review

Genetic evaluation for coronary artery disease

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There is substantial evidence that genetic factors contribute to coronary artery disease (CAD). Currently, family history collection and interpretation is the best method for identifying individuals with genetic susceptibility to CAD. Family history reflects not only genetic susceptibility, but also interactions between genetic, environmental, cultural, and behavioral factors. Stratification of familial risk into different risk categories (e.g., average, moderate, or high) is possible by considering the number of relatives affected with CAD and their degree of relationship, the ages of CAD onset, the occurrence of associated conditions, and the gender of affected relatives. Familial risk stratification should improve standard CAD risk assessment methods and treatment guidelines (e.g., Framingham CAD risk prediction score and Adult Treatment Panel III guidelines). Individuals with an increased familial risk for CAD should be targeted for aggressive risk factor modification. Individuals with a high familial risk might also benefit from early detection strategies and biochemical and DNA-based testing, which can further refine risk for CAD. In addition, individuals with the highest familial risk might have mendelian disorders associated with a large magnitude of risk for premature CAD. In these cases, referral for genetic evaluation should be considered, including pedigree analysis, risk assessment, genetic counseling and education, discussion of available genetic tests, and recommendations for risk-appropriate screening and preventive interventions. Research is needed to assess the feasibility, clinical validity, clinical utility, and ethical, legal, and social issues of an approach that uses familial risk stratification and genetic evaluation to enhance CAD prevention efforts. ***Genet Med* 2003:5(4):269–285.**

Despite remarkable successes in the treatment and prevention of coronary artery disease (CAD) in the past decades, it is still the leading cause of death and premature disability in the United States and other developed countries. An estimated 12,600,000 Americans have CAD, and in 2003, an estimated 650,000 Americans will have their first heart attack and another 450,000 will have a recurrent event.[1] The cumulative risk for CAD in males by age 70 is 35% and by age 90 is 49%. Women typically develop CAD about 10 years later then men with a cumulative risk of 24% and 32% by ages 70 and 90, respectively.[1] Although considered a disease of advancing age, approximately 15% of cases are diagnosed before age 65.[1] Disability and mortality from CAD at young ages is particularly devastating to families and has a substantial impact on our economy.

Individuals with genetic predisposition to atherosclerosis are at the greatest risk for developing CAD, especially at early ages, and they have the most to gain from preventive interventions.[2] This article will review the role of genetics in the development and progression of CAD, and the components of a genetic evaluation for CAD, including genetic risk assessment, risk factor modification, early detection strategies, and genetic counseling and education.

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Role of genetics in development and progression of CAD

The accumulation of atherosclerotic plaque in an artery wall is a chronic disease that begins early in life.[3] This process appears to be initiated and/or facilitated by chronic injury to the endothelium.[4] With progression, the lesions take the form of an acellular core of cholesterol esters bounded by a fibrous cap. Plaques may become symptomatic when they are large enough to restrict blood flow leading to tissue ischemia. Acute coronary syndromes such as unstable angina, myocardial infarction (MI), and sudden death occur when unstable plaques rupture or ulcerate leading to platelet accumulation and activation, fibrin deposition, thrombus formation, and possible vessel occlusion.[5,6]

Several biochemical process are involved in atherosclerosis formation and progression, including lipid and apolipoprotein metabolism, inflammatory response, endothelial function, platelet function, thrombosis, fibrinolysis, homocysteine metabolism, insulin sensitivity, and blood pressure regulation.[2] Each of these biochemical processes has multiple constituents such as enzymes, receptors, and ligands, which are encoded by our genes. Each process is also influenced by environmental factors.

Gene association studies

Variations in genes can alter the function of the constituents within a metabolic pathway, resulting in variable susceptibility to the development and progression of atherosclerosis. Table 1 reviews the candidate genes that have been associated with CAD or MI and categorizes these genes by the metabolic pathways that might be involved. However, many of these associations are controversial with varying results in the literature (e.g., angiotensin-converting enzyme, methylenetetrahydrofolate reductase (MTHFR), platelet glycoprotein receptor IIIa, and factor V).[73] The lack of consistency in findings may be due to positive reports that are due to chance, underestimation of the frequency of polymorphisms in the control populations, or not matching the race/ethnicity of cases and controls.

In the case of thrombosis-related genes, explanations for the differences in some studies reflects differences in these genes playing a role in the development of atherosclerosis versus the occurrence of acute coronary syndromes like MI and unstable angina. For example, the factor VII locus has been implicated in determining factor VII levels and risk of MI in patients with established CAD.[47] However, there is no association of factor VII levels in the development of CAD,[74] suggesting the importance of an atherosclerosis substrate for this risk factor. Similarly, several studies have identified a strong association between the platelet glycoprotein receptor IIIa (GPIIIa) A2 allele and acute coronary thrombosis and extent of CAD.[57,75,76] However, other studies have failed to demonstrate an association with CAD or MI.[58,77,78] Cooke and colleagues[79] argue that differences in aspirin use might account for some of the discrepancies in studies investigating this polymorphism, because aspirin has been shown to inhibit the increased platelet aggregation observed with this polymorphism and many study subjects were likely treated with aspirin.

Linkage studies

Investigations utilizing genome scan approaches have found novel genetic loci associated with CAD, which might provide additional insight to genetic factors contributing to atherosclerosis. Linkage analysis in families with premature CAD have found evidence for linkage to a region on chromosome 2q21.1-q22 and Xq23-q26.[80] A search for candidate genes in the Xq23-q26 region identified the angiotensin receptor 2 gene. This gene may play a role in cardiovascular and central nervous system functions.[81] A possible candidate gene in the 2q21.1-q22 region is the mitochondrial glycerophosphate dehydrogenase gene. Deficiency of this gene has been associated with impaired glucose-stimulated insulin release in animal models of diabetes.[80] A genome-wide scan of families with acute coronary syndrome, including MI and unstable angina before age 70, found linkage to chromosome 2q36-q37.3, which encompasses the insulin receptor substrate-1 gene, the HDL cholesterol-binding protein, and the type 2 diabetes locus *NIDDM1* in which the *CAPN10* gene has been implicated.[82] Two additional regions of interest were found in this study, 3q26-q27 and 20q11-q13.[82] The chromosome 3q locus has been linked to lipid variation in genome scans and contains genes encoding apoD (a glycoprotein component of HDL) and the glucose transporter 2 (part of the glucose sensor in pancreatic β cells). The 20q locus has been linked with maturity onset diabetes of the young.

A genome-wide scan for coronary artery calcification loci in sibships at high risk for hypertension found evidence for linkage to chromosomal regions 6p21.3 and 10q21.3.[83] Almost 95% of participants were asymptomatic for CAD yet had coronary artery calcification scores above the 70th percentile and thus were at high risk for a future event.[84] Candidate genes on chromosome 6q include collagen type XI α_2 and allograft inflammatory factor 1, and candidate genes in the chromosome 10 region include collagen type XIII α_1 and bone morphogenetic protein receptor type 1A.[83]

A population-based study of Icelandic families with peripheral arterial disease is the first of its kind and has found evidence for linkage to chromosome 1p31.[85] The locus called *PAOD* was associated with other forms of atherosclerosis, such as stroke and MI; however, when subjects with stroke and MI were excluded, the linkage of the *PAOD* locus with peripheral arterial disease remained significant. There was no correlation of this locus with hyperlipidemia, hypertension, or diabetes. Thus this locus is unlikely to be a gene contributing to these conditions.

There are also numerous studies that have found genetic associations or linkage with related disorders such as hypertension,[86–91] obesity,[92–100] diabetes,[101–111] lipids,[112–115] and oxidative stress.[116] Many of the gene associations identified in these studies are found when studying the phenotype of CAD.

Abbreviation definitions

CAD	coronary artery disease	LDL	low density lipoprotein
MI	myocardial infarction	ADH3	alcohol dehydrogenase type 3
MTHFR	methylenetetrahydrofolate reductase	ASHG	American Society of Human Genetics
GPIIIa	glycoprotein receptor IIIa	ACMG	American College of Medical Genetics
HTN	hypertension	PAI	plasminogen activator inhibitor
CETP	cholesterol ester transfer protein	ABI	ankle/brachial index
HRT	hormone replacement therapy	CCA-IMT	common carotid artery intima-media thickness
VTE	venous thromboembolic event	EBCT	electron beam computed tomography
ALP	atherogenic lipoprotein phenotype	SPECT	single photon emission computed tomography
hs-CRP	high sensitivity c-reactive protein		
HDL	high density lipoprotein		

Table 1
Candidate genes associated with increased risk for coronary artery disease and myocardial infarction.

Candidate Genes	OMIM entry	References
Lipid metabolism		
Apolipoprotein (a) (LPA)	152200	7, 8
Apolipoprotein B	107730	9
Apolipoprotein E	107741	10–18
Cholesterol ester transfer protein	118470	19–22
Lecithin cholesterol acetyl transferase	606961	23
LDL receptor	606945	24
Lipoprotein lipase	238600	25, 26
Blood pressure regulation		
Alpha-adducin	102680	27
Angiotensinogen	106150	28–30
Angiotensin II receptor, type 1	106165	30, 31
Angiotensin converting enzyme	106180	32, 33
Insulin sensitivity		
Insulin receptor substrate-1	147545	34
Homocysteine metabolism		
Cystathionine beta synthase	236200	35–37
Methylene tetrahydrofolate reductase	607093	38–41
Thrombosis		
Factor II (Prothrombin)	176930	42
Factor V (Factor V Leiden)	227400	43, 44
Factor VII	227500	45–47
Thrombospondin genes	188060	48
	188061	
	188062	
Fibrinolysis		
Fibrinogen genes	134820	49–52
	134830	
	134850	
Plasminogen activator inhibitor-1	173360	53, 54
Thrombin-activatable fibrinolysis inhibitor	603101	55
Platelet function		
Glycoprotein Ia/IIa receptor	192974	56
Glycoprotein IIIa receptor	173470	57–59
Endothelial/vessel function		
Connexin 37	121012	54
Endothelial nitric oxide synthase	163729	59
Matrix Gla protein	154870	60
Matrix metalloproteinase 9	120361	61
Stomelysin-1	185250	54
Inflammatory response		
Endothelial leukocyte adhesion molecule-1 (E-selectin)	131210	62,63
Granule membrane protein (P-selectin)	173610	64,65
Interleukin-6	147620	66
Paraoxonase	168820	67,68
Miscellaneous		
Ataxia-telangiectasia locus	607585	69
Werner syndrome locus	604611	70
Alcohol dehydrogenase type 3	103730	71
Adenosine monophosphate deaminase-1	102770	72

Assessing genetic susceptibility to CAD

Generally, the manifestation of CAD should be considered as the interaction of several genetic and nongenetic factors. The environmental and behavioral risk factors that predispose to most forms of CAD are prevalent in developed countries, including smoking, inactivity, excess calories, and high fat intake. Consequently, when CAD occurs at a young age or if there is a severe phenotype, the presence of multiple and/or highly penetrant genetic factors, is likely. Rarely, single gene disorders associated with a large magnitude of risk are responsible for CAD (Table 2).[117] This can be due to high-risk alleles that cause specific forms of CAD, or gene mutations that disrupt key metabolic pathways involved in atherothrombotic disease, such as lipid and homocysteine metabolism.

Pedigree analysis to assess CAD risk

The systematic collection and interpretation of family history information is the most appropriate initial screening approach to identify individuals with genetic susceptibility to CAD. Family history of CAD and related conditions reflects the interactions of genetic and nongenetic risk factors shared among family members. Once an individual is identified via pedigree analysis as having a familial risk, other risk assessment methods such as physical examination, biochemical and DNA-based testing, and early detection techniques can be applied to further stratify risk. This approach is in accordance with the global risk assessment concept that has evolved in the past decade.[118] Global risk assessment is the estimation of absolute risk based on the summation of risks contributed by each risk factor. The intensity of risk factor management is adjusted by the severity of risk.

The Framingham Risk Score is one of the most widely used risk assessment methods for prediction of CAD risk.[119] It considers the established risk factors of gender, age, smoking, total cholesterol, LDL cholesterol, HDL cholesterol, and diabetes;

Table 2
Mendelian disorders featuring coronary artery disease and myocardial infarction[117]

Disorder	Mode of inheritance	OMIM entry
Abdominal obesity-metabolic syndrome	MF	605552
Apolipoprotein(a) polymorphism/LPA excess	AD	152200.0001
Apolipoprotein A-I deficiency	AD, AR	107680.0011
		107680.0012
		107680.0013
		107680.0015
		107680.0017
		107680.0022
Atherosclerosis susceptibility/atherogenic lipoprotein phenotype (ALP)	AD, MF	108725
Coronary artery dissection, spontaneous	AD	122455
Cerebrotendinous xanthomatosis	AR	213700
Fabry disease	XLR	301500
Familial combined hyperlipidemia	AD, MF	144250
Familial defective apo B	AD	144010
Familial hypercholesterolemia	AD	143890
Familial hypercholesterolemia, autosomal recessive	AR	603813
Familial partial lipodystrophy	AD	151660
Familial pseudohyperkalemia due to red cell leak	AD and AR	177720
Fibromuscular dysplasia of arteries	AD	135580
Heparin cofactor II deficiency	AD	142360
Homocysteinemia	AD, MF	603174
Homocystinuria	AR	236200
Homocysteinemia/homocystinuria due to *N*(5,10)-methylenetetrahydrofolate reductase deficiency	AR	236250
Hyperlipoproteinemia, type III	AR with pseudodominance	107741
Methylcobalmin deficiency, cbl G type	AR	250940
Niemann-Pick disease, type E	AR	257200
Progeria	AD	176670
Protein C deficiency	AD	176860
Pseudoxanthoma elasticum	AR	264800
Pseudoxanthoma elasticum, autosomal dominant	AD	177850
Sitosterolemia	AR	210250
Tangier disease	AR	205400
Vitamin B12 metabolic defect, type 2	AR	277410
Vitamin B12 metabolic defect with methylmalonic acidemia and homocystinuria	AR	277400
Werner syndrome	AR	277700
Williams syndrome	AD	194050

AD, autosomal dominant; AR, autosomal recessive; MF, multifactorial; XLR, X-linked recessive.

however, it does not consider family history as a risk factor. Thus, the Framingham Risk Score will very likely underestimate CAD risk for individuals with a family history of CAD, especially at younger ages. Minimal family history information (parental history of MI before age 55) is taken into consideration by the National Cholesterol Education Program Expert

Characteristics of Genetic Susceptibility to Coronary Artery Disease

- **Early onset CAD (men less than age 55, women less than age 65)**
- **Angiographic severity**
- **Multiple vessels involved with atherosclerosis (e.g., coronaries, carotids, aorta)**
- **More than one close relative with CAD, especially female relatives**
- **Presence of multiple established and emerging CAD risk factors in family members with CAD**
- **Absence of established risk factors in family members with CAD**
- **Presence of related disorders in close relatives (e.g., diabetes, hypertension, stroke, peripheral vascular disease)**

Fig. 1 Personal and family history characteristics of genetic susceptibility to coronary artery disease. CAD, coronary artery disease; Close relative, first and/or second degree relative from one lineage; Established risk factors, elevated total and LDL cholesterol, low HDL cholesterol, hypertension, diabetes, smoking; Emerging risk factors, elevated C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), small LDL particles, reduced HDL2b fraction, hyperinsulinemia or other measures of insulin resistance/impaired glucose tolerance, MTHFR C677T, factor V Leiden, and prothrombin G20210A

Panel,[120] which provides algorithms for treatment of lipid disorders in adults. Unfortunately, these algorithms do not consider the risk associated with additional family history of CAD or family history of related disorders such as lipid disorders or diabetes.

To assess familial risk in the clinical setting, ideally family history should be collected regarding all first- and second-degree relatives. Demographic and medical information should be obtained for each relative including current age or age at death, cause of death if deceased, history of CAD and related conditions such as stroke, peripheral vascular disease, aortic aneurysm, hypertension, diabetes, and lipid abnormalities, and associated risk factors such as smoking. Documentation of ethnicity and country of origin is also useful because certain conditions might be more prevalent in certain ethnic groups, such as insulin resistance and Native American admixture[121,122] and the MTHFR C677T mutation and Ashkenazi Jewish ancestry.[123] Fig. 1 lists personal and family history characteristics of genetic susceptibility to CAD.

Once family structure and medical information regarding relatives are available, construction of a pedigree is possible and interpretation of the family history can be performed to determine the level of risk. Quantitative estimates of risk can be derived from case-control studies examining family history as a risk factor. On average, there is a 2- to 3-fold increase in risk for CAD in first-degree relatives of cases.[124–128] Having two or more first-degree relatives with CAD is associated with a 3- to 6-fold increase in risk.[129,130] The earlier the age of onset the greater the risk of CAD to relatives.[129–132] In addition, the risk of disease is typically greater in relatives of female cases compared to male cases, suggesting greater genetic burden in female cases.[127,132–134]

Much of the familial aggregation of CAD might be explained by the familial aggregation of established risk factors such as elevated LDL cholesterol, decreased HDL cholesterol, and diabetes.[132] In a recent analysis of the Third National Health and Nutrition Survey, adults with a parental history of CAD were more likely to have multiple risk factors (odds ratio for four or five risk factors compared with none was 2.9, 95% CI, 1.4–6.3).[132] Yet even after adjusting for these established risk factors in the case, the family history remains a significant independent risk factor for CAD.[132,133,135–141] An explanation for this remaining risk may be due to familial aggregation of emerging CAD risk factors including hyperhomocysteinemia,[142] C-reactive protein,[143] elevated fibrin D-dimer, tissue plasminogen activator and fibrinogen,[144] and insulin resistance.[145] Additionally, the interactions of the genetic and nongenetic risk factors shared by family members may be too complex to assess with usual statistical methods.

Absolute risks associated with a family history of CAD and related conditions would be most beneficial in the clinical setting. Unfortunately, these risk estimates are not available. However, stratification into average, moderate, and high-risk groups is possible, taking into consideration the degree of relationship of the affected relative(s), the age at disease onset, and the number of affected relatives.[146] Generally, an average risk can be assigned to individuals who lack family history of CAD, or if they report only one affected second-degree relative of later or unknown age of onset. An increased familial risk for CAD in individuals without clinically apparent disease can be defined as having at least one affected first-degree relative or two affected second-degree relatives from the same lineage. An example of an algorithm designed to stratify familial risk for CAD is provided in Fig. 2.

Pedigree analysis can also reveal characteristic patterns of disease suggestive of a genetic syndrome. Recognition of these features can have important implications for recommending appropriate diagnostic tests as well as individualized management and prevention strategies. For example, an inherited susceptibility to thrombosis may be suspected in a pedigree that features multiple affected relatives with early onset of CAD, stroke, and other thromboembolic events. Testing of thrombotic genetic markers, such as the prothrombin G20210A mutation or the MTHFR C677T mutation, might reveal important risk factors in the family. Familial aggregation of CAD, stroke, hypertension, dyslipidemia, and type 2 diabetes is consistent with Syndrome X[147] or the metabolic syndrome due to insulin resistance, which has significant genetic determinants[148–150] and aggregates in families.[145]

Accuracy of family history

Individuals often report "heart disease" or "heart problems" for their relatives. Most often these family members will have CAD because this is the most prevalent form of cardiovascular disease in adults.[1] Review of medical records and death certificates is recommended to clarify these reports, and often additional questioning can be helpful regarding specific forms of cardiovascular disease (e.g., myocardial infarction, angina, sudden death, heart failure, and "enlarged heart") and procedures (e.g., coronary bypass surgery, angioplasty, and pacemaker placement).

Several studies have shown that family history reports of CAD are generally accurate.[129,151,152] The Health Family Tree study, which was a population-based survey of 122,155 families, found that questionnaire data about CAD in relatives had 79% sensitivity, 91% specificity, 67% positive predictive value, and 96% negative predictive value.[129] In a case-control study, history of MI in first-degree relatives was validated using death certificates, physician records, and hospital records.[151] In the 174 cases, the sensitivity, positive predictive value, and specificity of a reported history of MI in first-degree relatives were 67.3%, 70.5%, and 96.5%, respectively. These values did not differ significantly from the corresponding figures for the 175 controls (68.5%, 73.8%, and 97.7%, respectively). In this study, only small differences were observed between odds ratios based on reported and verified data, indicating that neither misclassification nor recall bias had a substantial impact on the measurement of the effect of the family history. The Family Heart Study also characterized the validity of family history reports of CAD, as well as the related disorders of diabetes and HTN.[152] Using a relative's self report as a standard, the sensitivity of the case's report for CAD was 85% and 81% for parents and siblings, respectively. The sensitivity for hypertension was 76% and 56% for these relatives, and for diabetes it was 87% and 72%, respectively. The specificity values were above 90%. These studies suggest that a positive family history report can generally be used with a high degree of confidence for the identification of individuals who may be at increased risk for developing CAD. The lower sensitivity values do indicate some underreporting of disease in relatives; thus, a negative report should not be used as an indicator of a minimum or decreased disease risk (below the general population risk).

Familial Risk Stratification for Coronary Artery Disease

Average Familial Risk

- No personal or family history of CAD.
- Only one 2nd degree paternal relative affected with CAD (early and later onset).
- Only one 2nd degree maternal relative affected with later onset CAD.

Moderate Familial Risk

- Only personal history of later onset CAD, no family history.
- Only one 1st degree relative with later onset CAD.
- Only one 2nd degree maternal relative affected with early onset CAD.
- Two 2nd degree relatives from one lineage with late or unknown CAD onset.

High Familial Risk

- Personal history of early onset CAD.
- Personal history of later onset CAD and at least one 1st degree relative with early or later onset CAD and another related condition (e.g., diabetes, stroke, PVD, sudden death).
- Personal history of later onset CAD and at least one 2nd degree relative with early or later onset CAD and another related condition (e.g., diabetes, stroke, PVD, sudden death).
- At least one 1st degree relative with early onset CAD.
- At least two 1st degree relatives with CAD at any age of onset.
- At least one 1st degree relative with later onset CAD and at least one 1st degree relative from one lineage with early or later onset CAD and another related condition (e.g., diabetes, stroke, PVD, sudden death).
- At least one 1st degree relative with later onset CAD and at least one 2nd degree relative from one lineage with early or later onset CAD and another related condition (diabetes, stroke, PVD, sudden death).
- At least one 2nd degree relative with early onset CAD and at least one 2nd degree relative from the same lineage with CAD at any age of onset and another related condition (diabetes, stroke, PVD, sudden death).
- At least three 2nd degree relatives with CAD at any age of onset from one lineage.

Fig. 2 Example of familial risk stratification for CAD. CAD, coronary artery disease; PVD, peripheral vascular disease; Early onset CAD, less than age 55 in men and less than age 65 in women.

Prevalence of positive family history

Family history of CAD and related disorders is common. The Health Family Tree Study found that 14% had a positive family history of CAD.[153] Surprisingly, 72% of the early-onset CAD cases (men < age 55 and women < age 65) and 48% of all cases of CAD reported in the study were within this subset of families with a history of CAD. The prevalence of family history reports for CAD, stroke, HTN, diabetes, and common cancers has been estimated by reviewing pedigrees obtained by genetic counselors in a prenatal diagnosis clinic.[146] The population consisted of 400 healthy adults aged 18 to 66 years. None were seeking counseling because of a family history of one the chronic disorders under study. Forty-three percent reported a family history of at least one chronic disorder, 33% were at risk for one disorder, 8% were at risk for two disorders, and 2% were at risk for 3 disorders. Family history of CAD was most common, accounting for 29% of the pedigrees. Eleven percent of the subjects were classified as high risk and 18% were moderate risk for CAD. It is likely that only a few percent of families classified as high risk will have a mendelian form of CAD.

Biochemical tests that influence CAD risk

Tests to assess genetic risk for CAD are primarily biochemical analyses that measure the different pathways involved in development and progression of disease. Several of these biochemical risk factors are established risk factors, such as increased LDL cholesterol, decreased HDL cholesterol, and diabetes, which are known to be causally related to CAD.[118] Many others are considered emerging risk factors including hypertriglyceridemia, small dense LDL cholesterol particles, hyperhomocysteinemia, C-reactive protein, interleukin-6, and factors involved in fibrinolysis, such as plasminogen activating factor inhibitor type 1 (PAI-1) and fibrinogen. Strong associations between these emerging risk factors and CAD have been identified,[154–164] but for most, a causal relationship has not yet been determined. Although treatment strategies exist for many emerging risk factors (see below), for most, treatment has not been associated with primary prevention of CAD. Nonetheless, measuring these risk factors can aid in risk stratification, which is helpful because levels of one risk factor can modify treatment plans aimed at ameliorating another risk factor.

DNA-based tests that influence CAD risk

With few exceptions, currently there is limited usefulness in using DNA-based tests for prediction of CAD risk or to influence prevention strategies. However, several genetic polymorphisms associated with CAD progression and clinical coronary events influence the response to risk factor modification and lifestyle choices, such as use of medication, alcohol, postmenopausal hormone replacement therapy, antioxidant supplements, and diet. Some examples are reviewed below that demonstrate the potential of DNA testing in the clinical setting.

However, in most cases additional studies are needed to prove the clinical utility of this approach.

Kuivenhoven and coworkers[20] found a significant association between variation at the cholesterol ester transfer protein (CETP) locus and angiographic progression of coronary atherosclerosis in men with CHD, and there was a dose-dependent relation between the CETP *Taq*IB polymorphism and efficacy of pravastatin in slowing the progression of atherosclerosis defined by angiographic differences in lumen diameter. This association remained significant even after adjustment for baseline coronary characteristics as well as baseline HDL cholesterol and changes in HDL cholesterol, and hepatic and lipoprotein lipase activity. Although this CETP association with CAD progression was significant, the finding has limited clinical utility. Treatment with pravastatin improved the outcome for all study subjects abolishing any differences based on CETP genotype, although individuals with the B1B1 genotype derived the greatest benefit.

A population-based case-control study of patients treated for hypertension found a significant interaction between the α-adducin gene variant, Trp460, and diuretic therapy on the risk of MI or stroke.[27] The α-adducin variant was identified in more than one third of the participants. Diuretic therapy was not associated with the risk of MI or stroke in individuals with the wild-type genotype. However, diuretic therapy in carriers of the α-adducin variant was associated with a lower risk of MI and stroke than other antihypertensive therapies (odds ratio, 0.49; 95% CI, 0.32–0.77). Other traditional cardiovascular disease risk factors did not influence this interaction. These results suggest a role for genotyping hypertensive individuals for the α-adducin variant allele, Trp460, to determine benefit from diuretic therapy. However, these findings need to be confirmed in other studies, and other benefits and risks of diuretic therapy versus other antihypertensive therapies need to be considered before such testing translates to clinical practice.

Alcohol consumption has been associated with reduced risk of CAD. Risk of MI is lower in men with an alcohol dehydrogenase type 3 (ADH3) allele that is associated with a slow rate of ethanol oxidation (RR = 0.65; 95% CI, 0.43–0.99), and a significant interaction between this allele and alcohol intake was found.[71] Those who were homozygous for this allele and drank at least one drink a day had the greatest reduction in risk for MI (RR = 0.14; 95% CI, 0.04–0.45) and the highest HDL cholesterol levels (for interaction, $P = 0.05$). Again, this finding has limited clinical utility because all men in this study appeared to benefit from consuming at least one drink per day regardless of their genotype, and the overall value added of the ADH3 genotype is unknown because many other variables need consideration when counseling about alcohol intake.

Genetic risk information might be helpful for postmenopausal women who are considering use of hormone replacement therapy (HRT). Herrington and colleagues[166] have shown that sequence variation of the estrogen receptor-α gene (IVS1-401 C/C genotype) is associated with the magnitude of the response of HDL cholesterol levels to estrogen or combination HRT in women with CAD. However, this response has not yet been linked to variation in the risk of cardiovascular disease. In a study of postmenopausal women, risk of MI was significantly increased in those with hypertension who were current users of HRT who also had the prothrombin G20210A mutation (OR = 10.9, 95% CI, 2.15–55.2).[42] Adjusting for other risk factors did not significantly change the risk estimate and no other potential interactions with the prothrombin variant on the risk of MI were found. Those women who were wild type for the prothrombin mutation were not at substantial increased risk for MI regardless of their HRT status, and those with the prothrombin mutation who did not use HRT had only mild increases in risk of MI. Venous thromboembolic (VTE) risk is considerably higher for women with CAD.[167,168] In a nested case-control study, investigating HRT versus placebo conducted among women with established CAD, the adjusted odds ratio for VTE for women with the factor V Leiden mutation was 10.2 (95% CI, 0.3–344) compared to 4.5 (95% CI, 1.2–16.9) for wild-type women. The odds ratio for women with the factor V Leiden mutation and HRT use compared with wild-type women given placebo was 14.1 (95% CI 2.7–72.4, $P = 0.0015$).[169] Thus, in certain clinical situations, DNA-based testing for thrombotic markers might be useful in management regarding HRT use.

Smoking is a significant risk factor for CAD and MI. However, individuals with specific genotypes have greater risks for MI associated with smoking. Knowledge of this increased risk might improve smoking cessation efforts; however, this has not been demonstrated. Homozygosity for the platelet glycoprotein Ia/IIa receptor 807T is associated with about a 3-fold increase in risk for MI, and an interaction between the 807T allele and smoking was also found.[56] The odds ratio for MI among individuals who were homozygous for the 807T allele and smoked was 25, a hazard greater than the product of the risks of either smoking (OR = 4.3) or 807T homozygosity (OR = 3.3) alone.[56] Smoking has also been shown to modify the risk of MI associated with the Gln-Arg192 polymorphism of the human paraoxonase gene.[67]

The ApoE4 allele has been associated with CAD in several populations.[16–18] ApoE2/E2 homozygous individuals are at risk for type III hyperlipoproteinemia, which is associated with an increased risk for atherosclerosis. In addition, apoE genotyping can play a role in recommending lipid-lowering diets.[170–174] Forty percent of the individual variation in LDL cholesterol levels in response to a low-saturated fat diet is a familial trait due to shared genetic or lifestyle habits.[175] This might be due in part to the apoE locus. Several studies have shown that carriers of the apoE4 allele tend to be more responsive to the LDL-lowering effects of low-fat dietary interventions compared to noncarriers.[170–172] Carriers of the apoE2 allele may be particularly susceptible to coronary heart disease when they are exposed to diets high in saturated fat.[173] This is probably due to unfavorable changes in lipids, including increased VLDL cholesterol resulting from increased VLDL production from high saturated fat intake as well as decreased VLDL cholesterol clearance associated

with the apoE2 allele, smaller LDL cholesterol particles, and decreased HDL cholesterol.[173]

The apoE genotype influences the responsiveness of fish oil supplementation in subjects with an atherogenic lipoprotein phenotype (ALP),[174] which is characterized by fasting hypertriglyceridemia, exaggerated postprandial lipemic responses, low HDL cholesterol levels, and a predominance of small dense LDL particles and reduced HDL2b cholesterol fraction. Individuals with an apoE2 allele display a marked reduction in postprandial incremental TG response and a trend toward increased lipoprotein lipase activity compared to non-E2 carriers. This should have favorable effects because hypertriglyceridemia is an established CAD risk factor.[154] In apoE4 carriers, an unfavorable response was observed with a significant increase in total cholesterol and a trend toward a reduction in HDL cholesterol relative to E3/E3 homozygotes.[174]

Despite these important associations relating to diet and the aopE genotype, clinicians must proceed with caution when considering this genetic testing as a means to assess CAD risk and influence prevention because the apoE4 genotype is also associated with increased risk for Alzheimer disease.[176] Therefore, patients should be informed of this association when considering apoE genotyping for cardiovascular risk assessment. The American College of Medical Genetics and the American Society of Human Genetics have not endorsed apoE testing for diagnostic or predictive testing for Alzheimer disease.[177]

Homozygosity for the MTHFR C677T mutation has been associated with elevated levels of homocysteine,[178] and homocysteine levels have been associated with CAD risk.[164] A recent meta-analysis of case-control studies that included data on the MTHFR C677T mutation, homocysteine and folate levels, and CAD has demonstrated a significantly higher risk of CAD associated with the MTHFR C677T genotype, especially in the setting of low folate status.[41] The ASHG/ACMG Statement regarding measurement and use of total plasma homocysteine recommends determination of the basis of elevated homocysteine levels ($>$ 15 μmol/L), including environmental and genetic factors, to provide the most appropriate treatment because the inappropriate supplementation of involved cofactors can be harmful.[179]

Clinical application of genetic information for CAD prevention

Cholesterol lowering is viewed as an important clinical strategy in both primary and secondary prevention of CAD.[120] Use of cholesterol lowering agents has been effective in reducing atherosclerosis incidence, disease progression, and CAD mortality.[180–185] Yet treatment of elevated cholesterol is less than ideal as evidenced by estimates from more than 30 countries suggesting that 80% of people with familial hypercholesterolemia remain undiagnosed and only 7% have adequately treated cholesterol levels.[186] However, even when there is effective lipid lowering, a substantial proportion of individuals will develop CAD or have progression of their disease.[187] In addition, many investigators have concerns regarding the safety and cost-effectiveness of this population-based approach to CAD prevention.[188–193] Furthermore, an elevated cholesterol level is not a sensitive predictor of individuals with the greatest genetic susceptibility to CAD. In a study of adults with premature CAD, 43% had normal lipid values.[194] Of those with abnormal values, the most common abnormality was elevated lipoprotein(a) (19% of cases), which would not be detected with routine cholesterol screening, and only 3% had elevated LDL cholesterol consistent with a monogenic form of hyperlipidemia.

CAD is a heterogeneous disorder and there is considerable heterogeneity even among the small percentage of cases with mendelian disorders (Table 2). Therefore, it is not reasonable to expect that a single path of prevention (e.g., LDL cholesterol lowering) would be effective for every patient. Knowledge of genetic susceptibility to atherosclerosis can identify important biologic differences. Failure to recognize these differences may deny appropriate access to care for those patients who may benefit from more intensive risk factor modification or alternative management and prevention strategies. Guidelines for risk assessment and prevention strategies based on familial risk are provided in Fig. 3. Regardless of the familial risk level for CAD, public health prevention messages are appropriate for everyone, such as smoking cessation, achieving and maintaining an ideal weight, eating at least 5 servings of fruits and vegetables daily, participating in regular aerobic exercise and knowing your cholesterol level.

Modification of emerging biochemical risk factors

Evidence is accumulating regarding the effectiveness of therapies in modifying emerging risk factors with a genetic basis. Examples are discussed in the following paragraphs.

Extreme elevations in plasma homocysteine ($>$ 200 μmol/L) due to deficiency of cystathionine beta synthase or other key enzymes involved in homocysteine metabolism cause premature cardiovascular disease. More modest elevations of homocysteine ($>$ 10 to 15 μmol/L) are associated with increased risk for cardiovascular disease.[164] Homocysteine may increase the risk for cardiovascular diseases by decreasing endothelium-dependent vasodilation, increasing platelet adhesiveness, activating certain clotting factors, and inhibiting fibrinolysis by promoting lipoprotein(a) binding to fibrin.[195] Homocysteine levels are increased by deficiency of the B vitamins that are cofactors for enzymes involved in homocysteine metabolism, including folic acid and vitamins B6 and B12. Homocysteine also increases with declining renal function, pernicious anemia, thyroid dysfunction, psoriasis, certain malignancies, anticonvulsant therapies, certain oral contraceptives, methotrexate, niacin, fibrates, and metformin.[196,197] Homocysteine levels can often be lowered to a desirable range with folic acid and vitamins B6 and B12.[198–200] Lowering homocysteine with B vitamins has recently been shown to decrease the incidence of major cardiovascular events in a double-blind placebo-controlled trial in 553 subjects undergoing

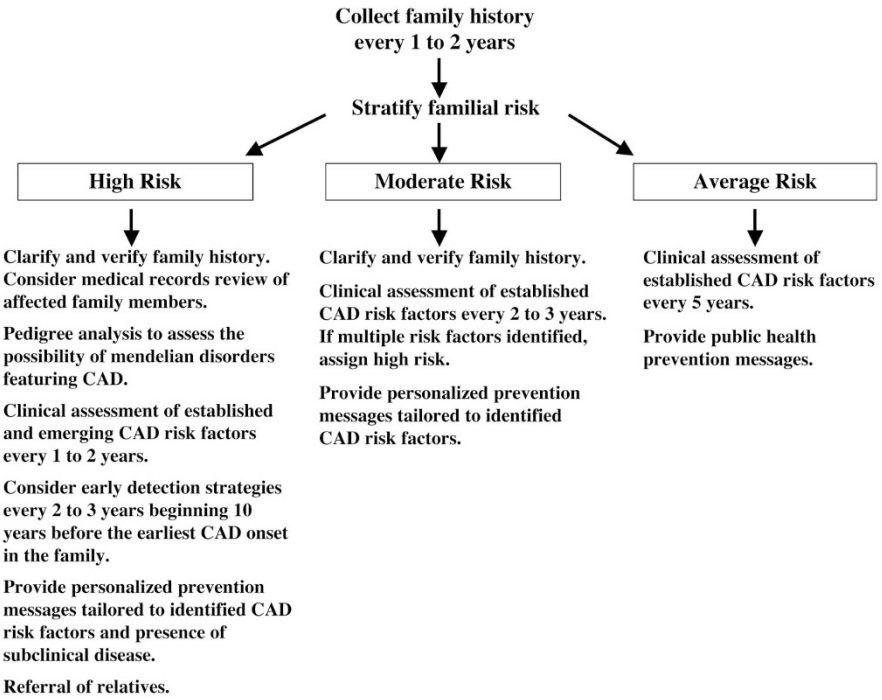

Fig. 3 Proposed scheme for using family history to guide early detection and prevention strategies for CAD. CAD, coronary artery disease; Established risk factors, elevated total and LDL cholesterol, low HDL cholesterol, hypertension, diabetes, and smoking; Emerging risk factors, elevated C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), small LDL particles, reduced HDL2b fraction, apolipoprotein B, hyperinsulinemia or other measures of insulin resistance/impaired glucose tolerance, MTHFR C677T, factor V Leiden, prothrombin G20210A, and apoE genotype.

successful angioplasty of at least one significant coronary stenosis.[201]

Lipoprotein(a) is a lipoprotein particle composed of an apolipoprotein B-100 particle covalently linked to an apolipoprotein(a) particle. Apolipoprotein(a) is homologous to plasminogen and may compete with plasminogen, thereby limiting fibrinolysis.[202] Lipoprotein(a) has also been implicated in foam cell formation, endothelium-dependent vasodilation reduction, and LDL cholesterol oxidation promotion.[203] Levels of lipoprotein(a) are strongly genetically determined. Lipoprotein(a) increases slightly with age and at the time of acute illness; also, females have greater values than males, with values increasing after menopause.[204] The distribution of levels varies widely among racial and ethnic groups.[205] Most of the associations with CAD have been found in Caucasians. Levels $>$ 20 to 30 mg/dL are considered high. Lipoprotein(a) levels can be reduced with niacin[206–209] and, in postmenopausal women, with estrogen replacement therapy[210] and, in men, with testosterone.[211] Reduction in lipoprotein(a) attributed to estrogen has been associated with a reduction in cardiovascular events in women.[212] However, hormone replacement therapy with either estrogen for women or testosterone for men is not the standard of care for reducing CAD risk. Aggressive LDL cholesterol lowering appears to abolish the CAD risk associated with elevated lipoprotein(a), even with unchanged lipoprotein(a) levels.[213]

Atherogenic small, dense LDL cholesterol, reduced fraction of HDL2b associated with inefficient reverse cholesterol transport, low HDL cholesterol, elevated triglycerides and excess apolipoprotein B are characteristic of the atherogenic lipoprotein phenotype (ALP). ALP occurs in up to 25% of middle-aged men[214] and is associated with a 3-fold increase in CAD risk.[215,216] ALP can be improved with regular exercise, fat weight loss, and restricted intake of simple carbohydrates and alcohol,[217] medical therapy including niacin and fibrates,[218,219] and avoidance of β-blockers if possible.[220] Fish oil supplementation also improves the lipid profile associated with ALP.[174] Modifying ALP with the above measures, particularly niacin alone or in combination with other lipid-lowering therapy, has been associated with prevention of progression and promotion of regression of coronary atherosclerotic lesions and reduction in coronary risk.[221]

Insulin resistance is associated with many of the emerging risk factors (hypertriglyceridemia, small LDL cholesterol particles, decreased HDL cholesterol, elevated PAI-1, fibrinogen, and high-sensitivity C-reactive protein) and can be considered as a predisposing CAD risk factor.[118] An estimated 24% of adults in the United States have the metabolic syndrome associated with insulin resistance.[165] The third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII)[120] highlights the importance of treating patients with the metabolic syndrome to prevent cardiovascular disease. Insulin resistance can be effectively treated with lifestyle changes and metformin.[222] Additionally, in postmenopausal women with CAD, overt diabetes

might be averted with use of hormone replacement therapy.[223] Any effective means to reduce insulin resistance and diabetes should result in substantial reduction in morbidity and mortality from CAD.

Measurement of high sensitivity C-reactive protein (hs-CRP) is a useful clinical marker of inflammation related to atherosclerosis. Statin drugs used for cholesterol lowering have been associated with reduction in hs-CRP.[224] This may be due in part to the anti-inflammatory effects of these drugs. A recent report has shown that HRT increases CRP levels,[163] suggesting a possible mechanism for increased CAD risk due to HRT, although avoiding HRT has not been shown to reduce the risk of CAD. Thus, hs-CRP could become a target of therapy for reducing CAD risk; however, at this time, measurement of hs-CRP is used primarily to stratify risk and guide recommendations for modification of other risk factors.

Several factors involved in promotion of thrombosis and inhibition of fibrinolysis are associated with CAD. Among this group of CAD risk factors, fibrinogen is one of the most important. Fibrinogen levels are also modifiable through smoking cessation, aerobic exercise, weight loss, fibric acid medications, and omega-3 fish oils,[225,226] which might result in reduced risk for CAD. Antiplatelet medications such as aspirin and other forms of anticoagulants might also reduce the thrombotic risk associated with elevated fibrinogen.

Individuals with a strong genetic susceptibility to CAD based on family history and the presence of established and emerging risk factors may derive the greatest benefit from traditional preventive strategies such as screening for and treatment of elevated cholesterol and blood pressure, and smoking cessation. Individuals with genetic susceptibility to CAD might also benefit from targeting emerging risk factors with specific interventions and lifestyle changes. However, for the most part, evidence regarding primary prevention of clinical cardiovascular events in individuals who have effectively modified emerging genetic risk factors is lacking and prospective clinical trials are necessary. Therefore, it is crucial to discuss these potential benefits and limitations with any patient undergoing assessment of emerging CAD risk factors.

Early detection strategies

As much as 25% of first coronary events (including sudden death) occur in asymptomatic people[1]; therefore, screening for early detection of disease should offer a window of opportunity to prevent acute coronary syndromes. However, early detection strategies for CAD are not recommended for the general population, due to poor predictive value of tests (e.g., exercise ECG testing and ambulatory ECG monitoring) or because the tests are too expensive (e.g., positron emission tomography) or too invasive (e.g., intravascular ultrasound). However, early detection strategies for CAD in asymptomatic subjects might be useful in stratifying risk for individuals with greater than average risk.[118] Noninvasive tests such as carotid artery duplex scanning (CCA-IMT), ankle/brachial blood pressure ratios (ABI), electron beam computed tomography scan (EBCT), ultrasound-based endothelial function studies, magnetic resonance imaging techniques, and testing for hs-CRP offer the potential for measuring and monitoring atherosclerosis in asymptomatic people.[118] Several of these methods are highly valid and predictive of CAD events (e.g., ABI, CCA-IMT, and EBCT).[118] Once a higher risk is confirmed with these methods, aggressive medical therapies for primary prevention can be recommended.

The EBCT is one of the most popular of these early detection methods. There is consistent evidence that coronary calcification correlates highly with the presence and degree of obstructive and nonobstructive plaque at autopsy and by intravascular ultrasound,[227] the presence of obstructive disease by angiography,[228,229] and nonfatal MI and need for subsequent coronary revascularization in both asymptomatic individuals,[230–232] and patients undergoing coronary angiography.[233] A prospective study has also shown that EBCT identifies a high-risk group of asymptomatic subjects with clinically important silent ischemia as demonstrated by stress myocardial perfusion tomography (SPECT).[234] None of the patients with coronary calcium scores < 10 had positive SPECT imaging. Abnormal SPECT was seen in 2.6% of patients with scores of 11 to 100, 11.3% with scores of 101 to 399, and 46% with scores of 400 or greater. Until recently, however, the added value of the coronary calcium score beyond the usual risk assessment methods had not been demonstrated. In a study of sibships at high risk for hypertension, a coronary artery calcium score above the 70th percentile was significantly associated with occurrence of coronary events after an average of five years, after adjusting for the Framingham Risk Score (OR = 2.8; 95% CI, 1.2 to 6.4).[84] Thus, for individuals with a greater than average CAD risk (which might be due to family history), the coronary calcium score obtained with EBCT has great potential in detecting advanced coronary atherosclerosis leading to recommendations regarding aggressive risk factor modification. At least one study has shown that knowledge of coronary calcium scores positively influenced behavior in self-referred subjects,[235] although additional outcomes research regarding the utility of this approach is necessary. In addition, low or absent coronary calcium scores may be valuable in defining a lower CAD event risk,[118] which could provide some reassurance to individuals assigned a high familial risk and for whom risk factor modification could be relaxed somewhat.

Approach to individuals with high familial risk for CAD

The components of a genetic evaluation for an individual referred because of concern due to a personal or family history of CAD include pedigree analysis (as reviewed above), personal medical history including medication, habits, and systems review, physical examination, laboratory testing, and screening for early detection of CAD.

Review of the personal medical history should include diagnoses of CAD, MI, peripheral vascular disease, stroke (including transient ischemic attacks), thrombosis, arrhythmia, heart failure, pulmonary disease, diabetes, and hypertension. Medical records, particularly procedural reports regarding any diagnoses, should be reviewed. Systems review should focus on

cardiac and pulmonary function, including questions regarding angina, dyspnea on exertion, shortness of breath, paroxysmal nocturnal dyspnea, claudication, and exercise tolerance. Inquiry regarding habits such as smoking history, alcohol history, exercise, and diet is important.

The physical examination should include blood pressure in the arms and the ankles (dorsalis pedis and posterior tibialis). In addition to identifying hypertension, these measurements can be used to calculate the ABI. Values < 0.9 are correlated with atherosclerosis. In addition, a blood pressure of 130/85 or greater is a criterion for the metabolic syndrome.[120] Weight and height should be obtained and body mass index should be calculated. This can helpful in identifying a need for achieving an ideal weight and monitoring diet and exercise interventions. Waist circumference should be obtained, as it can be a factor in identifying the metabolic syndrome.[120] Evaluation of lipid disorders should include examination of the eyes, assessing corneal arcus and lipemia retinalis. Examination of the skin should include assessment for xanthelasma and xanthomas involving the tendons. The cardiovascular exam should include careful assessment of the heart and lungs, as well as listening for bruits at major vessels in the neck, abdomen, and groin, and palpation of the aorta and distal pulses. Any abnormalities should be followed up with additional studies, such as ultrasound. Stigmata of mendelian disorders that feature cardiovascular disease such as Marfan syndrome, Ehlers-Danlos syndrome, type IV, pseudoxanthoma elasticum, and Fabry disease, should also be assessed.

Laboratory testing should include fasting lipid panel, glucose, insulin, lipoprotein(a), LDL cholesterol particle size, HDL cholesterol fractionation, apolipoprotein B, hs-CRP, homocysteine, and MTHFR mutation analysis for the C677T allele. Factor V Leiden testing can be performed in young women considering use of oral contraceptives, and prothrombin G20210A mutation analysis can be performed in postmenopausal women considering HRT. ApoE genotyping can be considered if there is a question regarding the diagnosis of type III hyperlipoproteinemia, or if the apoE genotype would significantly influence dietary recommendations.

With the above information, assessment for the metabolic syndrome is possible. Clinical identification of the metabolic syndrome includes at least three of the following: blood pressure of 130/85 mm Hg or greater, waist circumference > 102 cm in men and > 88 cm in women, HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women, triglycerides of 150 mg/dL or greater, and fasting blood glucose of 110 mg/dL or greater.[120] Hyperinsulinemia, ALP, and family history of diabetes are also indicators of the metabolic syndrome or insulin resistance. If the metabolic syndrome is present, or if there are signs of insulin resistance, oral glucose tolerance testing should be considered for detection of overt diabetes. The atherogenic lipoprotein phenotype can be identified if there is a preponderance of small dense LDL cholesterol particles (pattern B), decreased fraction of HDL2b cholesterol ($<15\%$), decreased HDL cholesterol, elevated triglycerides, and elevated apolipoprotein B. ALP can be effectively treated with lifestyle changes and/or medications (niacin or fibrates) as reviewed above.

Hypercholesterolemia should be treated with lifestyle changes and if necessary with lipid-lowering medications, with a goal to achieve an LDL cholesterol value of 100 mg/dL in high-risk individuals. If there are small LDL cholesterol particles, then niacin should be considered in doses of up to 3 to 4 g a day. This can be used in combination with a statin drug if LDL cholesterol is elevated. Niacin can also be prescribed in similar doses to treat elevated lipoprotein(a) levels, or if estrogen replacement therapy is an option, this can be considered. Niacin can also raise HDL cholesterol, as do exercise and moderate alcohol intake. With niacin therapy, monitoring of transaminases, uric acid, and blood glucose should be performed as abnormalities can arise.[236] Transaminases and creatinine kinase levels can also increase with statin drugs, although the usefulness of routine measurement is questionable.[237] Homocysteine levels can become abnormal with niacin, fibric acid derivatives, and metformin,[197] drugs that are often used in individuals at risk for CAD. If there is evidence of hyperhomocystinemia (values > 10 μmol/L in high risk subjects), then assessment of nongenetic factors should be performed (e.g., measurement of B vitamins, renal function, thyroid function, and review of medications) and B vitamin supplementation should be considered, titrating the amount of folic acid to the fasting homocysteine level. If there is homozygosity for the C677T allele with homocysteine values below 10 μmol/L, then at least annual follow-up of homocysteine would be reasonable.

Early detection strategies for CAD should be considered for unaffected high-risk individuals, especially if there are repeated measurements of elevated hs-CRP, ABI < 0.9, evidence of the metabolic syndrome or insulin resistance, and if identification of subclinical atherosclerosis will alter recommendations regarding risk factor modification or lifestyle choices.

Genetic counseling and education regarding CAD susceptibility

An important goal of genetic evaluation for CAD is the development of individualized preventive strategies based on the genetic risk assessment, as well as the patient's personal medical history, lifestyle, and preferences. The patients' participation in the process is vital to the success of the prevention plan. Genetic counseling and education is integral to achieving the goal of prevention. Genetic counseling is critical to delineating a patient's motivations and understanding of the genetic risk assessment and perceived barriers and benefits to learning of a genetic risk. Patients should also be educated about the role of genetic risk factors for CAD, their mode of inheritance and options for prevention and risk factor modification. This communication process ensures the opportunity to provide an informed consent, including discussion of the potential benefits, risks and limitations regarding genetic risk assessment, and options for prevention.[238]

Although family history of CAD has been shown to be a significant predictor of CAD risk, a recent report has shown that this familial risk does not translate to improvement in

risk-reducing lifestyles in at-risk relatives.[239] In the Coronary Artery Risk Development in Young Adults (CARDIA) study, CAD risk factors were assessed over two consecutive 5-year follow-up periods among 3950 participants aged 18 to 30 years. Kip and colleagues[239] found that the occurrence of a heart attack or stroke in an immediate family member did not lead to self-initiated, sustained change in modifiable risk factors in young adults. These results argue for the need to intervene and educate people about the importance of a positive family history of CAD because the opportunities for prevention are substantial.

Bamberg and colleagues[240] report on the improved effectiveness of CAD prevention achieved by informing individuals of a genetic risk for CAD. Based on self-reports of having a cholesterol level rechecked, seeking advice from a physician or a dietitian for weight loss, and limiting fat and cholesterol intake, there was at least a higher compliance rate and greater likelihood of performing these healthy behaviors in the genetic risk group than the "nongenetic" risk group. When those subjects with a blood cholesterol level above 200 mg/dL were analyzed as a subgroup, the genetic risk group had a statistically significant higher compliance rate for having a blood cholesterol level rechecked than the nongenetic risk group.[240]

Because most of the established and emerging risk factors for CAD aggregate in families, a family-based approach to risk factor modification should be an effective strategy, and this has been demonstrated in a few case-control studies.[241–243] Lifestyle changes, such as dietary modification, weight control, and smoking cessation might be more effective when delivered to the family than to an individual because family members can provide ongoing support to one another. This approach is reflected in the guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[244] that encourage involvement of family members in the treatment of hypertension.

Common barriers to obtaining genetic risk information for common disease include fear of discrimination both in the work place and by insurers, cost, and uncertainty about the value of interventions.[245–249] Evidence regarding genetic discrimination of otherwise healthy individuals is minimal.[249,250] Yet, because of the fear of discrimination, individuals might avoid genetic evaluation altogether, or they may choose to bear the financial liability not only for an initial genetic risk assessment, but also for the surveillance or therapeutic measures they undertake to reduce their disease risk. For genetic evaluation for CAD to become widely available and accepted, these ethical, legal, and social issues need to be addressed.

Summary

Several lines of evidence support the contribution of genes to the development and progression of CAD, and response to risk factor modification and lifestyle choices. Individuals with a genetic susceptibility for CAD generally have the highest risk and develop disease at an earlier age. The family history is the best method for initial identification and stratification of genetic risk for CAD, which can be refined further through biochemical and DNA testing. Knowledge of genetic susceptibility to CAD has value in providing risk information and can influence lifestyle choices and management options. Genetically susceptible individuals might benefit the most from aggressive treatment of established CAD risk factors. In addition, many emerging risk factors are modifiable, and targeting these risk factors with specific therapies may result in improved CAD prevention. Family-based prevention might be most effective for genetically predisposed individuals, because many established and emerging risk factors aggregate in families and most are amenable to lifestyle changes. Early detection of CAD may be appropriate for genetically susceptible individuals to guide decision-making about risk factor modification. Genetic evaluation, including pedigree analysis, biochemical and DNA-based testing, genetic counseling and education, and personalized recommendations for early detection, risk modification, and prevention strategies that are targeted to the genetic risk should result in improved health promotion and CAD prevention efforts. Future studies are needed that investigate the clinical utility of this approach and the associated ethical, legal, and social issues.

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