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Relevance of Genetics and Genomics for Prevention and Treatment of Cardiovascular Disease

A Scientific Statement From the American Heart Association Council on Epidemiology and Prevention, the Stroke Council, and the Functional Genomics and Translational Biology Interdisciplinary Working Group

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Abstract—Atherosclerotic cardiovascular disease (CVD) is a major health problem in the United States and around the world. Evidence accumulated over decades convincingly demonstrates that family history in a parent or a sibling is associated with atherosclerotic CVD, manifested as coronary heart disease, stroke, and/or peripheral arterial disease. Although there are several mendelian disorders that contribute to CVD, most common forms of CVD are believed to be multifactorial and to result from many genes, each with a relatively small effect working alone or in combination with modifier genes and/or environmental factors. The identification and the characterization of these genes and their modifiers would enhance prediction of CVD risk and improve prevention, treatment, and quality of care. This scientific statement describes the approaches researchers are using to advance understanding of the genetic basis of CVD and details the current state of knowledge regarding the genetics of myocardial infarction, atherosclerotic CVD, hypercholesterolemia, and hypertension. Current areas of interest and investigation—including gene–environment interaction, pharmacogenetics, and genetic counseling—are also discussed. The statement concludes with a list of specific recommendations intended to help incorporate usable knowledge into current clinical and public health practice, foster and guide future research, and prepare both researchers and practitioners for the changes likely to occur as molecular genetics moves from the laboratory to clinic. (*Circulation*. 2007;115:2878-2901.)

Key Words: AHA Scientific Statements ■ genetics ■ genomics ■ cardiovascular diseases

Atherosclerotic cardiovascular disease (CVD), which involves the heart, brain, and peripheral circulation, is a major health problem in the United States and around the world.^{1,2} The development of atherosclerosis is a complex process, and several major risk factors³ and a growing number of novel risk markers⁴ have been reported to contribute to its development. Evidence accumulated over decades convincingly demonstrates that family history in a parent or a sibling is associated with atherosclerotic CVD, manifested as coronary heart disease, stroke, and/or peripheral arterial disease.^{5–7} Several mendelian disorders contribute to CVD, and although the mutations are rare, they have a large relative

risk. Well-described examples include familial forms of hypercholesterolemia,⁸ often caused by mutations in the low-density lipoprotein (LDL) receptor gene or the apolipoprotein (apo) B gene (*APOB*), which encodes the major protein in the LDL particle. Other forms of familial CVD have been attributed to familial hyperhomocystinuria associated with mutations in the 5,10-methylenetetrahydrofolate reductase gene (*MTHFR*)^{9,10}; Hutchinson-Gilford progeria syndrome¹¹ caused by mutations in the lamin A/C gene (*LMNA*); Tangier disease related to mutations in the ATP-binding cassette, subfamily A, member 1 gene (*ABCA1*)¹²; an autosomal-dominant form of coronary artery disease associ-

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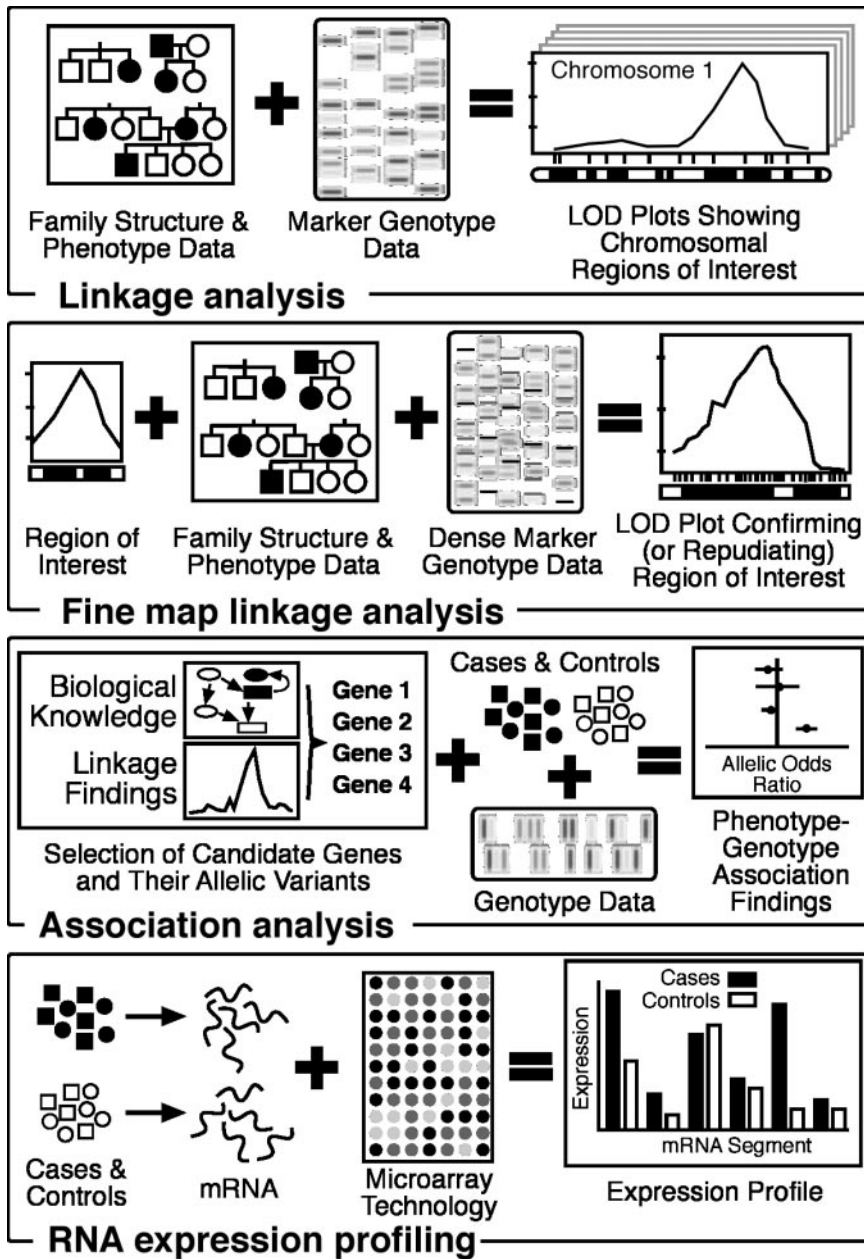


Figure. Fundamentals of the techniques used for the discovery of the genetic basis of CVD.

ated with the MADS box transcription enhancer factor 2, polypeptide A gene (*MEF2A*)¹³; and some forms of inherited primary electrical diseases (“channelopathies”) caused by variants of the sodium channel, voltage-gated, type V, α -subunit gene (*SCN5A*), the potassium channel, voltage-gated, KQT-like subfamily, member 1 gene (*KCNQ1*), and other genes.^{14,15}

However, the most common forms of CVD are believed to be multifactorial and to result from many genes, each with a relatively small effect, working alone or in combination with modifier genes and/or environmental factors. The “common disease, common variants” hypothesis proposes that genetic variants present in many normal individuals contribute to overall CVD risk.¹⁶ Additionally, susceptibility to some common diseases may, in part, be conferred by rarer variants.¹⁷ In this overview, we provide the state-of-the-art knowledge for 3

well-studied, genetically complex phenotypes: myocardial infarction (MI) and atherosclerotic CVD, hypercholesterolemia, and hypertension. The goal of this scientific statement is to detail the current state of knowledge regarding major gene disorders and more common, complex forms of CVD to inform practitioners about how genetic and genomic science may affect future clinical practice. First, however, we describe the fundamental approaches being used for the discovery of knowledge about the genetic basis of CVD.

In the study of CVD genetics, 2 main approaches have been used to discover or characterize causes of CVD (Figure): genome-wide linkage studies and gene association studies, which have historically been done with candidate genes. In the very recent past, genome-wide association studies using hundreds of thousands of markers and targeted gene-based resequencing, have been added as discovery methods. To

date, for discovery of new genes, the most frequently used method has been genome-wide linkage analysis conducted using genetic and phenotypic data from families. Linkage analysis is a useful method for identifying genes because analyses are initiated without any a priori assumptions regarding the genetic basis of the disease. Linkage analysis is a hypothesis-generating method intended to localize regions of the genome that might contain genes influencing a trait. Linkage analysis is, in effect, predicated on the extent to which Mendel's Second Law is observed to be broken. That is, because the random relation of alleles with respect to each other is decreased when the alleles reside on the same chromosome (ie, nonrandom assortment during meiotic synapsis) or when they lie physically near each other on the same chromosome (ie, decreased randomization during meiotic recombination or "crossing over"), alleles on the same chromosome and physically nearer each other are more likely to be inherited, or linked, together. To conduct a linkage analysis, laboratory methods are used to genotype polymorphic markers at known locations across the genome in families. These marker data, along with phenotype data and pedigree data, are entered into biostatistical algorithms to calculate the degree to which the marker information is identical by descent among family members in the pedigree and how this degree of genetic similarity for a marker correlates with the phenotypic resemblance among family members. The logarithm of the odds (LOD) is calculated for each marker (known as a LOD score) and is used to quantify the probability that a marker and putative causal locus are linked in pedigrees and contrasted to the null hypothesis of the absence of linkage in the pedigrees. In linkage analyses, a LOD score >3 traditionally is accepted to indicate significant linkage (ie, the likelihood of observing the result if the 2 loci—the marker locus and the causal locus—are not linked is <1 in 1000). LOD scores between 2 and 3 are considered "suggestive" statistical evidence, signaling the location of genes with small to moderate effects.¹⁸ Once likely chromosomal regions have been discovered through linkage analysis, efforts shift to identifying the causative genes. Gene maps are scrutinized near the region of significant or suggestive linkage, and potential causal genes are positionally identified on the basis of prior biological knowledge of gene function. Researchers typically follow linkage finding by constructing a "fine map" of the region of linkage. Fine mapping is done by adding markers to create a very dense set of genotypes, which is followed by repeated linkage analysis to determine whether the original evidence of linkage is a true positive finding. Linkage analyses have been quite successful in identifying the genetic basis of rare disorders but less successful in identifying more common forms of CVD that are likely due to common genetic variants that generally have moderate effects.¹⁹

For complex diseases such as CVD, high-resolution, whole-genome association studies that type hundreds of thousands of variants provide excellent power, markedly exceeding the power of the linkage methodology, to identify susceptibility CVD genes of modest effect.^{20–22} The first report of a genome-wide association in CVD has shown some success in identifying a candidate gene associated with MI.²³

It is anticipated that this technology will become the primary research methodology for the discovery of CVD genes in the very near future.

Candidate gene association studies, a common tool used for CVD genetic studies, are based on single polymorphisms or haplotypes. Haplotypes are combinations of polymorphisms on the same chromosome that are inherited together and statistically related to one another. Association studies are designed to compare allele or haplotype frequencies between case and control groups; a statistical difference in frequencies between cases and controls offers evidence that the allele or haplotype is associated with the trait. Candidate genes for association studies are often selected on the basis of prior biological knowledge of gene function, significant findings in a linkage study, or both. The availability of high-throughput genotyping has allowed candidate gene association studies to turn to increasingly large screens of genetic variation, both within the same gene and in ever-larger numbers of individual genes. Initial screens of >100 candidate gene loci have been conducted in small^{24,25} and large²⁶ case-control studies.

It is important to remember that genetic association is not equivalent to genetic causation. Under the assumption of linkage disequilibrium (ie, that combinations of alleles at different loci occur more or less frequently in a population than expected from random chance based on the allele frequencies), a genetic variant associated with a trait may be causal or may be associated with the nearby causal variant, within either the same or another gene. Association studies are particularly susceptible to population stratification, which leads to confounding because the LOD patterns differ across populations. When cases and controls are selected from genetically different populations, if they are not adequately matched for their genetic background, biased estimates of the effects of alleles or haplotypes can occur. Therefore, design methods (ie, restricting sample selection to 1 population or matching cases and controls to the population of origin) or analytical methods (ie, genomic controls) are recommended to control for population stratification in candidate gene association studies.

State-of-the-Art Knowledge for 3 Phenotypes: Examples of Mendelian and Complex Disorders

The Genetics of MI and Other Atherosclerotic CVD

MI, Atherosclerotic CVD, and Their Familial Nature

MI and other forms of atherosclerotic CVD are the leading causes of death in men and women.²⁷ Although there is no clear mendelian pattern of segregation for MI or atherosclerotic CVD, there is substantial evidence for a familial component to these diseases, particularly those with an early age of onset.⁷ A seminal twin study showed strong relative risks for MI among identical twins and less strong but significant associations among nonidentical twins, with the highest risks observed with a very early age of onset for MI in the affected twin.⁶ Prospective studies report relative risk estimates for MI and other atherosclerotic CVDs ranging from 1.2 to >3.0 for offspring who reported that their parents had the disease.^{28–30} More recently, the fully multivariable-

adjusted risk of offspring for all atherosclerotic CVD associated with premature-onset parental disease was placed at 1.7 for women and 2.0 for men using validated (instead of self-reported) parental and offspring outcomes,⁵ and similar magnitudes of multivariable-adjusted risk were noted for association with sibling CVD.³¹

Subclinical measures of atherosclerotic CVD, assessed in the carotid artery by ultrasound and the coronary and aortic arteries with computed tomography, have augmented the evidence for the role of genetics in CVD. Substantial heritability ($\approx 35\%$ to 60%) is reported for carotid intima-media thickness (IMT),³² coronary artery calcification,³³ and abdominal aortic calcification.³⁴ Moreover, a positive parental history of CVD is associated with a significantly increased burden of atherosclerosis determined by carotid IMT³⁵ or coronary artery calcification.^{36,37} Collectively, a substantial body of evidence suggests the role of genetics in atherosclerosis.

Genetic Linkage Studies for MI and Atherosclerotic CVD

A number of genetic linkage analyses have been done in at least 7 moderate to large collections of families selected for the occurrence of MI or measurements of subclinical atherosclerosis.^{38–47} Linkage has been observed for chromosomes 1, 2, 3, 13, 14, 16, and X, although there has been no strong replication for any single chromosomal region.^{38–45} This lack of replication exemplifies the difficulties inherent in the conduct and interpretation of linkage studies,⁴⁸ and very few causal genes have been identified from genetic linkage studies. One research group in Iceland has conducted fine mapping to identify the causal gene in their linkage region on chromosome 13q12–13. They identified a specific gene, *ALOX5AP*, the gene encoding the 5'-lipoxygenase activating protein, that is implicated in MI and stroke.⁴³ Although the evidence for statistical significance for linkage in this study has not been strong to date, the association of genetic variants in the *ALOX5AP* locus with MI or stroke has been replicated in some but not all follow-up studies.^{49–51} The Iceland study represents one of the first reported linkage findings that has successfully led to the identification of a strong candidate gene for an MI or stroke.⁴³

Linkage studies have also been conducted for subclinical measures of atherosclerotic CVD, although few studies have been reported. A genome-wide linkage scan for coronary artery calcium in a small number of families with hypertension has shown evidence for linkage on chromosome 10.⁵² Genome-wide linkage scans have been reported for carotid plaque⁵³ and IMT.⁵⁴ There was evidence for significant linkage of internal carotid IMT to chromosome 12 (LOD score 3.4).⁵⁴ Among the candidate genes residing in this region is scavenger receptor class B, member 1 (*SCARB1*), an important gene in atherosclerotic CVD.⁵⁴ However, replication studies have not been completed for any of these findings.

Candidate Gene Association Studies for MI and Atherosclerotic CVD

A large number of candidate gene association studies have been conducted for MI and subclinical measures of MI and atherosclerotic CVD. However, in general, relatively few gene polymorphism associations have been consistently rep-

licated for CVD.^{55,56} Reasons for inconsistencies may include genetic heterogeneity (ie, different genetic risks lead to CVD), differing patterns of linkage disequilibrium in varying population groups (ie, the causal variant captured by a genetic marker in 1 population is not captured by that same marker in another population), lack of statistical power or an excessive false-positive rate, confounding by other genetic or environmental factors, or phenotypic heterogeneity (ie, CVD is caused by many factors, and some factors may be operating in some forms of CVD but not others). These studies have been summarized in recent reviews,^{57,58} and it is beyond the scope of this report to provide a comprehensive tabulation of the candidate genes studied to date. Risk ratio findings have generally been quite modest in association studies, and meta-analyses often have been required to achieve statistical significance. Meta-analyses have been reported for polymorphisms studied in a very large number of independent studies, including variants of the apoE (*APOE*),^{59,60} plasminogen activator inhibitor 1 (*PAII*),⁶¹ angiotensin-1 converting enzyme (*ACE*),^{62,63} and *MTHFR* genes.⁶⁴ In general, results have not been consistent across studies, and the overall magnitude of association for these common polymorphisms is modest. Although meta-analyses of genetic studies are useful for providing a composite-effect measure for the genetic association, they are limited in that they may not properly capture the heterogeneity of designs across studies (eg, case-control versus population-based cohorts versus clinical trials), differences in phenotype definitions, and variation in the measured or unmeasured environmental factors that may lead to different levels of risk with the same genetic susceptibility.⁶⁵ Table 1 summarizes recent meta-analyses and overviews of association studies of candidate gene variants for atherosclerotic cardiovascular disease.

Recently, high-throughput genotyping has been used in case-control studies that have typed from 62 to $>13\,000$ genes. Genetic variants in the lymphotoxin-alpha (*LTA*)⁸⁶; *PAII*⁴⁰; gap junction protein, α -4 (*GJA4*, also known as connexin 37)^{26,61}; matrix metalloproteinase-3 (*MMP3*, also known as stromelysin-1)²⁶; and arachidonate 5-lipoxygenase (*ALOX5*)^{26,86} genes, as well as several thrombospondin (*THBS*) genes,²⁵ were associated with MI. These studies represent the first of a number of studies under way that are designed to comprehensively screen single-nucleotide polymorphism (SNPs) in coding regions or nearby regions of all known human genes.

A number of candidate gene association studies have been conducted for subclinical atherosclerosis phenotypes, particularly IMT and coronary artery calcification. The association data for dozens of gene variants with carotid IMT have recently been exhaustively reviewed.⁸⁷ Of the many studies conducted, only 1 variant that was previously linked to clinical disease, the 5A/6A polymorphism of the *MMP3* gene, showed consistently positive associations with carotid IMT, although in a small number of studies. The paraoxonase 1 (*PONI*) leu55met variant is weakly associated in subgroups only.

In summary, there is strong evidence that MI and atherosclerotic CVD, particularly diseases of early onset, have a genetic basis and a host of genes have been identified in

TABLE 1. Candidate Gene Variants for Atherosclerotic Cardiovascular Disease—Coronary Heart Disease, Arterial Ischemic Events, or Stroke—Implicated in Recent* Meta-Analyses or Overviews of Association Studies

Gene	Risk Allele	Reported Risk Ratio†	Reference(s)
Coronary heart disease			
<i>MTHFR</i>	C677T	1.14–1.21	64, 66, 67
Cholesterol ester transfer protein (<i>CETP</i>)	TaqIB	0.78	68
Paraoxonase (<i>PON1</i>)	Q192R	1.14–1.21	69, 70
Endothelial nitric oxide synthase (<i>eNOS</i>)	T-786C	1.31	71
Prothrombin	G20210A	1.21	72
<i>APOB</i>	Ins/Del (DD)	1.30	73
Glycoprotein IIIa	PI(A2)	1.10	74, 75
<i>APOE</i>	ε4/ε4	1.42	59
ACE insertion/deletion	DD	1.16–1.21	62, 76
<i>APOB</i>	Splns/Del (DD), EcorI (AA)	1.19–1.73	77
<i>PAI1</i>	4G/5G	1.20	61
Fibrinogen β-chain	G-455A	0.68	61
Endothelial nitric oxide	Glu298Asp, Intron-4	1.31–1.34	78
Arterial ischemic events or overall cardiovascular disease			
<i>MTHFR</i>	C677T	1.20	79
Prothrombin	G20210A	1.32	79
ACE insertion/deletion	DD	1.22	80
Glycoprotein IIIa	PI(A2)	1.13	80
Factor V Leiden	Arg506Gln	4.43	80
<i>APOE</i>	ε4/ε4	Positive	81
Cerebrovascular disease			
<i>APOE</i>	ε4/ε4	1.11	82
<i>MTHFR</i>	C677T	1.24–1.37	83, 84
Factor V Leiden	Arg506Gln	1.33	85
Prothrombin	G20210A	1.44	85
ACE insertion/deletion	DD	1.21	85

*Meta-analyses published since 2000 consisting of a total of at least 1000 subjects.

†All relative risks were reported to be statistically significantly different from 1.00.

connection with atherosclerotic CVD. However, much less is known about the genetic underpinnings of the common, complex forms of MI and atherosclerotic CVD, and much work remains to be done in this area.

The Genetics of Hypercholesterolemia and Related Lipid Phenotypes

Hypercholesterolemia, Lipid Levels, and Their Familial Nature

Population-based, long-term prospective studies and large clinical trials of the late 20th century incontrovertibly demonstrated that elevated LDL cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) were CVD risk factors.⁸⁸ Clinical trials have demonstrated that lowering LDL-C and raising HDL-C can ameliorate risk.⁸⁹ As this knowledge has been incorporated into clinical practice, mean serum total cholesterol concentrations have dropped in the United States in recent decades; however, ≈50% of US adults still have total cholesterol concentrations of at least 5.2 mmol/L (200 mg/dL),⁹⁰ the level that the National

Cholesterol Education Program Expert Panel considers “borderline-high risk.”⁹¹

Because at least half of the variation in serum cholesterol and other lipids can be explained by genetic variation,^{91,92} unraveling the genetic pathogenesis of hypercholesterolemia and other lipid abnormalities could reap significant public health benefits. For example, identifying the common variants in genes that contribute to LDL-C and HDL-C could provide a knowledge base for the development of novel treatments and/or screening tests to determine who would most benefit from lifestyle modification or treatment for dyslipidemias. Important strides to this end have, in fact, already been made.

Mendelian Forms of Hypercholesterolemia and Other Dyslipidemias

Mendelian forms of hypercholesterolemia have been thoroughly studied; these studies have proven critical in advancing our understanding of cholesterol metabolism and developing effective pharmacological therapies.⁹³ For example,

familial hypercholesterolemia (FH) is the most common and potentially severe mendelian form of hypercholesterolemia. Caused by mutations in LDL receptor (≈ 700 are known¹⁷), FH causes elevated serum LDL-C concentrations. In FH homozygotes, LDL-C levels are generally unresponsive to dietary and pharmacological intervention; patients often develop clinically significant CVD before 30 years of age.⁹⁴ FH heterozygotes have elevated LDL-C, albeit lower than homozygotes, and generally are more influenced by environment and responsive to drug treatment.

A condition known as familial defective apoB-100 presents in a manner virtually indistinguishable from heterozygous FH.^{95,96} apoB-100 is the major apolipoprotein present in LDL. Familial defective apoB-100 is caused by a mutation in *APOB* that influences the LDL receptor binding domain of apoB-100, ultimately resulting in decreased cellular uptake and processing of LDL-C. Familial defective apoB-100 is characterized by serum LDL-C concentrations that are 2.6 mmol/L (100 mg/dL) higher than LDL-C in individuals without mutations in *APOB*. Like those with heterogeneous FH, familial defective apoB-100 patients respond favorably to drug treatment.

Other forms of monogenic hypercholesterolemia not showing a connection to LDL receptor or *APOB* have been described. An autosomal-dominant form of hypercholesterolemia caused by a mutation of the proprotein convertase, subtilisin/kexin-type, 9 gene (*PCSK9*) leads to a clinical presentation similar to heterozygous FH. Although little is known about this form, recent research suggests that at least 1 mutation (ser127arg) of *PCSK9* is related to an overproduction of apoB-100.⁹⁷ Recessive forms of hypercholesterolemia such as autosomal-recessive hypercholesterolemia⁹⁸ (a mutation of the autosomal-recessive hypercholesterolemia protein gene, *ARH*) and cholesterol 7 α -hydroxylase deficiency hypercholesterolemia (a mutation of the cytochrome P450, subfamily VIIA, polypeptide 1 gene, *CYP7A1*) are also reported.⁹⁹

Linkage Studies for Cholesterol and Lipids

With prevalence for the monogenic disorders ranging from 0.00002% to 0.2%, these forms can account for only a small fraction of the total hypercholesterolemia observed in the population. This has led to intense investigation into identifying the genetic architecture of more common forms of elevated cholesterol and other dyslipidemias. Like the picture observed for MI and atherosclerotic CVD, the bulk of hypercholesterolemia and other dyslipidemias (ie, the common disease) are likely to result from common genetic variation; however, detection of these "common variants" has been a challenge. In contrast to MI and atherosclerotic CVD, many genome-wide linkage scans have been reported for cholesterol and related dyslipidemias, and many suggestive and several significant results have been obtained. These are summarized in Table 2. Linkage evidence for total cholesterol, triglycerides, and/or HDL-C has been observed on nearly every chromosome, with the bulk of the evidence present for HDL-C and triglycerides. In at least 2 studies, fine mapping of the regions has been conducted, but the actual genes within

these peaks that contribute to hypercholesterolemia and dyslipidemia remain elusive.

Candidate Gene Association Studies for Hypercholesterolemia and Other Dyslipidemias

Many candidate gene association studies have been conducted for hypercholesterolemia-related phenotypes, and the data for associations of dozens of gene variants with lipid-related traits have been reviewed.^{120,121} Of the many studies conducted, the most consistent evidence has been found for the *APOE* gene.

As described in the section on MI and atherosclerotic CVD, the more recent approach has been to dramatically expand both the number of genetic polymorphisms typed within a gene and the number of genes typed. For example, Knoblauch and colleagues⁹² recently used a multicandidate gene approach to explain variance in serum LDL-C and HDL-C. By the genotyping of 93 SNPs in 13 genes known to be important in lipid metabolism and constructing 230 SNP haplotypes (a linear array of genetic variants within a chromosomal region inherited as a block), genetic variance on LDL-C explained 26% of the total variance; the genetic variance on HDL-C explained 38%. Although the results of this study are limited to a "normal" population (subjects in families with known FH and those with known heart disease were excluded), the ability to explain a large part of the genetic variance of LDL-C and HDL-C on the basis of genetic variants in a small set of genes points to the possibility of using such genetic information to predict CVD risk.

The Genetics of Hypertension

Hypertension and Its Familial Nature

Hypertension is estimated to affect ≈ 60 million individuals in the United States and 1 billion individuals worldwide.¹²² Like MI, atherosclerotic CVD, and hypercholesterolemia, hypertension is a complex genetic trait. Because blood pressure is maintained by an intricate network of physiological systems, including renal, neuronal, endocrine, and vascular mechanisms, the fact that multiple genes play a role in blood pressure regulation is a logical extension of the physiology of blood pressure.¹²³ However, identifying and elucidating how each gene plays a role in these complex and interacting pathways remain to be accomplished. Like CVD and hypercholesterolemia, the impact of any 1 gene individually is likely to be small to moderate.¹⁸

The heritability of blood pressure levels and hypertension has been observed over the past century. The classic St Mary's Study described the inheritance of hypertension.¹²⁴⁻¹²⁷ Blood pressure measurements were taken from ≈ 2000 individuals to define a representative distribution of blood pressure. The St Mary's Study observed a continuous distribution of blood pressure with no clear demarcation between normal blood pressure and hypertension.¹²⁶ First-degree relatives were recruited for probands with "raised arterial pressures" (diastolic pressure >100 mm Hg) and normal pressures (diastolic pressure <85 mm Hg).¹²⁴ They found that familial aggregation of blood pressures in families of hypertensive probands was similar to normotensive probands.¹²⁴ As further evidence, the

TABLE 2. Summary of Reported Linkage Results for Total Cholesterol, HDL-C, and Triglycerides With LOD Scores >2.0

Chromosome Location (cM)	LOD Score	Phenotype	Published Study
Chromosome 1			
100	2.4	HDL	75 Families ascertained on obese and nonobese members (marker D1S405) ¹⁰⁰
146	2.6	HDL	Framingham Heart Study GAW13 data set (n=1702) ¹⁰¹
198	2.1	HDL	HyperGEN Study using 649 whites not taking lipid-lowering therapy ¹⁰²
298	2.1	HDL	HyperGEN Study using 649 whites not taking lipid-lowering therapy ¹⁰²
Chromosome 2			
16	2.2	TC	HyperGEN Study using 649 whites not taking lipid-lowering therapy ¹⁰²
131	3.5	TG	485 Hutterites (marker D2S410) ¹⁰³
145	3.5	HDL	Framingham Heart Study participants (n=1709) (marker D2S1334) ¹⁰⁴
150	3.4	HDL	Framingham Heart Study GAW13 data set, women only (marker D2S1326) ¹⁰⁵
163	3.7	TC	Extended 12-generation Talana pedigree with 572 phenotyped subjects (marker D2S2241) ¹⁰⁶
201	2.3	TG/HDL	Framingham Family Heart Study GAW13 data set identified by MCLINK (n=2461) (marker GATA65C03) ¹⁰⁷
Chromosome 3			
130	2.1	TG/HDL	99 Families of Northeastern Indian origin with early-onset CHD (n=535) (marker D3S1271) ⁴⁰
181	2.6	HDL	Pima Indians: 590 siblings from 201 nuclear families (marker D3S3053) ¹⁰⁸
194	2.0	TG/HDL	Framingham Family Heart Study GAW13 data set identified by MCLINK and LINKAGE (n=2461) (marker GATA3H01) ¹⁰⁷
Chromosome 4			
13	2.0	HDL	HyperGEN Study using 622 blacks not taking lipid-lowering therapy ¹⁰²
Chromosome 5			
39	3.6	HDL	101 White NHLBI Family Heart Study (n=1027) (marker D5S1470) ¹⁰⁹
48	2.7	HDL	HyperGEN Study using 649 whites not taking lipid-lowering therapy ¹⁰²
79	2.1	TC	23 Families with 576 subjects ascertained for 2 diabetic siblings (marker D1S305) ¹¹⁰
103	2.3	TG/HDL	Framingham Family Heart Study GAW13 data set identified by Genehunter (n=2461) (marker GATA69H12) ¹⁰⁷
125	2.7	TG/HDL	Framingham Family Heart Study GAW13 data set identified by Genehunter (n=2461) (marker ATA4D10) ¹⁰⁷
End	2.1	HDL	Extended 12-generation Talana pedigree with 572 phenotyped subjects (marker ATT079?) ¹⁰⁶
Chromosome 6			
72	2.0	HDL	99 Families of Northeastern Indian origin with early-onset CHD (n=535) (marker D6S282) ⁴⁰
129	2.2	HDL	Framingham Heart Study GAW13 data set (n=2117) (marker GATA23F08) ¹¹¹
138	2.3	TG/HDL	Framingham Heart Study GAW13 data set (n=2117) (marker GATA32B03) ¹¹¹
149	2.9	HDL	Framingham Heart Study GAW13 data set (n=1702) ¹⁰¹
150	2.7	HDL	Framingham Heart Study participants (n=1709) (marker D6S1009) ¹⁰⁴
Chromosome 7			
48	2.0	TG/HDL	Framingham Family Heart Study GAW13 data set identified by Genehunter (n=2461) (marker GATA13G11) ¹⁰⁷
74	2.1	HDL	27 Mexican American families from the San Antonio Family Diabetes Study (n=418) (marker D7S506) ¹¹²
155	2.5	TG/HDL	Framingham Heart Study (n=1702) (marker D7S1805) ¹¹³
155	2.4	TG	Framingham Heart Study GAW13 data set (n=2117) (marker GATA112F07) ¹¹¹
161	2.1	TG/HDL	Framingham Family Heart Study GAW13 data set identified by SOLAR (n=2461) (marker GATA32C12) ¹⁰⁷
174	3.4	TG	European American families ascertained with discordant siblings for obesity (n=1447) (marker D7S3058) ¹¹⁴
Chromosome 8			
176	2.3	TG/HDL	Framingham Family Heart Study GAW13 data set identified by Genehunter (n=2461) (marker UT721) ¹⁰⁷
Chromosome 9			
41	3.4	HDL	Mexican American Families in the San Antonio Family Diabetes Study (n=415) (marker D9S925) ¹¹⁵
104	2.3	TG	European American families ascertained with discordant siblings for obesity (n=1447) (marker D9S910) ¹¹⁴
Chromosome 10			
69	3.2	HDL	92 Finnish dyslipidemic families (marker D10S1772) ¹¹⁶

TABLE 2. Continued

Chromosome Location (cM)	LOD Score	Phenotype	Published Study
Chromosome 10			
69	3.2	HDL	92 Finnish dyslipidemic families (marker D10S1772) ¹¹⁶
Chromosome 11			
135	2.0	TG	28 Amish Diabetes Study families (n=612) (marker D11S1345) ¹¹⁷
Chromosome 13			
28	2.4	HDL	101 White NHLBI Family Heart Study (n=1027) (marker D5S1470) ¹⁰⁹
36	2.1	TG/HDL	Framingham Family Heart Study GAW13 data set identified by LINKAGE (n=2461) (marker GATA86H01) ¹⁰⁷
111	2.7	TG	Black families ascertained with discordant siblings for obesity (n=276) (marker ATAT113z) ¹¹⁴
Chromosome 15			
20	3.9	TG	27 Mexican American families from the San Antonio Family Diabetes Study (n=418) (marker D15S165) ¹¹²
29	2.6	TG	Genetic Epidemiology of Hypertriglyceridemia Study: 26 families totaling 140 subjects (marker D15S643) ¹¹⁸
61	2.4	TG	Genetic Epidemiology of Hypertriglyceridemia Study: 26 families totaling 140 subjects (marker D15S211) ¹¹⁸
Chromosome 16			
64	3.7	TG	Black families ascertained with discordant siblings for obesity (n=276) (marker D16S3396) ¹¹⁴
92	3.7	HDL	Mexican American families in the San Antonio Family Heart Study (n=472) (marker D16S2624) ¹¹⁹
100	2.6	TG	Black families ascertained with discordant siblings for obesity (n=276) (marker MFD466) ¹¹⁴
Chromosome 17			
126	2.1	TG/HDL	Framingham Family Heart Study GAW13 data set identified by Genehunter (n=2461) (marker 044xg3) ¹⁰⁷
Chromosome 18			
13	3.2	TC	Framingham Heart Study GAW13 data set (n=2117) (marker GATA88A12) ¹¹¹
Chromosome 19			
0	3.9	TC	Pima Indians: 998 siblings from 292 nuclear families (marker D19S1034) ¹⁰⁸
0–11	2.1	TG/HDL	Framingham Family Heart Study GAW13 data set identified by Genehunter (n=2461) (marker GATA44F10) ¹⁰⁷
68	3.2	HDL	Framingham Heart Study GAW13 data set (n=2117) (marker Mfd139) ¹¹¹
78	3.2	TG	23 Families with 576 subjects ascertained for 2 diabetic siblings (marker D19S178) ¹¹⁰
Chromosome 20			
29	2.8	TG	HyperGEN Study using 622 blacks not taking lipid-lowering therapy ¹⁰²
39	2.3	TG	Framingham Heart Study GAW13 data set (n=2117) (marker GGAA7E02) ¹¹¹
49	2.1	TG	Framingham Heart Study GAW13 data set (n=1702) ¹⁰¹
98	2.2	TG	92 Finnish dyslipidemic families (marker D20S173) ¹¹⁶
101	2.5	TG	Black families ascertained with discordant siblings for obesity (n=276) (marker D20S164) ¹¹⁴
Chromosome 21			
48	2.3	TC	HyperGEN Study using 622 blacks not taking lipid-lowering therapy ¹⁰²
54	3.9	TG/LDL	Bivariate linkage in HyperGEN using 1636 white and 1747 black sibs and first-degree relatives ¹⁰⁵
Chromosome 22			
21	3.4	TG/HDL	Framingham Family Heart Study GAW13 data set identified by LINKAGE (n=2461) (marker Mfd313) ¹⁰⁷

TC indicates total cholesterol; TG, triglycerides; CHD, congestive heart disease; and NHLBI, National Heart, Lung, and Blood Institute.

Montreal Adoption Study found that correlations between 2 biological siblings were much higher (0.38 and 0.53 for systolic and diastolic blood pressures, respectively) compared with adopted siblings (0.16 and 0.29 for systolic and diastolic blood pressures, respectively).¹²⁸ The correlation between the biological siblings captured the effects of both shared genes and shared environment, whereas the correlation between adopted siblings reflects only the effects of shared environment. Looking across studies and across populations, the heritability estimates have remained remarkably consistent, with genetic factors estimated to account for ≈30% of the population variability of blood pressure.¹²⁷

Mendelian Disorders of Hypertension

Several rare mendelian forms of hypertension have been identified, with most involving increased renal sodium reabsorption.^{129–131} Discovery of the mechanisms underlying these rare forms of hypertension has led to greater understanding of the pathways involved in blood pressure control. For instance, glucocorticoid-remediable aldosteronism has a phenotype ranging from mild blood pressure elevation to severe early-onset hypertension. In this autosomal-dominant disorder, the cytochrome P450, subfamily XIB, polypeptide 2 gene (*CYP11B2*, also known as aldosterone synthase) is fused at the 5' regulatory end with the cytochrome P450, subfamily

XIB, polypeptide 1 gene (*CYP11B1*, also known as 11-beta-hydroxylase), bringing the expression of aldosterone synthase under the control of adrenocorticotrophic hormone instead of angiotensin II.¹³² The increase in aldosterone leads to an increase in sodium retention by the kidney.¹⁹ Liddle's syndrome is also an autosomal-dominant form of hypertension with increased activity of the amiloride-sensitive epithelial sodium channel caused by mutations in the sodium channel, non-voltage-gated 1, β -subunit gene (*SCNN1B*), resulting in an increased number of sodium channels in the apical membrane.^{133,134} The increased number of sodium channels in the apical membrane leads to increased renal sodium reabsorption. An autosomal-recessive disorder with a phenotype that includes hypertension is apparent mineralocorticoid excess. Apparent mineralocorticoid excess results from mutations in the 11-beta-hydroxysteroid dehydrogenase, type II gene (*HSD11B2*), preventing the normal rapid conversion of endogenous cortisol to cortisone, with the cortisol acting on mineralocorticoid receptors to increase renal sodium reabsorption.¹³⁵ Gordon's syndrome, pseudohypoaldosteronism type II, also includes hypertension as a phenotype with renal sodium and chloride retention observed with impaired potassium excretion. This disorder results from mutations in the serine-threonine kinases encoded by the protein kinase, lysine-deficient 1 (*WNK1*) and protein kinase, lysine-deficient 4 (*WNK4*) genes.¹³⁶

Other syndromes with low blood pressure as part of the phenotype also have pointed to mechanisms related to renal ion handling. These include Gitelman's syndrome with mutations in the solute carrier family 12 (sodium/chloride transporter), member 3 gene (*SLC12A3*)¹³⁷; Bartter's syndrome with mutations in the solute carrier family 12 (sodium/potassium/chloride transporter), member 1 gene (*SLC12A1*),¹³⁸ the potassium channel, inwardly rectifying, subfamily J, member 1 gene (*KCNJ1*),¹³⁹ or the chloride channel, kidney, B gene (*CLCNKB*)¹⁴⁰; and pseudohypoaldosteronism type I with mutations in *SCNN1B* and the sodium channel, non-voltage-gated 1, gamma subunit gene (*SCNN1G*),¹⁴¹⁻¹⁴⁴

Linkage Studies for Blood Pressure and Hypertension

Genome-wide linkage analyses with the phenotypes of hypertension status and blood pressures have been conducted by numerous investigators.¹⁴⁵⁻¹⁷⁵ There is suggestive linkage evidence for hypertension susceptibility genes spread across the genome. With the abundance of these linkage peaks not reaching genome-wide significance levels, some are likely due to chance alone (ie, false-positive results). However, when genome-wide linkage scans from multiple, independent studies point to the same chromosomal region, it is plausible that ≥ 1 genes influencing hypertension susceptibility may be found in this location.

The Family Blood Pressure Program has conducted fine mapping in the linkage regions on chromosome 2 to search for hypertension susceptibility genes.¹⁷⁶ After adjustment for multiple comparisons, the solute carrier family 4 (sodium bicarbonate cotransporter), member 5 gene (*SLC4A5*) maintained statistical significance.¹⁷⁶ Although further study and validation of the result are necessary, *SLC4A5* was identified

as an important biological candidate gene for hypertension susceptibility on the basis of this linkage follow-up work.

As for CVD and lipids, further linkage follow-up work through detailed fine mapping, in addition to positional candidate gene investigation, is needed to elucidate the hypertension susceptibility gene(s) underlying the linkage peaks already reported in the literature. Finding these genes and characterizing the proteins they encode may identify new pathways in blood pressure regulation and hypertension development.

Candidate Gene Association Studies

Like the other 2 complex traits described above, hypertension candidate gene association studies have served to connect specific genes with high blood pressure. Almost every published positive result, however, has been followed by a published negative result,¹⁴⁴ most likely for the reasons described above. Some of the a priori biological candidate genes implicated as having an effect on blood pressure and hypertension status are listed in Table 3.

It is beyond the scope of this report to provide a comprehensive review of hypertension candidate gene association studies. The interested reader is referred to the works of Luft,²¹⁶ Turner and Boerwinkle,²¹⁷ and Kaplan et al¹²⁹ for such a review. In addition, several recent meta-analyses have been published for some of the more well-studied genes.²¹⁸⁻²²¹ Most of the biological candidate gene work has focused on various renal sodium transport proteins and members of the renin-angiotensin-aldosterone system.^{129,222} However, many complex interactions of the renin-angiotensin-aldosterone system with other pathways and systems, as well as all of the mechanisms of sodium reabsorption, have yet to be elucidated. Knowledge of these mechanisms and interactions must, in turn, be incorporated into the design of subsequent hypertension association studies.

Conclusions From 3 Phenotypes

Finding genes influencing MI, atherosclerotic CVD, lipids, and blood pressure through linkage studies and candidate gene studies has been somewhat successful. Future efforts will undoubtedly take advantage of the explosive growth in genomic resources and advanced statistical methods that will provide the ability to conduct sophisticated research studies at relatively low cost. Advances in genotyping must be complemented with commensurate progress in defining and accurately measuring phenotypes. Identification of important intermediate phenotypes (ie, phenotypes that mediate disease as opposed to phenotypes that represent the ultimate manifestation of a disease) may prove to be more amenable to genetic analysis. The relative success in identifying genes associated with lipid abnormalities versus wholesale atherosclerosis (as outlined above) supports this suspicion. With respect to phenotype measurement, others^{223,224} have noted that the quality of linkage and association studies is only as good as our ability to measure phenotypes. Even a phenotype as ostensibly simple to measure as blood pressure is fraught with complexity.²²⁵ Yet beyond issues of phenotype definition and measurement, some of the inconsistency of statistical findings observed across genetic and genomic studies of CVD

TABLE 3. Select Candidate Genes Implicated in High Blood Pressure and Essential Hypertension

Gene Symbol (Former Gene Symbol)	Gene	Selected References
<i>HSD11B2</i>	11- β -Hydroxysteroid dehydrogenase type II	177
<i>ADD1</i>	Adducin 1	178
<i>ADRA1B</i>	α -1b Adrenergic receptor	179, 180
<i>ADRA2A</i>	α -2a Adrenergic receptor	181
<i>CYP11B2</i>	Cytochrome P450, subfamily XIB, polypeptide 2	182, 183
<i>ACE</i>	Angiotensin I-converting enzyme	184, 185
<i>AGTR1</i>	Angiotensin receptor 1	186
<i>NPPA (ANP)</i>	Natriuretic peptide precursor A	187
<i>AGT</i>	Angiotensin I	188
<i>ADRB2</i>	β -2 Adrenergic receptor	189, 190
<i>BDKRB2</i>	Bradykinin receptor B2	191, 192
<i>C3</i>	Complement component 3	193
<i>EDNRA</i>	Endothelin receptor, type A	194
<i>NOS3 (ENOS)</i>	Nitric oxide synthase 3	195
<i>EDN1</i>	Endothelin 1	196
<i>EDN2</i>	Endothelin 2	197
<i>SCNN1B</i>	Sodium channel, non-voltage-gated 1, β -subunit	134
<i>GNB3</i>	Guanine nucleotide-binding protein, β -3	198
<i>GCCR (NR3C1, GCR)</i>	Glucocorticoid receptor	199
<i>GH1</i>	Growth hormone 1	200
<i>INSR</i>	Insulin receptor	201
<i>IGF1</i>	Insulin-like growth factor I	202
<i>LPL</i>	Lipoprotein lipase	203
<i>PLA2G1B (PLA2)</i>	Phospholipase A2, group IB	204
<i>PTGIS</i>	Prostaglandin I2 synthase	205
<i>PTGER2</i>	Prostaglandin E receptor 2, EP2 subtype	206
<i>REN</i>	Renin	207
<i>SAH</i>	Hypertension-associated SA, rat, homolog of	208
<i>SLC4A5</i>	Solute carrier family 4 (sodium bicarbonate cotransporter), member 5	176
<i>SLC12A3 (TSC)</i>	Solute carrier family 12 (sodium/chloride transporter), member 3	209
<i>SLC12A1 (NKCC2)</i>	Solute carrier family 12 (sodium/potassium/chloride transporter), member 1	210
<i>SLC9A3 (NHE3)</i>	Solute carrier family 9, isoform a3	211
<i>TNFRSF1B</i>	Tumor necrosis factor receptor subfamily, member 1B	212
<i>DRD1</i>	Dopamine receptor D1	213

Portions adapted from tables presented in Oparil and Weber¹⁴⁴ (copyright 2000, with permission from Elsevier) and Kaplan et al¹²⁹ (copyright 2002, with permission from Lippincott Williams and Wilkins).

is likely indicative of genetic heterogeneity of complex traits. When gene–gene and gene–environment interactions exist, negative results may stem from genes with relative phenotypic effects that are smaller in the presence of specific genetic and environmental backgrounds. Elucidating such gene–gene and gene–environment interactions will be a major research focus in the upcoming era of cardiovascular genomics.

Current Areas of Focus for the Genetics of CVD

Gene–Environment Interaction

Complex diseases such as CVD, hypercholesterolemia, and hypertension are influenced by multiple genes interacting with each other and with the environment. Gene–environment interaction occurs when the same genotype produces a different phenotype under different environmental expo-

sure, such as cigarette smoking or age, or a pharmacological treatment, such as statins. Interventional studies, in which an environmental exposure is standardized across individuals, are an excellent way to identify gene–environment interactions and to provide an evidence base for translation of those findings into clinical practice. For example, blood pressure response to a low-sodium diet has been shown to vary by polymorphisms of renin-angiotensin-aldosterone system genes, in particular, the angiotensin 1 (*AGT*) -6 G-A polymorphism. Results from the Dietary Approaches to Stop Hypertension (DASH) study showed that the *AGT* -6 AA genotype is associated with a significant decrease in blood pressure (–6.93 mm Hg systolic and –3.68 mm Hg diastolic) for individuals on the DASH diet.²²⁶ Similarly, in the Treatment of Hypertension Pre-

vention Trial, the incidence of hypertension was significantly lower after sodium reduction for persons with the AA genotype (relative risk, 0.57; 95% confidence interval, 0.34 to 0.98 versus usual care) but not for persons with the GG genotype (relative risk, 1.2; 95% confidence interval, 0.79 to 1.81; test for trend, $P=0.02$).²²⁷ On the basis of such results, individuals with the *AGT* -6 AA genotype could be placed on a low-sodium diet before exhibiting elevated blood pressure, thereby avoiding hypertension and consequent end-organ damage. Similar approaches evaluating response to dietary fat intake²²⁸ and physical activity²²⁹ have demonstrated variable efficacy according to genotype, although a considerable amount of work remains to be done to elucidate both the genes contributing to CVD and the optimal interventions to address the genetic risk.

Pharmacogenetics

Pharmacogenetics is the study of genetic determinants of individual variation in response to drugs, including variation in the primary domain of drug action and variation in risk for rare or unexpected side effects of drugs. Given the large number of drugs currently available for the treatment and prevention of CVD and the large number of patients eligible to receive these drugs, even small sources of variation in drug efficacy and safety have important implications for clinical and public health. For example, withholding a drug from individuals predisposed to a diminished response or an adverse effect could reduce the financial and personal costs of ineffective or dangerous therapy while ensuring that the remaining drug-eligible subjects receive greater benefit and safety.²³⁰ Pharmacogenetics also has the potential to influence drug development and clinical trial design to achieve greater efficiency, thereby allowing a larger number of more highly effective and cheaper drugs to be available for treatment and prevention of CVD.

In simple terms, pharmacogenetics concerns genetic variants that alter the structure and function or abundance of proteins that influence the effect of drugs through effects on drug handling, metabolism, and clearance; drug targets; or the phenotypes that influence the indication for use of the drug. Initially, the field of pharmacogenetics focused extensively in the first domain, with special emphasis on variants in the cytochrome P450 system responsible for the metabolic elimination of many drugs. However, recent advances have led to the recognition of genetic variants that directly influence drug action through alteration of the primary drug targets such as surface and intracellular receptors, elements of various signaling cascades, and phenotypes involved in the indication for the drug.

Genetic variants in the cytochrome P450 system and related enzymes indirectly influence drug effects by altering the bioavailability of the active compounds and are one of the most well-studied areas in pharmacogenetics.^{231–233} Genetic variants in this system of metabolizing enzymes have the capacity to affect the metabolism of a number of commonly used CVD medications. For example, *CYP2D6* facilitates oxidative metabolism of CVD drugs, including flecainide, propafenone, and β -blockers.^{231,234–239} Depending on the population studied, 1% to 10% of subjects have a variant

coding for multiple copies of the gene, producing a rapid or extensive metabolizing phenotype. Other variants produce unstable, diminished, or absent enzyme activity, yielding a poor drug-metabolizing phenotype. Similarly, the enzymatic metabolism of the S (-) enantiomer of warfarin and losartan is reduced in persons with certain allelic variants of the cytochrome P450, subfamily IIC, polypeptide 9 gene (*CYP2C9*) that occur in 2% to 13% of subjects studied.²⁴⁰

Despite the evidence of enhanced or impaired inactivation or clearance of these CVD drugs, there are surprisingly few data concerning the impact of these variants on the clinical safety or efficacy of the drugs in question. The major exception concerns the use of warfarin. Persons with 1 or 2 copies of the ile359leu allele in the *CYP2C9* gene require lower warfarin doses to achieve anticoagulation and are at a higher risk for hemorrhagic complications.²⁴¹

There are also examples of gene variants that affect the primary target for drugs or key steps in drug-effector pathways. For example, Chasman et al²⁴² identified 2 SNPs in the hydroxymethylglutaryl coenzyme A reductase gene that are associated with significantly smaller reductions in cholesterol in subjects treated with pravastatin. Similarly, several common variants in the estrogen receptor 1 gene (*ESR1*) augment the effects of estrogen therapy on HDL-C (ie, further increase HDL-C); however, more studies are needed to confirm this finding and to describe the molecular mechanisms involved.²⁴³ Blood pressure levels and the prevalence of hypertension have been associated with a gly460trp polymorphism of the adducin 1 gene (*ADD1*) in some but not all populations.^{244–253} Recently, carriers of some *ADD1* alleles taking diuretic therapy were found to be at lower risk of MI or stroke than individuals using other types of antihypertensive medications²⁵⁴; however, this finding was not replicated in a larger study.²⁵⁵ Other studies have reported interactions with respect to blood pressure response between diuretics and variants in the nitric oxide synthase 3 gene (*NOS3*)²⁵⁶; β -blockers and the guanine nucleotide-binding protein, $\beta 3$ gene (*GNB3*)^{257,258}; and angiotensin II type 1 receptor antagonists and angiotensin-converting enzyme. Table 4 lists other examples of gene variants that influence the safety or efficacy of cardiovascular medications.

Despite the promise of pharmacogenetics, several barriers to the translation of pharmacogenetic findings into routine clinical CVD care remain. First, because effective clinical practice has not, to date, been contingent on a detailed knowledge of genetics, many practitioners are not familiar with the principles of genetics and the mechanisms by which gene variants might influence clinical decision making. Second, only limited genetic testing services are available for relevant pharmacogenetic variants, and the services that are available are costly and not well standardized. Third, there is a need for incentives to promote the development and implementation of a pharmacogenetic approach to clinical therapeutics because agencies may be uninterested in strategies designed to restrict the use of products to a select subgroup of patients. Finally, and most important, there is still a lack of rigorously performed clinical research that provides the evidence necessary to justify incorporation of pharmacogenetic testing into routine clinical practice. To

TABLE 4. Examples of Genes Implicated in Variable Outcomes of Drug Therapy in Cardiovascular Medicine

Drug	Gene	Reported Association
Pharmacokinetic mechanisms		
Digoxin	<i>ABCB1</i>	Variable drug levels resulting from variable bioavailability and clearance
Warfarin	<i>CYP2C9</i>	Greater anticoagulation with hypofunctional alleles
Losartan, irbesartan	<i>CYP2C9</i>	Greater blood pressure drop with hypofunctional alleles
Metoprolol, timolol, propafenone	<i>CYP2D6</i>	Poor metabolizers display greater β -blockade
Procainamide	<i>NAT2</i>	Poor acetylators at greater risk for drug-induced lupus
Pharmacodynamic mechanisms		
QT-prolonging drugs	<i>KCNH2, KCNE2, KCNQ1, KCNE1, SCN5A</i>	Increased torsade de pointes risk
β -Blockers	<i>ADRB1, ADRB2</i>	Altered extent of heart rate slowing or blood pressure lowering
ACE inhibitors	<i>ACE</i>	Decreased response in subjects with the DD genotype
β -Blockers	<i>ACE</i>	Increased response in subjects with the DD genotype
Fluvastatin	<i>ABCA1</i>	Fluvastatin resistance
Pravastatin	<i>CETP</i>	Variable regression of atherosclerosis
Estrogen	<i>ESR1</i>	Variable HDL elevation during estrogen therapy
Lipid-lowering therapy	<i>LIPC</i>	Variable lipid lowering
Antiplatelet drugs	<i>ITGB3</i>	Variable antiplatelet effects ex vivo
Antihypertensive drugs	<i>AGTR1</i>	No relation to antihypertensive effects
Amiloride	Epithelial sodium channel genes	Antihypertensive effect in black subjects
Antihypertensive drugs	<i>GNAS</i>	Variable blood pressure lowering
Diuretics	<i>ADD1</i>	Variable stroke incidence, variable blood pressure response (especially when analyzed as a function of ACE polymorphism)

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definitively show that pharmacogenetic testing has value in clinical practice, it is not enough to simply demonstrate that drug response varies by genotype. There must also be an alternative treatment strategy that could be triggered by knowledge of genotype and proof that testing for the genotype and subsequently tailoring the treatment strategy based on genetic information are more clinically effective or cost effective (or both) than merely treating everyone in the usual manner. These will be difficult and costly studies to perform. On the other hand, the total costs of CVD and its treatment in our society are so great that even modest gains achieved through application of pharmacogenetics to CVD care could have substantial impact on attributable risk and cost.

Whole-Genome Association Studies

Subsequent to completion of the Human Genome Project²⁶⁰ and the first draft of the human HapMap project,²⁶¹ technological advances have led to development of dense genotyping arrays of $\geq 500\,000$ SNPs that are available at continually lower costs and cover the majority of the human genome.¹⁶ An initial whole-genome association study using $\approx 100\,000$ SNPs led to the discovery of a common genetic variant in the complement factor H gene (*CFH*) underlying macular degeneration,²⁶² a finding that has subsequently been replicated. Subsequently, a screen of $\approx 100\,000$ SNPs in a community-based white population led to discovery of a common variant of the insulin-induced gene 2 (*INSIG2*) underlying obesity, a finding replicated in several independent cohorts.²⁶³ A separate study of $\approx 100\,000$ SNPs in a population of whites led to the discovery of a common variant in the nitric oxide synthase 1 (neuronal) adaptor protein gene (*NOS1AP*) under-

lying QT-interval length on the ECG, a finding replicated in other cohorts.²⁶⁴ These studies provide proof of principle for the potential of whole-genome association studies for the discovery of novel genetic determinants of CVD. A rapidly growing number of whole-genome association studies are now under way to map the genetic determinants of numerous CVD traits in disease-based case-control studies and large populations.

Resequencing

Studies that focus on common (ie, minor allele frequency $>1\%$) genetic variation do not detect whether rarer variants play a role in common CVD. Whole-genome resequencing would resolve the question regarding the relative contribution of rare and common variants to common CVD. At present, whole-genome resequencing is prohibitively expensive in cohorts of men and women.²⁶⁵ However, several sentinel studies have recently performed more focused resequencing of coding regions of candidate genes, providing evidence for a small but important contribution of rare variants to common CVD. In a first such study, subjects with low HDL-C were significantly more likely to harbor protein-sequence-altering genetic variants in candidate genes previously implicated in mendelian forms of dyslipidemia.²⁶⁶ In a second study, sequence variants in the *PCSK9* gene were associated with lower LDL-C and protection from CVD.²⁶⁷ Finally, single-gene mutations in genes encoding sarcomere proteins were associated with a small but significant proportion of men and women with left ventricular hypertrophy in a community population.²⁶⁸ Such studies are laying the groundwork for far more extensive resequencing studies that may provide fully

“personalized” characterization of an individual’s genome once costs are no longer prohibitively high.

RNA Expression Profiling

The previous sections focused on how genetic mutations and more common variants—ie, interindividual variations in the DNA sequence—are statistically (and perhaps causally) associated with CVD. A more recent approach, known as gene expression profiling or RNA expression profiling, is to study the mRNA levels in a tissue sample to assess gene activity. By simultaneously measuring the levels of mRNA of thousands of genes, RNA expression profiling creates a snapshot of the rate at which those genes are expressed in a tissue sample. Because gene expression changes under pathological conditions, RNA expression profiling can point to genes that may be involved in disease pathogenesis resulting from both environmental and genetic factors, along with any associated interactions. Dynamic changes in these processes also can be studied over time. Promising applications of gene expression profiling in CVD include identification of panels of genes for disease risk prediction, for diagnosis, or for prediction of clinical outcomes.²⁶⁹ Results from RNA expression profiling in CVD research are beginning to emerge. The first studies in atherosclerotic aortic plaque show a correlation of gene groupings with the grade of atherosclerosis.²⁷⁰ Acute stroke was associated with upregulation of genes related to white blood cell activation and differentiation and with upregulation of genes in response to the altered cerebral microenvironment.²⁷¹ This signature has proven to be reproducible, and a panel of 22 genes developed is being evaluated as a rapid diagnostic test for acute ischemic stroke. A further panel of genes is under investigation for its potential value in the assessment of an individual’s future risk of vascular disease. Gene expression profiling may be used to study target organ damage resulting from hypertension and hypercholesterolemia^{272,273} and is currently being used to evaluate in-stent restenosis.²⁷⁴

Although RNA expression profiling shows great promise, there are some obstacles to this rapidly evolving methodology. The main difficulties include obtaining appropriate tissue samples and extracting sufficient quantities of high-quality RNA from tissues. Because CVD tissue is not readily accessible for this type of research, many researchers use peripheral blood leukocytes as a source of RNA, although the specificity of these signatures for CVD needs to be confirmed.²⁷⁵ Other obstacles include the cost to conduct these studies and the need to assemble a multidisciplinary team with expertise in molecular biology, bioinformatics, and clinical medicine. The reproducibility of the array findings must be determined in large, independent patient cohorts, although a number of recent studies have demonstrated the reproducibility of microarray studies to be good across platforms and across laboratories if strict laboratory methods are used.^{276–279}

In summary, gene expression profiling has potential application in clinical practice once specific molecular and clinically meaningful CVD signatures are developed so that gene products are identified that may have therapeutic targets for intervention.^{280,281} Knowledge about when, where, and to

what extent a gene is expressed is critical for understanding the activity and biological roles of the protein product of the gene in relation to CVD.

Genetic Counseling for CVD

Although genetic discoveries relating to common, complex forms of CVD are emerging at a rapid pace, the clinical application of many of these findings is currently limited; successful application of genetic testing is currently limited to monogenic disorders. However, continued research into the genetic contributions to common, complex forms of CVD will set the stage for eventual incorporation of DNA-based testing into strategies for diagnosis, counseling, and treatment of at-risk individuals, although much work remains to be done. Studies to date have largely focused on white individuals; the applicability of CVD associations to other populations is unclear.^{233,234}

FH is a common and important cause of mendelian-inherited premature CVD and provides a well-studied condition that can serve as a model for genetic counseling for families with multifactorial MI and atherosclerotic CVD. Genetic counseling of FH families can educate them about the hereditary nature of the condition and guide screening for family members genetically at risk of FH who will benefit from treatment. Although molecular diagnoses for FH can occasionally be helpful, at this time, counseling usually can be based on family history, signs of disease on physical examination (eg, tendon xanthomas, arcual cornealis), and laboratory data such as lipid profiles. In the future, however, molecular diagnosis is likely to become increasingly important in the context of FH and other disorders. For instance, current evidence suggests that an SNP in the LDL receptor also may increase stroke risk independent of lipid levels and highlights the importance of these genes in the broader spectrum of CVD.²⁸² More recently, mutations in *PCSK9* have been shown to alter cholesterol metabolism and to predict CVD.²⁶⁷ Such single-marker molecular testing has the potential to augment current clinical diagnoses used to inform genetic counseling.

As one considers how to apply genetic tests for common variants associated with common forms of CVD, evolving approaches with personal and family history of venous thromboembolism provide a useful model. Although the value of knowing a given patient’s genetic status in management of recurrent venous thromboembolism remains controversial and requires further study,²⁸³ the identification of common genetic polymorphisms associated with venous thromboembolism nonetheless provides an example of how genetic testing may be put into practice in the future. Approximately 5% of white individuals are heterozygous for the factor V Leiden variant of the coagulation factor V gene, resulting in a 4- to 7-fold-increased risk for venous thromboembolism, making it the most common inherited risk factor for thrombophilia.^{284,285} Women with factor V Leiden have a greater risk for venous thromboembolism if treated with oral contraceptives or hormone replacement therapy.^{286,287} The coagulation factor II gene (*F2*, also known as prothrombin) 20210G-A mutation is the next most common inherited risk factor for thrombophilia and is present in ≈2% to 4% of

white individuals.²⁸⁸ About 1 in 1000 individuals will carry both the factor V Leiden and *F2 20210G-A* mutations, resulting in a relative risk for venous thromboembolism of ≈ 20 .²⁸⁹ Although there is not universal consensus about how to apply genetic testing for these disorders yet, the American College of Medical Genetics and the College of American Pathologists are examples of professional associations that have proposed guidelines for their members about the utility of genetic testing for factor V Leiden and other thrombophilias.^{290,291} Four common themes are present that could be applied more generally to CVD: restricted screening to high-risk individuals, assessment of other genetic and nongenetic risk factors in the individuals, appropriate consideration for screening of family members, and the importance of efficacious and safe treatments for the condition.

As discoveries in CVD genetics grow, we anticipate that we will be able to improve predisease screening of the population. As the availability of genetic testing increases, it is anticipated that the demand for genetic counseling is likely to show a commensurate increase in the coming years. Additional resources will be required to provide a sufficient number of well-trained genetic counselors to accommodate this increased demand.

Summary and Recommendations for Clinical and Public Health Practice and Further Research

The identification and characterization of genes that enhance prediction of disease risk and improve prevention, treatment, and quality of care for MI and atherosclerotic CVD remain important goals. We now stand on the threshold of a new era in molecular genetics, and the integration of the fruits of genomic science into clinical and public health practice will likely occur rapidly. This transformation has been likened to the computer revolution. Medical molecular genetics is now at a stage in its development analogous to the era of large, bulky, slow computers: great potential is clearly within sight, but widespread, everyday utility remains just outside our grasp. We recognize that a large amount of research is required before genetics can be translated into clinical practice.

The lack of reproducible genetic findings across studies and populations has contributed to uncertainty about the nature and number of genes contributing to CVD risk. Given our current understanding, we question whether genetic testing is “ready for prime time” in CVD public health and clinical medicine, in which most patients are afflicted with complex forms of the disease. However, we anticipate that we soon will be able to determine genetically based disease susceptibility within individuals, families, and populations, thus allowing us to lower risk and create tailored treatment strategies appropriate to the genetic susceptibility. We conclude this statement with a set of recommendations intended to help incorporate usable knowledge into current clinical and public health practice, to foster and guide future research, and to prepare both researchers and practitioners for the changes likely to occur as molecular genetics moves from the laboratory to clinic.

Specific Recommendations

- Continue to use family history as a screening tool to identify susceptible individuals and families.
- Develop a research infrastructure that includes the following:
 - Incentives for researchers to assemble multidisciplinary, collaborative research teams.
 - Incentives for researchers who are not currently conducting genetic research to collect DNA and consent to use specimens and data in future studies.
 - Incentives for researchers to undertake translational research.
 - Public-private partnerships that expedite the translation of genetic/genomic findings to clinical and public health practice.
- Prioritize the following research agendas:
 - Characterize genes and genetic variants that are associated with CVD across individuals, communities, and populations.
 - Evaluate how behavioral and environmental factors interact with genetic variants to influence CVD risk.
 - Develop new technologies in CVD characterization, risk assessment, and outcome prediction.
 - Assess gene-drug interaction and the impact of these findings on intervention strategies and drug development.
 - Develop new methods to analyze and understand the wealth, breadth, and complexity of genetic and genomic data.
- Prepare proactively for effective genetic screening programs.
 - Establish prevalence criteria that would trigger screening programs in at-risk populations.
 - Create standards and laboratory oversight mechanisms for genetic testing facilities.
 - Match appropriate treatment guidelines to particular genetic susceptibility findings.
 - Assess the potential cost effectiveness of genetic screening programs.
- Educate researchers, clinicians, public health professionals, and the general public.
 - Effective researchers must be proficient in genetic epidemiology, computational biology, and statistical genetics.
- Clinicians should become aware of the genetic tools at their disposal and understand and put to use the results of genetic screening for complex CVDs. Graduate educational curricula should include population biology and genetics.
 - Public health professionals must continue to incorporate genetic knowledge into their understanding of population risk of CVDs.
 - The general public will need a basic genetic literacy to understand the technical and negotiate the ethical aspects of molecular genetic screening.

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Appendix

Allele: Alternative sequence of a gene. One of the different variants of a gene that can exist at a single location on a chromosome.

Candidate gene: A gene that is thought to cause or play a part in a disease.

Chromosomes: Structures made of DNA and proteins found in the nuclei of cells. Chromosomes come in pairs, and a normal human cell contains 46 chromosomes, 22 pairs of autosomes, and a pair of sex chromosomes. Genes, regulatory sequences, and noncoding DNA segments comprise chromosomes.

Functional genomics: The study of genes, their resulting proteins, and the role played by the proteins in the biochemical processes of the body.

Gene: A unit of inheritance; a working subunit of DNA. Each of the 20 000 to 25 000 genes in the body contains the code for a specific product, typically a protein such as an enzyme.

Gene expression: The process by which the coded information of a gene is translated into the structures present and operating in the cell (either proteins or ribonucleic acids).

Gene markers: Landmarks for a target gene, either detectable traits that are inherited along with the gene or distinctive segments of DNA.

Gene map: A description of the relative positions of genes on a chromosome and the distance between them.

Genetic counseling: A short-term educational counseling process for individuals and families who have a genetic disease or who are at risk for such a disease. Genetic counseling provides patients with information about their condition and helps them make informed decisions.

Genetic linkage maps: DNA maps that assign relative chromosomal locations to genetic landmarks—either genes for known traits or distinctive sequences of DNA (ie, genetic markers)—on the basis of how frequently they are inherited together.

Genetic testing: Examining a sample of blood or other body fluid or tissue for biochemical, chromosomal, or genetic markers that indicate the presence or absence of genetic disease.

Genetics: The scientific study of heredity, how particular qualities or traits are transmitted from parents to offspring.

Genome: All the genetic material in the chromosomes of a particular organism.

Genome-wide: Descriptor that indicates that the entire breadth of the genome has been examined in a study (eg, a linkage or association study). Genome-wide studies do not resequence the entire genome but type (an increasingly large set of) markers distributed throughout the genome.

Genomics: A “scaled-up” version of the science of genetics that investigates the structure and function of large sections of the genome simultaneously.

Genotype: The actual genes carried by an individual (as distinct from phenotype—ie, the physical, bodily characteristics into which genes are translated).

Haplotype: A way of denoting the collective genotype of a number of closely linked loci on a chromosome.

Heritability (h^2): For any trait, the proportion of the phenotypic variability resulting from genetic variance. Note that heritability does not indicate the degree to which a trait is “genetic.” Nor does a high h^2 mean that the trait cannot be influenced by environment. A heritability significantly >0 , however, can provide a rationale for further genetic and genomic study of a trait of interest.

Heterozygous: Possessing 2 different sequences (ie, genotypes) of a particular gene, 1 inherited from each parent.

High-throughput genotyping: In contrast to the older labor- and time-intensive genotyping methods, high-throughput genotyping

makes use of robots, computers, and other evolving technologies, thus enabling laboratories to type up to hundreds of thousands of polymorphisms in many samples in a relatively short period of time.

Homozygous: Possessing 2 identical sequences of a particular gene, 1 inherited from each parent.

Interaction: The differing effect of 1 independent variable on the dependent variable, depending on the particular level of another independent variable. For example, there would be an interaction between the factors sex and treatment if the effect of treatment was not the same for male and female subjects in a drug trial.

Linkage analysis: A gene-hunting technique that traces patterns of heredity in large, high-risk families in an attempt to locate a disease-causing gene mutation by identifying traits that are co-inherited with it.

Linkage disequilibrium: Two alleles at different loci that occur together on the same chromosome more often than would be predicted by chance alone. It is a measure of cosegregation of alleles in a population.

LOD score: An abbreviation of “logarithm of the odds” score. A statistical estimate of whether 2 loci are likely to lie near each other on a chromosome and are therefore likely to be inherited together. A LOD score of ≥ 3 is generally taken to indicate that the 2 loci are close.

Marker: See gene markers.

Microarray technology: A new way of studying how large numbers of genes interact with each other and how the regulatory networks of a cell control vast batteries of genes simultaneously. The method uses a robot to precisely apply tiny droplets containing functional DNA to glass slides. Researchers then attach fluorescent labels to DNA from the cell they are studying. The labeled probes are allowed to bind to cDNA strands on the slides. The slides are put into a scanning microscope that can measure the brightness of each fluorescent dot; brightness reveals how much of a specific DNA fragment is present, an indicator of how active it is.

Mendelian diseases: Pathological conditions that usually appear in families in dominant or recessive patterns.

Mutation: A change, deletion, or rearrangement in an individual’s DNA sequence that may lead to the synthesis of an altered protein or the inability to produce the protein. Note that mutations are observed in individuals and polymorphisms are observed in populations.

Nucleotide: A building block of DNA or RNA, consisting of 1 nitrogenous base, 1 phosphate molecule, and 1 sugar molecule.

Pharmacogenetics: The study of genetically determined responses to drugs (or of genetic variation in drug metabolizing enzymes and the effect on drug response).

Pharmacogenomics: The general study of the entire spectrum of genes that affect drug behavior.

Phenotype: The observable manifestation of a genetic trait, resulting from specific genotypes and their interactions with the environment.

Polymorphism: A common variation in the sequence of DNA among individuals in a population. Note that polymorphisms are observed in populations and mutations are observed in individuals.

Resequencing: Precisely determining the sequence of nucleotides in the DNA of a sample of individuals. Resequencing is used to identify single-nucleotide polymorphisms.

Single-nucleotide polymorphism: A polymorphism in which the alleles differ by the replacement of a single nucleotide in the DNA sequence.

Whole-genome: See genome-wide.

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