonance imaging have also allowed visualization of the coronary arteries and detection of stenoses (115). Using these approaches to image coronary arteries will provide additional noninvasive measures to identify genes involved in the development and progression of coronary atherosclerosis.

New statistical approaches have been developed for genetic studies. Understanding the limitations of linkage analysis for finding genes with modest effects for complex diseases has led to new methodologies (116–118). It has been suggested that future studies will rely heavily on genomnic association studies in related individuals to find important genes (90). Since many of the predisposing genes are neither necessary nor sufficient for the development of coronary artery disease, researchers are considering gene by gene interactions, as well as gene by environment interactions, in their statistical analyses.

Many studies in progress using candidate genes as well as anonymous markers will begin to provide information about new genes for subclinical atherosclerosis. A large community-based study of coronary artery calcification (102) is currently using sibling-pair linkage methods to localize genes for quantity of coronary artery calcification. Association studies will also be used to assess whether these genes are acting through pathways of measurable coronary artery disease risk factors or through novel pathways that have not been or cannot be directly measured in vivo. The multicenter population-based National Heart Lung and Blood Institute Family Heart Study (119) seeks to identify genetic and nongenetic determinants of coro-

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nary artery disease. This study is using carotid artery ultrasonography to measure atherosclerosis and is investigating newer coronary artery disease risk factors. There are numerous other studies initiated by the National Heart, Lung, and Blood Institute, such as Atherosclerosis Risk in Communities, as well as by individual investigators seeking to identify genes for both coronary artery disease risk factors and coronary artery disease endpoints.

Many ethical, legal, and social issues exist concerning the use and misuse of information about susceptibility genes for complex diseases. Hopefully, many of these issues will be resolved in the near future so that we can look forward to the day when use of information about genes for coronary artery disease susceptibility will lead to improved prevention strategies as well as earlier diagnosis and treatment.

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REFERENCES


