The Application of Clinical Genetics

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REVIEW

Pathogenesis of coronary artery disease: focus on genetic risk factors and identification of genetic variants

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Abstract: Coronary artery disease (CAD) is the leading cause of death and disability worldwide, and its prevalence is expected to increase in the coming years. CAD events are caused by the interplay of genetic and environmental factors, the effects of which are mainly mediated through cardiovascular risk factors. The techniques used to study the genetic basis of these diseases have evolved from linkage studies to candidate gene studies and genome-wide association studies. Linkage studies have been able to identify genetic variants associated with monogenic diseases, whereas genome-wide association studies have been more successful in determining genetic variants associated with complex diseases. Currently, genome-wide association studies have identified approximately 40 loci that explain 6% of the heritability of CAD. The application of this knowledge to clinical practice is challenging, but can be achieved using various strategies, such as genetic variants to identify new therapeutic targets, personal genetic information to improve disease risk prediction, and pharmacogenomics. The main aim of this narrative review is to provide a general overview of our current understanding of the genetics of coronary artery disease and its potential clinical utility.

Keywords: coronary artery disease, pathogenesis, genetic risk factors, genetic variants

Introduction

Coronary artery disease (CAD) is the principal individual cause of mortality and morbidity worldwide. A recent report on the Global Burden of Disease, which proposes disability-adjusted life years (DALYs, calculated as the sum of years of life lost and years lived with disability) as a new metric to measure disease burden, indicates that CAD accounted for the largest proportion of DALYs due to a single cause worldwide in 2010, explaining 5% of the total number of DALYS (Figure 1).[1]

CAD is a complex chronic inflammatory disease, characterized by remodeling and narrowing of the coronary arteries supplying oxygen to the heart. It can have various clinical manifestations, including stable angina, acute coronary syndrome, and sudden cardiac death. It has a complex etiopathogenesis and a multifactorial origin related to environmental factors, such as diet, smoking, and physical activity, and genetic factors[2] that modulate risk of the disease both individually and through interaction.

In this narrative review, we summarize the main etiopathogenic mechanisms that underlie CAD, with a focus on current knowledge concerning the genetic architecture of the disease and the clinical utility of this knowledge.

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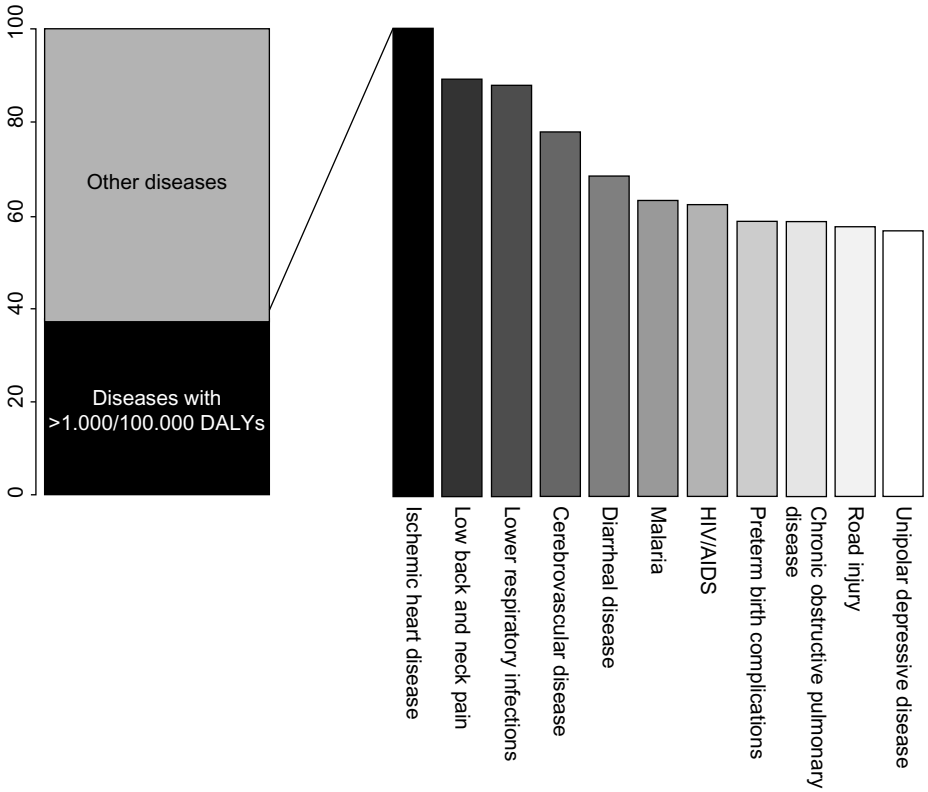

Figure 1 The top eleven diseases explain 37.7% of the global burden of disease measured as DALYs, with coronary artery disease as the leading cause of DALYs in 2010.
Abbreviations: DALYs, disability-adjusted life years; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

Atherosclerosis, the main etiopathogenic mechanism of CAD

Atherosclerosis is the main etiopathogenic process that causes CAD, and its progression is related to an interplay between environmental and genetic factors, with the latter exerting their effects either directly or via cardiovascular risk factors (Figure 2). Although clinical ischemic cardiovascular events usually appear after the fifth decade of life in men and the sixth decade of life in women, this process starts early in life, even during fetal development.[3]

Briefly, atherosclerosis is a silent progressive chronic process characterized by accumulation of lipids, fibrous elements, and inflammatory molecules in the walls of the large arteries.[4–8] This process begins with the efflux of low-density lipoprotein (LDL) cholesterol to the subendothelial space, which can then be modified and oxidized by various agents. Oxidized/modified LDL particles are potent chemotactic molecules that induce expression of vascular cell adhesion molecule and intercellular adhesion molecule at the endothelial surface, and promote monocyte adhesion and migration to the subendothelial space. Monocytes differentiate to macrophages in the intima media. Recently, different subsets of monocytes have been identified, and their roles appear to be different according to the phase of

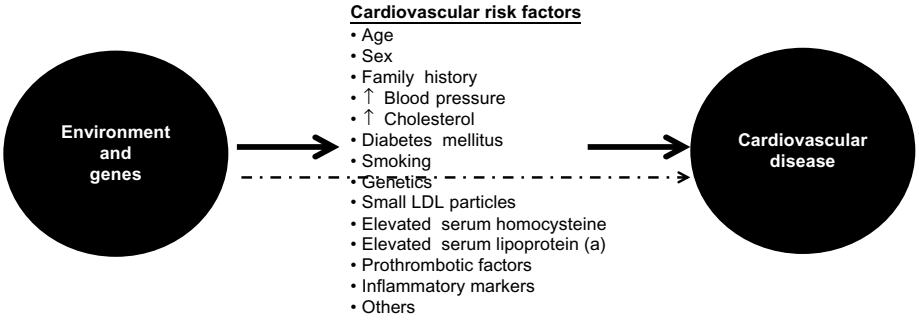

Figure 2 Genetic and environmental causes of development and progression of atherosclerosis act directly or through known intermediate traits.
Abbreviation: LDL, low-density lipoprotein.

atherosclerosis in which they are involved.[9] Macrophages bind oxidized LDL via scavenger receptors to become foam cells,[5] and also have proinflammatory functions, including the release of cytokines such as interleukins and tumor necrosis factor. The final result of this process is formation of the first typical atherosclerotic lesion, ie, the fatty streak, in which foam cells are present in the subendothelial space.

Other types of leukocytes, such as lymphocytes and mast cells, also accumulate in the subendothelial space.[10] The cross-talk between monocytes, macrophages, foam cells, and T-cells results in cellular and humoral immune responses, and ultimately in a chronic inflammatory state with the production of several proinflammatory molecules.[11,12] This process continues with the migration of smooth muscle cells from the medial layer of the artery into the intima, resulting in the transition from a fatty streak to a more complex lesion.[5] Once smooth muscle cells are in the intima media, they produce extracellular matrix molecules, creating a fibrous cap that covers the original fatty streak. Foam cells inside the fibrous cap die and release lipids that accumulate in the extracellular space, forming a lipid-rich pool known as the necrotic core.[13] The result of this process is formation of the second atherosclerotic lesion, the fibrous plaque.

The thickness of the fibrous cap is key for maintaining the integrity of the atherosclerotic plaque,[8] and two types of plaque can be defined depending on the balance between formation and degradation of this fibrous cap, ie, stable and unstable or vulnerable. Stable plaques have an intact, thick fibrous cap composed of smooth muscle cells in a matrix rich in type I and III collagen.[14] Protrusion of this type of plaque into the lumen of the artery produces flow-limiting stenosis, leading to tissue ischemia and usually stable angina. Vulnerable plaques have a thin fibrous cap made mostly of type I collagen and few or no smooth muscle cells, but abundant macrophages and proinflammatory and prothrombotic molecules.[8,10] These plaques are prone to erosion or rupture, exposing the core of the plaque to circulating coagulation proteins, causing thrombosis, sudden occlusion of the artery lumen,[8,10] and usually an acute coronary syndrome. Intraplaque hemorrhage is also a potential contributor to progression of atherosclerosis, and appears to occur when the vasa vasorum invades the intima from the adventitia.[15]

Study of the genetic architecture of disease

In order to study the genetic factors associated with a disease, several sequential steps must be followed. The first step involves quantification of the genetic component of the disease, which can be expressed as its heritability, ie, the proportion of the total population variance of the phenotype at a particular time or age that is attributable to genetic variation.[16] The heritability of some phenotypes associated with arteriosclerosis has already been determined, and generally ranges from 40% to 55% (Table 1).[17,18]

The second step is to study the genetic architecture of the disease, ie, identify the loci, and within these loci, the genetic variants that modulate disease susceptibility. However, this task is one of the greatest challenges in current genetic research. Depending on the observed patterns of inheritance, it is possible to classify genetic diseases in two broad classes, ie, monogenic or Mendelian diseases, in which genetic variation in one gene accounts for most or all of the variation in disease risk;[19] and complex diseases, which are characterized by complex patterns of inheritance caused by the combination of multiple genetic variants (often with a small effect) and environmental factors, and modulated by their mutual interaction.[20] For example, in the case of CAD, the effects of known genetic variants range from an odds ratio of 1.04 to approximately 1.30 per copy of the risk allele.[21] Studies of the genetic architecture of a disease generally have two approaches, ie, linkage and association studies.[17]

Linkage studies

In these studies, large families with several affected and unaffected relatives across one or more generations are identified and recruited.[22,23] Classically, large numbers of genetic markers, uniformly distributed throughout the genome, are analyzed to see if their transmission from generation to generation is associated with the presence of the disease (segregation). The initial objective is to identify regions of the genome that contain genes predisposing to or causing the disease under study. Thereafter, the chromosomal

Table 1 Main results of different studies analyzing the heritability of several phenotypes associated with arteriosclerosis

Phenotype	Heritability	References
CAD		
Acute myocardial infarction	0.56	Nora et al[89]
Mortality from CAD	0.53–0.57 (men) 0.58 (women)	Zdravkovic et al,[90] Wienke et al[91]
Coronary artery calcification	0.42	Peyser et al[92]
Atherosclerosis		
Carotid artery atherosclerosis	0.21– 0.64	Xiang et al,[93] Fox et al,[94] Swan et al,[95] North et al,[96] Hunt et al[97]

Abbreviation: CAD, coronary artery disease.

region that segregates with the disease can be fine-mapped to identify the causal gene.[17,22,23] This type of study has been successful in identifying many disease genes, particularly those that cause Mendelian traits, but less successful in identifying genes associated with complex diseases.[24] In the case of CAD, notable successes include the identification of variants in *ALOX5AP* as being associated with coronary and cerebrovascular diseases,[25] in *MEF2A* as being associated with CAD,[26] and in *PCSK9* as a gene for which variation is relevant in the metabolism of cholesterol.[27]

Association studies

Association studies are likely to be more effective tools than linkage studies for studying genetically complex traits because they can have greater statistical power to detect genetic variants with small effects.[28] These types of studies evaluate the association between genetic variants (usually single nucleotide polymorphisms or copy number variations) and the presence/absence of a disease or a specific phenotype. The biggest challenges for this type of study are the accuracy of phenotype definition and replication of the findings. In order to identify genetic variants with small effects, large sample sizes are required, which are usually obtained by pooling different samples and populations, potentially with different phenotyping methods or criteria. In many cases, this heterogeneity results in dilution of the effects of causal genetic variants. In other cases, the phenotype itself may be difficult to define (eg, fibromyalgia) or show substantial intraindividual variability (eg, blood pressure), diluting the observable effect of the causal variant on the phenotype of interest. There are several types of association studies, as follows.

Candidate gene studies

Association studies in candidate genes, usually known to be related to intermediate traits, have been widely used for the study of complex diseases.[4,29,30] This approach is based on an a priori hypothesis generated from knowledge of the disease pathogenesis or previous results.[17,31] In the 1990s, this type of research became very popular and many studies analyzing the relationship between genetic variants and phenotypes were published, although their main findings were often difficult to replicate.[32]

Genome-wide association studies

The goal of genome-wide association studies (GWAS) is to identify genetic variants associated with complex phenotypes without the need for prior selection of candidate loci or genes.[33] GWAS are based on two assumptions: first, a large proportion of common variation in the genome can be captured by a relatively small number of genetic variants, an hypothesis that is supported by evidence from the HapMap project;[34] and, second, common complex diseases are mainly caused by common genetic variants.

This type of study became possible through technologic advances that allowed large numbers of single nucleotide polymorphisms to be genotyped throughout the genome and common patterns of linkage disequilibrium in different populations to be determined, thanks to studies like the Human Genome Project and the HapMap Project.[34,35] This evidence allowed the possibility of searching the human genome for common variants associated with a huge variety of phenotypes and diseases.[36] Moreover, powerful association analysis methods and software have also been developed.[37,38] These studies are hypothesis-free, and due to the multiple comparisons and the need to reduce the burden of potential type I errors, they have to correct the *P*-value to be considered statistically significant according to the number of tests performed. Usually, this statistical significance threshold is located at a *P*-value $<10^{-8}$.

In parallel, international collaborations and consortia have provided new insights in medical research.[39] While the number of studies that use this methodology has increased rapidly in recent years (Figure 3), this type of design is known to have some limitations (Table 2). These include the low proportion of heritability explained by the genetic variants identified, which has been found to be lower than 10% for most phenotypes,[4,40] and the fact that the results are based on statistical association and do not provide functional insights. However, these studies have consistently identified hundreds of loci in dozens of clinically important phenotypes,[4,41] providing further insights into the genetics of complex diseases.

Whole-genome sequencing studies

The human genome contains approximately 3.1 billion nucleotides with approximately 56 million genetic variants. The exome, ie, the part of the genome formed by protein-coding exons, comprises approximately 30 million nucleotides and 23,500 genes.[42] Rapidly improving whole-genome sequencing (WGS) technologies are creating new research avenues based on sequencing entire individuals,[39,42] and the rapidly decreasing costs of WGS will soon allow this technology to be used for tackling the genetic architecture of disease.[43] WGS are expected to contribute to better definition of the genetic basis of a range of phenotypes, responses to therapy,

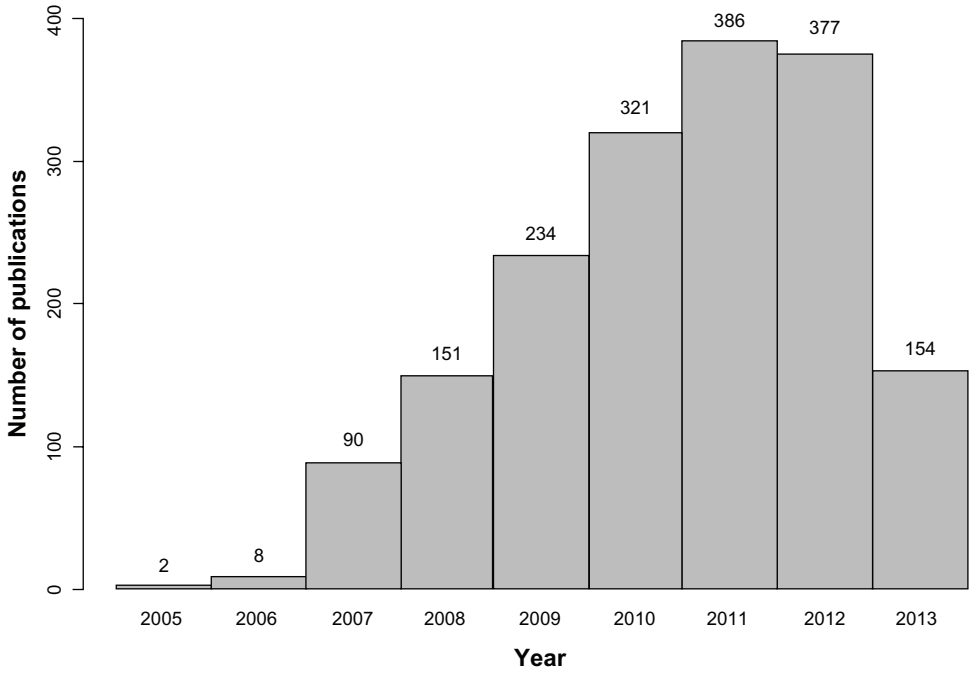

Figure 3 Number of articles published per year according to the genome-wide association studies catalog (accessed on September 27, 2013).

and clinical outcomes. Although WGS mainly focus on Mendelian disorders, the WGS approach is becoming important for identifying and analyzing rare variants, which might have larger effects on disease risk than the common variants identified by GWAS.[42]

Table 2 Comparison between candidate gene studies and GWAS

Feature	Candidate gene studies	Genome-wide association studies
Hypothesis	Need a priori hypothesis	Hypothesis-free
Number of genetic variants	Limited (one to hundreds)	Large (hundreds of thousands to millions, with imputation)
Sample size	Limited (usually hundreds)	Large (hundreds to hundreds of thousands)
Biases	Selection bias	Selection bias
	Confounding	Confounding
	Population stratification	Population stratification (methods to control)
	Publication bias	
Limitations	Sample size	Control for multiple testing
	Nonreplicability of results	Phenotype definition
	Lack of thoroughness	Based on common variants
	Low genetic coverage	Statistical versus functional association
False positive rate	Large	Low
False negative rate	Low	Large

Note: Data summarized from many studies.[28,98–104]
Abbreviation: GWAS, genome-wide association studies.

One of the main disadvantages of WGS is the rate of false positive/false negative results in variant calling, and identification of the true causal genetic variant. Considering a false positive rate of 2%, an analysis of three billion genetic variants per genome would yield 60,000,000 miscalled variants. Therefore, false positives are expected to remain a major limitation of WGS, and alternative methods for validating variants identified by this approach will be necessary. Also, WGS will have a real challenge in identifying the true causal genetic variants among all alleles because all genes and proteins carry several nonpathogenic variants. For this reason, a classification of genetic variants according to the strength of the evidence for causality has been proposed as follows: disease-causing, likely disease-causing, disease-associated, functional but not associated with disease; and unknown biological function.[42]

Current knowledge of genetic architecture of CAD

Our understanding of the genetic architecture of CAD has improved considerably since 2007 when the first GWAS of this disease were published. The first two studies were published simultaneously and identified the 9p21 locus to be associated with myocardial infarction[44] and CAD,[45] and a third study replicated these findings.[46] At the beginning of 2013, a meta-analysis of several GWAS identified a final set of about 40 genetic variants associated with CAD (Table 3)

Table 3 Summary of main findings of most recent meta-analysis of genome-wide association studies in coronary artery disease, showing the lead single nucleotide polymorphism of each locus, the closest gene, chromosomal location, risk allele and frequency, *P*-value, and effect size of the reported associations

rsID	Gene located at or near loci	Chr	Risk/nonrisk allele (risk allele frequency)	Combined *P*-value	Combined OR
rs602633	*SORT1*	1	C/A (0.77)	1.47×10^{-25}	1.12
rs17114036	*PPAP2B*	1	A/G (0.91)	5.80×10^{-12}	1.11
rs4845625	*IL6R*	1	T/C (0.47)	3.64×10^{-10}	1.09
rs67258870	*WDR12*	2	C/T (0.11)	1.16×10^{-15}	1.12
rs515135	*APOB*	2	G/A (0.83)	2.56×10^{-10}	1.03
rs2252641	*ZEB2-AC074093*	2	G/A (0.46)	5.30×10^{-8}	1.06
rs1561198	*VAMP5-VAMP8-GGCX*	2	A/G (0.45)	1.22×10^{-10}	1.07
rs6544713	*ABCG5-ABCG8*	2	T/C (0.30)	2.12×10^{-9}	0.96
rs9818870	*MRAS*	3	T/C (0.14)	2.62×10^{-9}	1.07
rs7692387	*GUCY1A3*	4	G/A (0.81)	2.65×10^{-11}	1.13
rs1878406	*EDNRA*	4	T/C (0.15)	2.54×10^{-8}	1.09
rs273909	*SLC22A4-SLC22A5*	5	C/T (0.14)	9.62×10^{-10}	1.11
rs12190287	*TCF21*	6	C/G (0.59)	4.94×10^{-13}	1.07
rs2048327	*SLC22A3-LPAL2-LPA*	6	G/A (0.35)	6.86×10^{-11}	1.06
rs9369640	*PHACTR1*	6	A/C (0.65)	7.53×10^{-22}	1.09
rs10947789	*KCKN5*	6	T/C (0.76)	9.81×10^{-9}	1.01
rs4252120	*PLG*	6	T/C (0.73)	4.88×10^{10}	1.07
rs11556924	*ZC3HC1*	7	C/T (0.65)	6.74×10^{-17}	1.09
rs2023938	*HDAC9*	7	G/A (0.10)	4.94×10^{-8}	1.13
rs264	*LPL*	8	G/A (0.86)	2.88×10^{-9}	1.06
rs2954029	*TRIB1*	8	A/T (0.55)	4.75×10^{-9}	1.05
rs1333049	*CDKN2BAS1*	9	C/G (0.47)	1.39×10^{-52}	1.23
rs3217992		9	A/G (0.38)	7.75×10^{-57}	1.16
rs579459	*ABO*	9	C/T (0.21)	2.66×10^{-8}	1.07
rs12413409	*CYP17A1-CNNM2-NT5C2*	10	G/A (0.89)	6.26×10^{-8}	1.10
rs2505083	*KIAA1462*	10	C/T (0.42)	1.35×10^{-11}	1.06
rs501120	*CXCL12*	10	A/G (0.83)	1.79×10^{-9}	1.07
rs2047009		10	C/A (0.48)	1.59×10^{-9}	1.05
rs974819	*PDGFD*	11	A/G (0.29)	3.55×10^{-11}	1.07
rs3184504	*SH2B3*	12	T/C (0.40)	5.44×10^{-11}	1.07
rs4773144	*COL4A1-COL4A2*	13	G/A (0.42)	1.43×10^{-11}	1.07
rs9515203		13	T/C (0.74)	5.85×10^{-12}	1.08
rs9319428	*FLT1*	13	A/G (0.32)	7.32×10^{-11}	1.10
rs2895811	*HHIPL1*	14	C/T (0.43)	4.08×10^{-10}	1.06
rs7173743	*ADAMTS7*	15	T/C (0.58)	6.74×10^{-13}	1.07
rs17514846	*FURIN-FES*	15	A/C (0.44)	9.33×10^{-11}	1.04
rs12936587	*RAI1-PEMT-RASD1*	17	G/A (0.59)	1.24×10^{-9}	1.06
rs2281727	*SMG6*	17	C/T (0.36)	7.83×10^{-9}	1.05
rs1122608	*LDLR*	19	G/T (0.76)	6.33×10^{-14}	1.10
rs9982601	Gene desert (*KCNE2*)	21	T/C (0.13)	7.67×10^{-17}	1.13

Abbreviations: Chr, chromosome; OR, odds ratio.

that explains approximately 6% of the heritability of CAD.[21] Some of these variants are related to lipid metabolism, blood pressure, and inflammation, which confirms the importance of these pathways in the pathogenesis of CAD.[21] In contrast, this study found no overlap between these CAD loci and those associated with type 2 diabetes or glucometabolic traits. Moreover, most of these CAD loci are located in intergenic regions, or in regions with unknown function or where the relationship to atherosclerosis or its intermediate traits is unknown.

Genetics of cardiovascular risk factors

Classical cardiovascular risk factors, such as hypertension, diabetes, dyslipidemia, and obesity, are also considered to be complex traits caused by the interplay between genetic and environmental factors, as in the case of CAD. The GWAS

approach has had a similar degree of success in identifying the genetic architecture of these risk factors and that of CAD, in that only a small fraction of the heritability of these phenotypes has been explained (Table 4).[47–53] While some of these genetic variants are also associated with CAD risk, others are not, ie, they have such small effects that very sample sizes would be required to detect them.

Clinical utility of genetic knowledge

The identification of genetic variants associated with disease has allowed us to improve our understanding of its pathogenesis, and ultimately to reduce the burden of disease at both the individual and population levels. Information derived from genetic studies could potentially help to reduce the burden of disease in three main ways, ie, the identification of new pharmacologic targets, improvements in identification of high-risk individuals, and pharmacogenomics.

Identification of new pharmacologic targets

Genetic studies can shed light on new metabolic pathways associated with the development and progression of atherosclerosis, and provide clues for identifying new pharmacologic targets. The following two examples illustrate the promise as well as the potential difficulties of this field.

PCSK9

A clear example of the success of genetic studies in identifying molecules that may become new therapeutic targets is the *PCSK9* gene. This gene was initially discovered by linkage studies to be associated with autosomal dominant hypercholesterolemia,[27] for which new causal mutations were identified in 2003.[54] The PCSK9 protein is crucial for metabolism of LDL cholesterol through its role in degradation of the LDL receptor, such that inhibition of this protein could become a viable treatment for hypercholesterolemia.[55] Recent clinical trials in patients with primary hypercholesterolemia have shown that combination treatment with REGN727/SAR236553, a human monoclonal antibody to PCSK9, and either 10 mg or 80 mg of atorvastatin resulted in significantly greater reduction of LDL cholesterol than that obtained by 80 mg of atorvastatin alone.[56]

9p21 region

The genetic variants associated with CAD at the 9p21 locus, which has been the top hit in all CAD GWAS since 2007, lie in an intergenic region close to a cluster of cell-cycle regulating tumor suppressor genes (*CDKN2A* and *CDKN2B*) that overlap with a nonprotein coding RNA (*CDKN2BAS* or *ANRIL*). While various hypotheses have been proposed to explain the functional basis of this association, the mechanism remains unclear,[39,57] and this has prevented the identification of a therapeutic target.

Improved identification of high-risk individuals

In the case of CAD, primary prevention strategies in healthy asymptomatic individuals are very important because the first clinical manifestation of the disease is often catastrophic (MI or sudden death). Two main prevention strategies can be defined: the population approach, based on public health policies that affect the whole population, such as smoking bans;[58] and the approach that targets high-risk individuals, based on implementing intensive preventive treatment in individuals at high risk of having the disease, based on their cardiovascular risk factor profile.[59] Two main screening strategies are usually undertaken to identify high-risk individuals, ie, opportunistic screening and high-risk screening. In opportunistic screening, evaluation of cardiovascular risk factors and estimation of CAD risk is carried out in all individuals who come into contact with the health care system for any reason. Risk functions are the most commonly used method for estimating individual risk of having a CAD event, usually for a 10-year period.[59–61] Risk functions are mathematical equations that estimate the probability of developing CAD/cardiovascular disease using information about cardiovascular risk factors that are strongly and independently related to CAD and can be evaluated by simple procedures in the laboratory or doctor's office.

Depending on their estimated risk, it is possible to categorize individuals into different risk categories (low, intermediate, high, and very high), and these categories are used to determine the intensity of preventive cardiovascular measures to be applied, which may range from lifestyle recommendations to prescription of drugs with various clinical objectives. Although risk functions can accurately predict the numbers of events that will occur in each risk category, many CAD events occur in individuals whose risk is too low to justify intensive treatment.[62] For this reason, considerable effort has been invested in improving the classification of these intermediate-risk individuals into more appropriate risk categories.

Several biomarkers, including genetic variants, have been analyzed as candidates for improving the predictive capacity of risks functions.[63] The main advantage of genetic variants is that they remain invariable throughout life, so it

Table 4 Summary of main findings of most recent meta-analyses of genome-wide association studies of cardiovascular risk factors, showing the lead single nucleotide polymorphism of each locus, the closest gene, chromosomal location, risk allele and frequency, and *P*-value of the reported associations

rsID	Loci	Chr	Risk allele (Risk allele frequency)	Combined *P*-value	Known effect on CAD	Reference
Obesity						
rs2815752	*NEGR1*	1	A (0.61)	1.61×10^{-22}	No	50
rs543874	*SEC16B*	1	G (0.19)	3.56×10^{-23}	No	50
rs1514175	*TNNI3K*	1	A (0.43)	8.16×10^{-14}	No	50
rs1555543	*PTBP2*	1	C (0.59)	3.68×10^{-10}	No	50
rs984222	*TBX15-WARS2*	1	G (0.64)	3.81×10^{-14}	No	49
rs2867125	*TMEM18*	2	C (0.83)	2.77×10^{-49}	No	50
rs713586	*RBJ*	2	C (0.47)	6.17×10^{-22}	No	50
rs887912	*FANCL*	2	T (0.29)	1.79×10^{-12}	No	50
rs10195252	*GRB14*	2	T (0.60)	2.09×10^{-24}	No	49
rs13078807	*LRP1B*	2	C (0.18)	1.35×10^{-10}	No	50
rs9816226	*ETV5*	3	T (0.82)	1.69×10^{-18}	No	50
rs13078807	*CADM2*	3	G (0.20)	3.94×10^{-11}	No	50
rs6795735	*ADAMTS9*	3	C (0.60)	9.79×10^{-14}	No	49
rs6784615	*NISCH-STAB1*	3	T (0.94)	3.84×10^{-10}	No	49
rs13107325	*SLC39A8*	4	T (0.07)	1.50×10^{-13}	No	50
rs10938397	*GNPDA2*	4	G (0.43)	3.78×10^{-31}	No	50
rs2112347	*FLJ35779*	5	T (0.63)	2.17×10^{-13}	No	50
rs4836133	*ZNF608*	5	A (0.48)	1.97×10^{-9}	No	50
rs681681	*CPEB4*	5	A (0.34)	1.91×10^{-9}	No	49
rs987237	*TFAP2B*	6	G (0.18)	2.90×10^{-20}	No	50
rs206936	*NUDT3*	6	G (0.21)	3.02×10^{-8}	No	50
rs9491696	*RSPO3*	6	G (0.48)	1.84×10^{-40}	No	49
rs6905288	*VEGFA*	6	A (0.56)	5.88×10^{-25}	No	49
rs1294421	*LY86*	6	G (0.61)	1.75×10^{-17}	No	49
rs1055144	*NFE2L3*	7	T (0.21)	9.97×10^{-18}	No	49
rs10968576	*LRRN6C*	9	G (0.31)	2.65×10^{-13}	No	50
rs10767664	*BNF*	11	A (0.78)	4.69×10^{-26}	No	50
rs3817334	*MTCH2*	11	T (0.40)	1.59×10^{-12}	No	50
rs4929949	*RPL27A*	11	C (0.52)	2.80×10^{-9}	No	50
rs7138803	*FAIM2*	12	A (0.38)	1.82×10^{-17}	No	50
rs718314	*ITPR2-SSPN*	12	G (0.26)	1.14×10^{-17}	No	50
rs1443512	*HOXC13*	12	A (0.24)	6.38×10^{-17}	No	49
rs4771122	*MTIF3*	13	G (0.24)	9.48×10^{-10}	No	50
rs10150332	*NRXN3*	14	C (0.21)	2.75×10^{-11}	No	50
rs11847697	*PRKD1*	14	T (0.04)	5.76×10^{-11}	No	50
rs2241423	*MAP2K5*	15	G (0.78)	1.19×10^{-18}	No	50
rs1558902	*FTO*	16	A (0.42)	4.8×10^{-120}	No	50
rs7359397	*SH2B1*	16	T (0.40)	1.88×10^{-20}	No	50
rs12444979	*GPRC5B*	16	C (0.87)	2.91×10^{-21}	No	50
rs571312	*MC4R*	18	A (0.24)	6.43×10^{-42}	No	50
rs29941	*KCTD15*	19	G (0.67)	3.01×10^{-9}	No	50
rs2287019	*QPCTL*	19	C (0.80)	1.88×10^{-16}	No	50
rs3810291	*TMEM160*	19	A (0.67)	1.64×10^{-12}	No	50
rs4823006	*ZNRF3-KREMEN1*	22	A (0.57)	1.10×10^{-11}	No	49
Diabetes						
rs340874	*PROX1*	1	C (0.52)	6.6×10^{-12}	No	47
rs560887	*G6PC2*	2	C (0.70)	8.7×10^{-218}	No	47
rs780094	*GCKR*	2	C (0.62)	5.6×10^{-38}	No	47
rs243021	*BCL11A*	2	A (0.46)	2.9×10^{-15}	No	52
rs7578326	*IRS1*	2	A (0.64)	5.4×10^{-20}	No	52

(*Continued*)

Table 4 (*Continued*)

rsID	Loci	Chr	Risk allele (Risk allele frequency)	Combined *P*-value	Known effect on CAD	Reference
rs11708067	*ADCY5*	3	A (0.78)	7.1×10^{-22}	No	47
rs11920090	*SLC2A2*	3	T (0.87)	8.1×10^{-13}	No	47
rs4457053	*ZBED3*	5	G (0.26)	2.8×10^{-12}	No	52
rs4607517	*GCK*	7	A (0.16)	6.5×10^{-92}	No	47
rs2191349	*DGKB-TMEM195*	7	T (0.52)	3.0×10^{-44}	No	47
rs972283	*KLF14*	7	G (0.55)	2.2×10^{-10}	No	52
rs11558471	*SLC30A8*	8	A (0.68)	NA	No	47
rs896854	*TP53INP1*	8	T (0.48)	9.9×10^{-10}	No	52
rs7034200	*GLIS3*	9	A (0.49)	1.0×10^{-12}	No	47
rs13292136	*CHCHD9*	9	C (0.93)	2.8×10^{-8}	No	52
rs10885122	*ADRA2A*	10	G (0.87)	2.9×10^{-16}	No	47
rs4506565	*TCF7L2*	10	T (0.31)	NA	No	47
rs10830963	*MTNR1B*	11	G (0.30)	5.8×10^{-175}	No	47
rs7944584	*MADD*	11	A (0.75)	2.0×10^{-18}	No	47
rs174550	*FADS1*	11	T (0.64)	1.7×10^{-15}	No	47
rs11605924	*CRY2*	11	A (0.49)	1.0×10^{-14}	No	47
rs231362	*KCNQ1*	11	G (0.52)	2.8×10^{-13}	No	52
rs1552224	*CENTD2*	11	A (0.88)	1.4×10^{-22}	No	52
rs1387153	*MTNR1B*	11	T (0.28)	7.8×10^{-15}	No	52
rs1531343	*HMGA2*	12	C (0.10)	3.6×10^{-9}	No	52
rs7957197	*HNF1A*	12	T (0.85)	2.4×10^{-8}	No	52
rs11634397	*ZFAND6*	15	G (0.60)	2.4×10^{-9}	No	52
rs11071657	*C2CD4B*	15	A (0.63)	3.6×10^{-8}	No	47
rs8042680	*PRC1*	15	A (0.22)	2.4×10^{-10}	No	52
rs5945326	*DUSP9*	X	A (0.79)	3.0×10^{-10}	No	52
Total cholesterol						
rs12027135	*LDLRAP1*	1	T (0.45)	4×10^{-11}	Yes	51
rs7515577	*EVI5*	1	A (0.21)	3×10^{-8}	No	51
rs2642442	*MOSC1*	1	T (0.32)	6×10^{-13}	No	51
rs514230	*IRF2BP2*	1	T (0.48)	5×10^{-14}	No	51
rs7570971	*RAB3GAP1*	2	C (0.34)	2×10^{-8}	No	51
rs2290159	*RAF1*	3	G (0.22)	4×10^{-9}	No	51
rs12916	*HMGCR*	5	T (0.39)	9×10^{-47}	No	51
rs6882076	*TIMD4*	5	C (0.35)	7×10^{-28}	No	51
rs3177928	*HLA*	6	G (0.16)	4×10^{-19}	No	51
rs2814982	*C6orf106*	6	C (0.11)	5×10^{-11}	No	51
rs9488822	*FRK*	6	A (0.35)	2×10^{-10}	No	51
rs12670798	*DNAH11*	7	T (0.23)	9×10^{-10}	No	51
rs2072183	*NPC1L1*	7	G (0.25)	3×10^{-11}	No	51
rs2081687	*CYP7A1*	8	C (0.35)	2×10^{-8}	No	51
rs2737229	*TRPS1*	8	A (0.30)	2×10^{-8}	No	51
rs2255141	*GPAM*	10	G (0.30)	2×10^{-10}	No	51
rs10128711	*SPTY2D1*	11	C (0.28)	3×10^{-8}	No	51
rs7941030	*UBASH3B*	11	C (0.38)	2×10^{-10}	No	51
rs11065987	*BRAP*	12	A (0.42)	7×10^{-12}	No	51
rs1169288	*HNF1A*	12	A (0.33)	1×10^{-14}	No	51
rs2000999	*HPR*	16	G (0.20)	3×10^{-24}	No	51
rs4420638	*CILP2*	19	T (0.07)	3×10^{-38}	No	51
rs492602	*FLJ36070*	19	A (0.49)	2×10^{-10}	No	51
rs2277862	*ERGIC3*	20	C (0.15)	4×10^{-10}	No	51
rs2902940	*MAFB*	20	A (0.29)	6×10^{-11}	No	51
Triglycerides						
rs2131925	*ANGPTL3*	1	T (0.32)	9×10^{-43}	No	51

(*Continued*)

Table 4 (*Continued*)

rsID	Loci	Chr	Risk allele (Risk allele frequency)	Combined *P*-value	Known effect on CAD	Reference
rs1042034	*APOB*	2	T (0.22)	1×10^{-45}	Yes	51
rs1260326	*GCKR*	2	C (0.41)	6×10^{-133}	No	51
rs10195252	*COBLL1*	2	T (0.40)	2×10^{-10}	No	51
rs645040	*MSL2L1*	3	T (0.22)	3×10^{-8}	No	51
rs442177	*KLHL8*	4	T (0.41)	9×10^{-12}	No	51
rs9686661	*MAP3K1*	5	C (0.20)	1×10^{-10}	No	51
rs2247056	*HLA*	6	C (0.25)	2×10^{-15}	No	51
rs13238203	*TYW1B*	7	C (0.04)	1×10^{-9}	No	51
rs17145738	*MLXIPL*	7	C (0.12)	6×10^{-58}	No	51
rs11776767	*PINX1*	8	G (0.37)	1×10^{-8}	No	51
rs1495741	*NAT2*	8	A (0.22)	5×10^{-14}	No	51
rs12678919	*LPL*	8	A (0.12)	2×10^{-115}	Yes	51
rs2954029	*TRIB1*	8	A (0.47)	3×10^{-55}	Yes	51
rs10761731	*JMJD1C*	10	A (0.43)	3×10^{-12}	No	51
rs2068888	*CYP26A1*	10	G (0.46)	2×10^{-8}	No	51
rs174546	*FADS1-2-3*	11	C (0.34)	5×10^{-24}	No	51
rs964184	*APOA1*	11	C (0.13)	7×10^{-240}	Yes	51
rs11613352	*LRP1*	12	C (0.23)	4×10^{-10}	No	51
rs2412710	*CAPN3*	15	G (0.02)	2×10^{-8}	No	51
rs2929282	*FRMD5*	15	A (0.05)	2×10^{-11}	No	51
rs11649653	*CTF1*	16	C (0.40)	3×10^{-8}	No	51
rs439401	*APOE*	19	C (0.36)	1×10^{-30}	No	51
rs5756931	*PLA2G6*	22	T (0.40)	4×10^{-8}	No	51
Low-density lipoprotein						
rs2479409	*PCSK9*	1	A (0.23)	2×10^{-28}	No	51
rs629301	*SORT1*	1	T (0.22)	1×10^{-170}	Yes	51
rs1367117	*APOB*	2	G (0.30)	4×10^{-114}	Yes	51
rs499376	*ABCG5/8*	2	T (0.30)	2×10^{-47}	Yes	51
rs3757354	*MYLIP*	6	C (0.22)	1×10^{-11}	No	51
rs1800562	*HFE*	6	G (0.06)	6×10^{-10}	No	51
rs1564348	*LPA*	6	T (0.17)	2×10^{-17}	Yes	51
rs11136341	*PLEC1*	8	A (0.40)	4×10^{-13}	No	51
rs9411489	*ABO*	9	C (0.20)	6×10^{-13}	Yes	51
rs11220462	*ST3GAL4*	11	G (0.14)	1×10^{-15}	No	51
rs8017377	*NYNRIN*	14	G (0.47)	5×10^{-11}	No	51
rs7206971	*OSBPL7*	17	G (0.49)	2×10^{-8}	No	51
rs6511720	*LDLR*	19	G (0.11)	4×10^{-117}	Yes	51
rs4420638	*APOE*	19	A (0.17)	9×10^{-147}	No	51
rs6029526	*TOP1*	20	T (0.47)	4×10^{-19}	No	51
High-density lipoprotein						
rs4660293	*PABPC4*	1	A (0.23)	4×10^{-10}	No	51
rs1689800	*ZNF648*	1	A (0.35)	3×10^{-10}	No	51
rs4846914	*GALNT2*	1	A (0.40)	4×10^{-21}	No	51
rs2972146	*IRS1*	2	T (0.37)	3×10^{-9}	No	51
rs12328675	*COBLL1*	2	T (0.13)	3×10^{-10}	No	51
rs13107325	*SLC39A8*	4	C (0.07)	7×10^{-11}	No	51
rs6450176	*ARL15*	5	G (0.26)	5×10^{-8}	No	51
rs2814944	*C6orf106*	6	G (0.16)	4×10^{-9}	No	51
rs605066	*CITED2*	6	T (0.42)	3×10^{-8}	No	51
rs1084651	*LPA*	6	G (0.16)	3×10^{-8}	Yes	51
rs2293889	*TRPS1*	8	G (0.41)	6×10^{-11}	No	51
rs4731702	*KLF14*	7	C (0.48)	1×10^{-15}	No	51
rs9987289	*PPP1R3B*	8	G (0.09)	6×10^{-25}	No	51

(*Continued*)

Table 4 (*Continued*)

rsID	Loci	Chr	Risk allele (Risk allele frequency)	Combined *P*-value	Known effect on CAD	Reference
rs581080	*TTC39B*	9	C (0.18)	3×10^{-12}	No	51
rs1883025	*ABCA1*	9	C (0.25)	2×10^{-33}	No	51
rs2923084	*AMPD3*	11	A (0.17)	5×10^{-8}	No	51
rs3136441	*LRP4*	11	T (0.15)	3×10^{-18}	No	51
rs7134594	*PDE3A*	12	C (0.42)	4×10^{-8}	No	51
rs7134594	*MVK*	12	T (0.47)	7×10^{-15}	No	51
rs4759375	*SBNO1*	12	C (0.06)	7×10^{-9}	No	51
rs4765127	*ZNF664*	12	G (0.34)	3×10^{-10}	No	51
rs838880	*SCARB1*	12	T (0.31)	3×10^{-14}	No	51
rs1532085	*LIPC*	15	G (0.39)	3×10^{-96}	No	51
rs2652834	*LACTB*	15	G (0.20)	9×10^{-9}	No	51
rs3764261	*CETP*	16	C (0.32)	7×10^{-380}	No	51
rs16942887	*LCAT*	16	G (0.12)	8×10^{-33}	No	51
rs2925979	*CMIP*	16	C (0.30)	2×10^{-11}	No	51
rs11869286	*STARD3*	17	C (0.34)	1×10^{-13}	No	51
rs4148008	*ABCA8*	17	C (0.32)	2×10^{-10}	No	51
rs4129767	*PGS1*	17	A (0.49)	8×10^{-9}	No	51
rs7241918	*LIPG*	18	T (0.17)	3×10^{-49}	No	51
rs12967135	*MC4R*	18	G (0.23)	7×10^{-9}	No	51
rs7255436	*ANGPTL4*	19	A (0.47)	3×10^{-8}	No	51
rs737337	*LOC55908*	19	T (0.08)	3×10^{-9}	No	51
rs386000	*LILRA3*	19	G (0.20)	4×10^{-19}	No	51
rs1800961	*HNF4A*	20	C (0.03)	1×10^{-15}	No	51
rs6065906	*PLTP*	20	T (0.18)	2×10^{-22}	No	51
rs181362	*UBE2L3*	22	C (0.20)	1×10^{-8}	No	51

rsID	Loci	Chr	Risk allele (Risk allele frequency)	*P*-value		Known effect On CAD	Reference
				SBP	DBP		
Blood pressure							
rs2932538	*MOV10*	1	G (0.75)	1.2×10^{-9}	9.9×10^{-10}	No	48
rs17367504	*MTHFR-NPPB*	1	G (0.15)	8.7×10^{-22}	3.5×10^{-19}	No	48
rs13002573	*FIGN*	2	G (0.20)	3.25×10^{-7}	4.02×10^{-2}	No	53
rs1446468	*FIGN*	2	T (0.53)	1.82×10^{-12}	6.88×10^{-9}	No	53
rs319690	*MAP4*	3	T (0.51)	4.74×10^{-8}	1.84×10^{-8}	No	53
rs13082711	*SLC4A7*	3	T (0.78)	1.5×10^{-6}	3.8×10^{-9}	No	48
rs419076	*MECOM*	3	T (0.47)	1.80×10^{-13}	2.1×10^{-12}	No	48
rs3774372	*ULK4*	3	T (0.83)	0.39	9.0×10^{-14}	No	48
rs871606	*CHIC2*	4	T (0.86)	3.04×10^{-4}	8.85×10^{-1}	No	53
rs13107325	*SLC39A8*	4	T (0.05)	3.3×10^{-14}	2.3×10^{-17}	No	48
rs13139571	*GUCY1A3-GUCY1B3*	4	C (0.76)	1.2×10^{-6}	2.2×10^{-10}	Yes	48
rs1458038	*FGF5*	4	T (0.29)	1.5×10^{-23}	8.5×10^{-25}	No	48
rs1173771	*NPR3-C5orf23*	5	G (0.60)	1.8×10^{-16}	9.1×10^{-12}	No	48
rs11953630	*EBF1*	5	T (0.37)	3.0×10^{-11}	3.8×10^{-13}	No	48
rs1799945	*HFE*	6	G (0.14)	7.7×10^{-12}	1.5×10^{-15}	No	48
rs805303	*BAT2-BAT5*	6	G (0.61)	1.5×10^{-11}	4.4×10^{-10}	No	48
rs17477177	*PIK3CG*	7	T (0.72)	5.67×10^{-11}	1.40×10^{-1}	No	53
rs2071518	*NOV*	8	T (0.17)	2.08×10^{-2}	3.89×10^{-3}	No	53
rs2782980	*ADRB1*	10	T (0.20)	7.66×10^{-7}	9.60×10^{-8}	No	53
rs4373814	*CACNB2*	10	G (0.55)	4.8×10^{-11}	4.4×10^{-10}	No	48
rs932764	*PLCE1*	10	G (0.44)	7.1×10^{-16}	8.1×10^{-7}	No	48
rs1813353	*CACNB2*	10	T (0.68)	2.6×10^{-12}	2.3×10^{-15}	No	48
rs4590817	*C10orf107*	10	G (0.84)	4.0×10^{-12}	1.3×10^{-12}	No	48
rs11191548	*CYP17A1-NT5C2*	10	T (0.91)	6.9×10^{-26}	9.4×10^{-13}	Yes	48

(*Continued*)

Table 4 (*Continued*)

rsID	Loci	Chr	Risk allele (Risk allele frequency)	*P*-value		Known effect On CAD	Reference
				SBP	DBP		
rs11222084	*ADAMTS8*	11	T (0.38)	4.00×10^{-4}	3.44×10^{-2}	No	53
rs7129220	*ADM*	11	G (0.89)	3.0×10^{-12}	6.4×10^{-8}	No	48
rs633185	*FLJ32810-TMEM133*	11	G (0.28)	1.2×10^{-17}	2.0×10^{-15}	No	48
rs381815	*PLEKHA7*	11	T (0.26)	5.3×10^{-11}	5.3×10^{-10}	No	48
rs17249754	*ATP2B1*	12	G (0.84)	1.8×10^{-18}	1.2×10^{-14}	No	48
rs3184504	*SH2B3*	12	T (0.47)	3.8×10^{-18}	3.6×10^{-25}	Yes	48
rs10850411	*TBX5-TBX3*	12	T (0.70)	5.4×10^{-8}	5.4×10^{-10}	No	48
rs2521501	*FURIN-FES*	15	T (0.31)	5.2×10^{-19}	1.9×10^{-15}	Yes	48
rs1378942	*CYP1A1-ULK3*	15	C (0.35)	5.7×10^{-23}	2.7×10^{-26}	No	48
rs17608766	*GOSR2*	17	T (0.86)	1.1×10^{-10}	0.017	No	48
rs12940887	*ZNF652*	17	T (0.38)	1.8×10^{-10}	2.3×10^{-14}	No	48
rs1327235	*JAG1*	20	G (0.46)	1.9×10^{-8}	1.4×10^{-15}	No	48
rs6015450	*GNAS-EDN3*	20	G (0.12)	3.9×10^{-23}	5.6×10^{-23}	No	48

Abbreviations: Chr, chromosome; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure.

is possible to determine a person's genetic risk profile before the development of an adverse cardiovascular risk factor profile, which would allow primary prevention measures to be undertaken earlier in life.[2,63] Another advantage is the lower cost and higher replicability of genotyping compared with other cardiovascular risk factors. Among the limitations, the small effect sizes of known variants are most notable, despite the highly statistically significant associations between these variants and CAD risk.

Several studies have evaluated the effects on the predictive capacity of classical risk functions when genetic factors are taken into account. While most of the studies have found that these genetic variants (usually expressed as a single variable corresponding to the number of risk alleles carried, known as a genetic risk score) are associated with risk of future CAD events, they have not been found to improve the ability to discriminate between those individuals at particular risk who will develop the disease, although they do improve the reclassification of individuals into more appropriate risk categories, especially those at intermediate risk (Table 5).

Pharmacogenomics

Pharmacogenomics is the study of the relationship between genetic variability and a patient's response to drug treatment, ie, the efficacy of the drug and/or its adverse effects.[64–68] Candidate gene and GWAS approaches have been used to identify genetic variants associated with variability in drug response, including several examples in the cardiovascular field,[69,70] the majority of which have focused on statins, antiplatelet drugs, oral anticoagulants, or beta-blockers. The case of statins and the antiplatelet agent clopidogrel provide two interesting examples in this area.

Statins are widely prescribed to reduce plasma cholesterol levels and cardiovascular risk, and although the majority of patients show a 30%–50% reduction in LDL cholesterol, high interindividual variability is observed.[71] Several genetic variants in the *HMGCR*, *APOE*, *CETP*, and *CLMN* genes have been reported to be associated with this interindividual variability, but the results have been discordant.[69,70] Similarly, a variant in the *KIF6* gene has been reported to modulate the effect of statins on clinical outcome,[72,73] but recent studies have not corroborated this finding.[74,75] Finally, more than one variant in the *SLCO1B1* gene is consistently associated with the risk of simvastatin-induced myopathy, with an odds ratio >4.[69,76]

Our second example concerns the prodrug clopidogrel, which is converted into an active metabolite that selectively and irreversibly binds to the P2Y12 receptor on the platelet membrane. Conversion is achieved by the hepatic cytochrome P450 system in a two-step oxidative process, and cytochrome P450 2C19 is involved in both of these steps. The response to treatment with clopidogrel varies markedly between individuals, and the causes of a poor response are not clearly understood, but have been suggested to be related to clinical, cellular, or genetic factors.[66,77,78] In March 2010, the US Food and Drug Administration added a "boxed warning" to the labeling of clopidogrel, including a reference to patients who do not effectively metabolize the drug and therefore may not receive the full benefits on the basis of their genetic characteristics.[79] Recently, the American College of Cardiology Foundation and the American Heart Association have published a consensus document addressing this US Food and Drug Administration warning,[80] stating that the role of genetic tests and the clinical implications and consequences

Table 5 Main characteristics and results of studies assessing improvement of predictive capacity of classical cardiovascular risk functions after inclusion of genetic information

Author	Population	Clinical outcome	Genetic variants	Other covariates		Results			
				Risk factors	Family history	Association	Discrimination	NRI	Clinical NRI
Case-control									
Davies et al[105]	OHGS 3,323 Ca/2,319 Co WTCC: 1,926 Ca/2,938 Co	CAD	One SNP (9p21) 12 SNPs (related and unrelated CVRF)	Yes	No	NR	ΔAUC 0.003 ΔAUC 0.008‡	–	–
Anderson et al[106]	Patients undergoing coronary angiography: 1,086 Ca/482 Co	CAD	5 SNPs (related and unrelated CVRF)	Yes	Yes	OR 1.24‡	ΔAUC 0.008	16.0%‡	28.3%‡
Qi et al[107]	Hispanic: 1,989 Ca/2,096 Co	MI	3 SNPs (related and unrelated CVFR)	Yes	No	OR 1.18‡	ΔAUC 0.010‡	–	–
Qi et al[108]	Type II DM patients: 1,076 Ca/1,430 Co	CAD	5 SNPs (related and unrelated CVRF)	Yes	No	OR 1.19‡		–	–
Lv et al[109]	Chinese Han population: 1,007 Ca/889 Co	CAD	8 SNPs (related and unrelated CVRF)	Yes	No	OR 1.28‡	ΔAUC 0.022‡	–	–
Patel et al[110]	US population: 1,338 Ca/ 1,649 Co (>70 years)	MI <70 years	11 SNPs	Yes	Yes	OR 1.12‡	ΔAUC 0.012‡	–	–
Case-cohort									
Hughes et al[111]	Middle-aged men, European general population 632 Ca/1,361 subcohort	CAD	11 SNPs + two haplotypes 11 SNPs + 4 SNPs (unrelated CVRF)	Yes Yes	No No	NR NR	ΔAUC 0.009 ΔAUC 0.011‡	7.5%‡ 6.5%‡	6.3% 5.1%
Vaarhorst et al[112]	European general population 742 Ca/2,221 subcohort	12.1 years follow-up, CAD	29 SNPs (unrelated CVRF)	Yes	No	HR 1.12‡		2.8%‡	NR
Cohort									
Morrison et al[113]	ARIC, US general population 13,907	13 years follow-up, 1,452 CAD	10 SNPs – White population 11 SNPs – Black population	Yes	No	HR 1.10‡ HR 1.20‡	ΔAUC 0.002 ΔAUC 0.011‡	NR	NR
Kathiresan et al[114]	Malmö, European general population, 4,232	10.6 years follow-up, 238 CVD	9 SNPs, lipid-related	Yes	No	HR 1.15‡	ΔAUC 0.003		
Talmud et al[115]	NPHS-II, UK middle-aged men, 2,742	15 years follow-up, 270 CAD	1 SNP (9p21)	Yes	Yes	AA versus AG 1.38‡ AA versus GG 1.57‡	ΔAUC 0.02	13.8%‡	NR
Brautbar et al[116]	ARIC, US general population (Whites), 9,998	14.6 years follow-up, 1,349 CAD	1 SNP (9p21)	Yes	No	HR 1.20‡	ΔAUC 0.004*	0.8%	6.2‡
Paynter et al[117]	WGHS, US middle-aged White women, 22,192	10.2 years follow-up, 1,349 CVD	1 SNP (9p21)	Yes	Yes	AA versus AG 1.25‡ AA versus GG 1.32‡	ΔAUC 0.002	Framingham, 2.7% Reynolds, 0.2%	NR
Paynter et al[118]	WGHS, US White women, 19,313	12.3 years follow-up, 777 CVD	101 SNPs 12 SNPs (related and unrelated CVRF)	Yes	Yes	HR 1.00 HR 1.04	ΔAUC 0.000 ΔAUC 0.001	0.5% 0.5%	NR

(*Continued*)

Table 5 (*Continued*)

Author	Population*	Clinical outcome†	Genetic variants	Other covariates		Results¶			
				Risk factors	Family history	Association	Discrimination	NRI	Clinical NRI
Ripatti et al[119]	General European population, 30,725	10.7 years follow-up, 1,264 CHD	13 SNPs (related and unrelated CVRF)	Yes	Yes	HR 1.66 (Q5 versus Q1)‡	ΔAUC 0.001	2.2%	9.7%‡
Shiffman et al[120]	CHS, US old population (>65 years), 4,284	12.6 years follow-up, MI	1 SNP (9p21) 1 SNP (KIF6719 Arg) carriers	Yes	No	HR 1.22 (White men)‡ HR 1.16 (White women)‡ HR NR (Black men) HR 1.42 (White men)‡ HR 1.05 (White women)	ΔAUC 0.005 ΔAUC 0.002 ΔAUC 0.034 ΔAUC 0.015‡ ΔAUC –0.001	2.1% –1.8% 18.2%‡ 2.7% 0.7%	
Thanassoulis et al[121]	Framingham, US general population, 3,014	11 years follow-up, 182 hard CHD	13 SNPs (related and unrelated CVRF)	Yes	Yes	HR 1.07‡	ΔAUC 0.002	19.0%‡	NR
Lluis-Ganella et al[122]	General population, Framingham 3,537 + REGICOR 2,351	11.9 years follow-up, 536 CHD	8 SNPs (unrelated CVRF)	Yes	Yes	HR 1.13‡	ΔAUC No	6.4%	17.4%‡
Gransbo et al[123]	Malmö, 24,777	11.7 years follow-up, 2,668 CVD	9p21 variant	Yes	No	HR 1.17‡	ΔAUC 0.001	1.2%‡	–
Isaacs et al[124]	Erasmus Family study 2,269 + Rotterdam Study 8,130	9.5 years follow-up, 924 CHD	Lipid-related GRS	Yes	No	GRS_{TC} HR 1.09‡ GRS_{LDL} HR 1.08‡ GRS_{HDL} HR 0.99 GRS_{TG} HR 1.04	ΔAUC 0.000	–	–
Ganna et al[125]	6 Swedish cohorts, 10,612	781 CHD	GRS_{global}, 395 GRS_{CHD}, 46	Yes	No	HR 1.54‡ HR 1.52‡	ΔAUC 0.002 ΔAUC 0.004‡	4.2%‡ 4.9%‡	–
Tikkanen et al[126]	4 Finnish cohorts, 24,124	12 years follow-up, 1,093 CHD	28 SNPs (related and unrelated CVRF)	Yes	Yes	HR 1.27‡	ΔAUC 0.003‡	5.0%‡	27.0%‡

Notes: ‡*P*-value<0.05.

Abbreviations: ARIC, Atherosclerosis Risk in Communities study; CAD, coronary artery disease; MI, myocardial infarction; CVD, cardiovascular disease; OHGS, Ottawa Heart Genomics Study; WTCCC, Wellcome Trust Case Control Consortium; Ca, Cases; Co, Controls; DM, diabetes mellitus; NPHS-II: Northwick Park Heart Study II; WGHS, Women Genome Health Study; CHS, Cardiac Health Study; REGICOR, Registre Gironi del Cor (Girona Heart Registry); OR, odds ratio; HR, hazard ratio; NR, not reported; AUC, area under the receiver operating curve; NRI, Net Reclassification Index; CVRF, cardiovascular risk factors; GRS, genetic risk score; SNP, single nucleotide polymorphism.

of this testing remain to be determined. Moreover, three recent meta-analyses question the validity of this warning based on the fact that the reported associations are mainly driven by studies with small sample sizes;[78,81,82] thus, they concluded that current evidence does not support the use of individualized clopidogrel regimens guided by the *CYP2C19* genotype.

Conclusion

In the past 7 years, GWAS have contributed substantially to our understanding of the genetic architecture of complex diseases, including CAD. To date, approximately 40 unique loci have been found to be robustly associated with disease risk in large samples from several populations, a much higher number than those identified by linkage and candidate gene association studies. However, these variants explain only a small proportion of the heritability of CAD.[40] Additional efforts to improve the analysis strategies, including new imputation and meta-analytic methods, analysis of gene-gene and gene-environment interactions, the integration of different omics, and use of sequencing technologies, are being performed.[83–85]

Although it is not yet clear if or how all of this information on the genetic architecture of CAD can be translated into clinical practice,[86] we already have some exciting examples of its potential utility. To identify new therapeutic targets, we must first make the difficult transition from the statistical associations reported in GWAS to the functional mechanisms behind these associations. Research on the use of genetic information to improve cardiovascular risk estimation in individuals at intermediate risk can be carried out as a second step or in parallel, and further studies to develop new ways to include this information in risk functions, to evaluate its cost-effectiveness, and to explore the ethical issues are also warranted.[87–89] Finally, although medicine is always a "personalized science and art", use of genetic information to identify the most effective and least harmful drug for each patient is also a goal of so-called genetic personalized medicine.

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Disclosure

The authors report no other conflicts of interest in this work.

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