Reviews

Genetics of Coronary Artery Disease in the 21st Century

Address for correspondence:
Robert Roberts, MD
John and Jennifer Ruddy Canadian Cardiovascular Genetics Centre
University of Ottawa Heart Institute
40 Ruskin Street
Ottawa, ON K1Y 4W7 Canada
rroberts@ottawaheart.ca

Robert Roberts, MD, FRCPC, MACC and Alexandre F. R. Stewart, PhD
John and Jennifer Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, Ottawa, Canada

ABSTRACT

Coronary artery disease (CAD) is still the number-one killer in the world, and clinical trials indicate that it is preventable. Mortality and morbidity can be reduced by at least 30% to 40% by treating known risk factors. Genetic susceptibility is claimed to account for 50% of predisposition. The challenge of preventing CAD in this century, as claimed by some investigators, will require a more comprehensive prevention and treatment of environmental and genetic risk factors. Part of that challenge has been met by genome-wide association studies, which have identified 36 genetic variants with increased risk for CAD. All of these genetic variants have reached genome-wide significance (5×10^{-8}) and replicate in independent populations with large sample sizes. More than 50% of these variants occur in >50% of the population, with 10 occurring in >75% of the population. The challenge and the opportunity lie in the observation that >66% of these risk variants do not mediate their risk through known conventional risk factors. These results suggest that genetic predisposition for CAD is conferred by common DNA variants and many factors contributing to the pathogenesis of CAD are yet to be determined. Comprehensive prevention of CAD will most likely require combating genetic and environmental risk factors. We are on the cusp of genetic screening, and new therapeutic targets are becoming available to manage both genetic and environmental risk factors for CAD.

Introduction

The clinical mantra of the 21st century is prevention, through which coronary artery disease (CAD) is likely to be markedly attenuated, if not eliminated. In 1961, the major risk factors for CAD were identified,[1] followed by the Surgeon General's announcement of smoking as a risk factor in 1964.[2] Elevated cholesterol, hypertension, obesity, smoking, and a sedentary way of life were well established by several studies, including the Framingham longitudinal follow-up studies.[1] In randomized placebo-controlled clinical trials, intense modification of these conventional risk factors for CAD is associated with 30%–40% reduction in mortality and morbidity.[3,4] Investigators have claimed prevention of CAD is an attainable goal for the 21st century.[5,6]

The 21st century appears to be taking this challenge seriously; the first new risk factor for CAD in 2007 was independently and simultaneously identified by 2 groups,[7,8] namely the genetic variant at 9p21. It is not only the first new risk factor to be defined since 1964, but it is the first genetic risk factor to be defined for CAD. The discovery of 9p21 in 2007 catalyzed a genetic epoch; in the subsequent 5 years it was followed by the discovery of 36 genetic risk variants for CAD and a total of >1100 variants associated with risk for >160 diseases. This review will concentrate on the 36 genetic risk variants predisposing to CAD that have been identified and confirmed in large populations around the world.

Evidence for Genetic Predisposition to Coronary Artery Disease

Multiple epidemiological, familial, and other studies have documented a genetic predisposition for CAD. Overall these studies indicate that genetic predisposition accounts for about 50% of susceptibility to CAD.[9] Studies from Framingham have shown that a family history of CAD or stroke is associated with a 2.4-fold increased risk of CAD in men and a 2.2-fold increase in women.[10] Studies have documented a 2- to 3-fold increase in risk of CAD in first-degree relatives.[11,12] In families with CAD onset before the age of 46, heritability was estimated to be nearly 100%; whereas within families with older-onset cases, the heritability ranged from 15% to 30%.[13] Several studies involving twins, particularly those of the Danish Twin Registry,[14] showed a higher incidence of CAD and death in monozygotic twins compared with dizygotic twins, averaging 44% vs 14%. In more recent studies, such as the INTERHEART study, a family history of CAD increases the risk to 1.5 and to 1.45 after corrections for other risk factors.[6] A family history of myocardial infarction (MI) in the Prospective Cardiovascular Münster (PROCAM) study indicated it was an independent risk factor for CAD.[15] It is perhaps important to note that epidemiological studies have

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indicated that genetic predisposition exists for essentially all diseases.

Coronary Artery Disease and the Genome-Wide Association Study

It has been a golden era for rare single-gene disorders. Of the estimated 6000 single-gene disorders, the genes for >2000 have been discovered.[16] The chromosomal location of these genes was mapped by genotyping the DNA of pedigrees that include individuals affected by the disease using a few hundred DNA markers followed by linkage analysis. These diseases are rare (<0.1%) and are inherited in specific Mendelian patterns. In contrast, polygenic diseases such as CAD and hypertension are due to more common genes and have their genetic predisposition transmitted by multiple genes, each imparting only minimal to moderate increased risk for the disease. Genetic-linkage analysis of pedigrees is not applicable to map genetic predisposition for polygenic disorders. Polygenic disorders require thousands of DNA markers and thousands of unrelated individuals analyzed by a different method, referred to as the case-control association study.[17] The DNA markers required for this approach became available in 2005 in the form of microarrays for genotyping of single nucleotide polymorphisms (SNPs). These SNPs are distributed throughout the genome, with approximately 1 SNP per 1000 nucleotides, and are estimated to account for >80% of human variation, including susceptibility to disease.[18]

The first computerized microarray was assembled in 2005 containing 50 0000 SNPs, with a more recent version of 1 million SNPs.[19] This, in combination with high-throughput platforms, made it possible to analyze DNA samples from thousands of cases and controls. The basis of the case-control association study is very simple. One compares the frequency of the DNA markers in cases to that of their frequency in controls. A greater frequency of a SNP in cases indicates the SNP is in close proximity to a genetic risk variant for the disease. It also requires DNA markers showing a significant association with CAD in the discovery population be confirmed in an independent population. Because the SNPs are scattered throughout the genome, albeit unevenly, it is referred to as a genome-wide association study (GWAS). The GWAS approach is unbiased and enables one to scan the whole of the human genome without a preconception of which marker associates with the disease. The results of the GWAS over a very short time have been remarkable, identifying >1100 risk variants affecting >160 diseases.[20,21]

Thirty-Six Genetic Risk Variants With Predisposition for CAD

We were fortunate in 2007 to identify the first genetic risk variant for CAD, 9p21.[7] Independently and simultaneously, the deCode Group in Iceland also identified 9p21 to be associated with increased risk for CAD.[8] In a short interval, 9p21 was confirmed by several groups throughout the world to be a risk variant for CAD and was followed by the mapping of 11 other genetic risk variants for CAD.[22] Studies confirmed most genetic variants would have modest to minimal effect on risk, with relative risk ratios varying from 10% to 30%. In response to this observation, we and several GWAS pursuing genetic predisposition for CAD were brought together by Drs Schunkert and Samani into an international consortium referred to as CARDIoGRAM (Coronary Artery Disease Genome-Wide Replication and Meta-Analysis).[23] It is the largest collaboration in cardiology, with an estimated total budget of >$200 million.

CARDIoGRAM resulted in a discovery population with a sample size of 86 995 (22 233 cases and 64 762 controls) and a replication sample size of 56682, all of European ancestry. We identified 13 new genetic risk variants for CAD and confirmed 10 of the previous identified risk variants.[24] Reilly et al,[25] in collaboration with CARDIoGRAM investigators, identified 2 novel risk variants for CAD, ADAMTS7 and the ABO blood group locus. The Coronary Artery Disease (C4D) Genetics Consortium, with a sample size of 71 075, mapped 4 novel genetic variants related to CAD.[26] Wang et al mapped a novel genetic variant at 6p21 that increases the risk for CAD in the Chinese population but has no effect in the Caucasian population.[27] The IBC50K CAD Consortium et al[28] mapped 4 novel risk variants for CAD with a sample size of 50 588 (15 596 cases and 34 992 controls) with replication in a sample size of 57 594 (17 121 cases and 40 473 controls). So, in a short span of 5 years, 36 genetic risk variants associated with increased risk for CAD were identified, as shown in the Table 1.

Genetic Predisposition: A Prerequisite for Comprehensive Prevention of Coronary Artery Disease

Thirty-six risk variants strongly indicate the importance of genetic predisposition for CAD and also confirm that these variants are even more common than expected. Because these variants account for a small proportion of expected genetic predisposition, there are more to be discovered. More than 50% of these genetic variants occur in >50% of the population, and ten of the risk variants occur in >75% of the population. As predicted, most variants for CAD impart minimal risk, varying from 6% to 17%. The major surprise is that >66% of the risk variants mediate their risk independent of known risk factors (eg, cholesterol). This provides ample evidence that there are molecular pathways contributing to the pathogenesis of atherosclerosis and its sequelae that have yet to be discovered. Prevention of CAD is unlikely to be successful without the screening and prevention of genetic predisposing factors. Further, the novel networks mediating genetic risk for CAD are likely to provide many molecular targets for development of new drugs and dietary factors that will play a major role in the future management of CAD and MI. Lastly, DNA risk variants offer several advantages over blood biomarkers, as they do not change during one's lifetime and neither do they change with age, meals, drugs, or environmental stimuli. Thus, DNA genotyped at birth is adequate for a lifetime.

Genetic Implication for the Management of Myocardial Infarction

Because MI is almost always superimposed on coronary atherosclerosis, most GWAS have used these phenotypes interchangeably. However, it is self-evident that certain

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Table 1. Thirty-Six Genetic Variants Predisposing to Coronary Artery Disease/Myocardial Infarction

Band	SNP	Nearby Genes	Risk Allele Frequency (Allele)	OR (95% CI)	Year Discovered
Associated with lipoproteins					
1p13.3	rs599839	SORT1	0.78 (A)	1.29 (1.18–1.40)	2007
1p32.3	rs11206510	PCSK9	0.82 (T)	1.15 (1.10–1.21)	2009
19p13.2	rs1122608	LDLR	0.77 (G)	1.14 (1.09–1.19)	2009
2p21	rs4299376	ABCG8	0.29 (G)	1.07 (1.04–1.11)	2011
8q24.13	rs10808546	TRIB1	0.65 (A)	1.08 (1.04–1.12)	2011
11q23.3	rs964184	ZNF259, APOA5-A4-C3-A1	0.13 (G)	1.13 (1.10–1.16)	2011
19q13.32	rs2075650	APOE	0.14 (G)	1.14 (1.09–1.19)	2011
Associated with hypertension					
12q24.12	rs3184504	SH2B3	0.44 (T)	1.13 (1.08–1.18)	2009
10q24.32	rs12413409	CYP17A1, CNNM2, NT5C2	0.89 (G)	1.12 (1.08–1.16)	2011
Associated with myocardial infarction (MI)					
9q34.2	rs579459	ABO	0.21 (C)	1.10 (1.07–1.13)	2011
Mechanism of risk unknown					
9p21.3	rs4977574	CDKN2A, CDKN2B	0.46 (G)	1.25 (1.18–1.31)	2007
1q41	rs17465637	MIA3	0.74 (C)	1.20 (1.12–1.30)	2007
10q11.21	rs1746048	CXCL12	0.87 (C)	1.33 (1.20–1.48)	2007
2q33.1	rs6725887	WDR12	0.15 (C)	1.16 (1.10–1.22)	2009
6p24.1	rs12526453	PHACTR1	0.67 (C)	1.13 (1.09–1.17)	2009
21q22.11	rs9982601	MRPS6	0.15 (T)	1.19 (1.13–1.27)	2009
6q25.3	rs3798220	LPA	0.02 (C)	1.92 (1.48–2.49)	2009
3q22.3	rs2306374	MRAS	0.18 (C)	1.15 (1.11–1.19)	2009
10p11.23	rs2505083	KIAA1462	0.42 (C)	1.07 (1.04–1.09)	2010
1p32.2	rs17114036	PPAP2B	0.91 (A)	1.17 (1.13–1.22)	2011
5q31.1	rs2706399	IL5	0.48 (A)	1.02 (1.01–1.03)	2011
6p21.31	rs17609940	ANKS1A	0.75 (G)	1.07 (1.05–1.10)	2011
6q23.2	rs12190287	TCF21	0.62 (C)	1.08 (1.06–1.10)	2011
7q22.3	rs10953541	BCAP29	0.75 (C)	1.08 (1.05–1.11)	2011
7q32.2	rs11556924	ZC3HC1	0.62 (C)	1.09 (1.07–1.12)	2011
10q23.31	rs1412444	LIPA	0.34 (T)	1.09 (1.07–1.12)	2011
11q22.3	rs974819	PDGF	0.29 (T)	1.07 (1.04–1.09)	2011
13q34	rs4773144	COL4A1, COL4A2	0.44 (G)	1.07 (1.05–1.09)	2011
14q32.2	rs2895811	HHIPL1	0.43 (C)	1.07 (1.05–1.10)	2011
15q25.1	rs3825807	ADAMTS7	0.57 (A)	1.08 (1.06–1.10)	2011
17p13.3	rs216172	SMG6, SRR	0.37 (C)	1.07 (1.05–1.09)	2011
17p11.2	rs12936587	RASD1, SMCR3, PEMT	0.56 (G)	1.07 (1.05–1.09)	2011

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Table 1. *Continued*

Band	SNP	Nearby Genes	Risk Allele Frequency (Allele)	OR (95% CI)	Year Discovered
17q21.32	rs46522	UBE2Z, GIP, ATP5G1, SNF8	0.53 (T)	1.06 (1.04–1.08)	2011
5p13.3	rs11748327	IRX1, ADAMTS16	0.76 (C)	1.25 (1.18–1.33)	2011
6p22.1	rs6929846	BTN2A1	0.06 (T)	1.51 (1.28–1.77)	2011
6p24.1	rs6903956	C6orf105	0.07 (A)	1.65 (1.44–1.90)	2011

Abbreviations: A, adenine; C, cytosine; CI, confidence interval; G, guanine; OR, odds ratio; SNP, single nucleotide polymorphism; T, thymine.

genes will relate to plaque rupture and/or thrombosis, rather than the process of atherosclerosis. The rapid explosion in the mapping of risk variants for CAD has not provided ample time to explore the biology and function of most of these variants. In fact, of the variants of unknown function, only 1 has been explored, namely 9p21. There is consistent agreement that 9p21 acts at the vessel wall and contributes to the pathogenesis of atherosclerosis and is not involved with the precipitation of MI.[29–32] Only 1 risk variant has been documented to be associated with MI, namely the ABO blood group locus.[25] Genome-wide association studies consistently show A and B genes to associate with MI and exhibit no association with coronary atherosclerosis.[25] This association with MI has been postulated from epidemiological studies for several decades.[33] The blood group genes A, B, and O each encode for a transferase protein that adds a carbohydrate moiety onto von Willebrand factor (vWF).[34] This moiety inhibits proteolysis, leading to higher plasma levels of vWF and increased susceptibility for thrombosis. The O gene encodes for a transferase that is inactive, does not transfer the carbohydrate moiety onto vWF, and is not associated with any increased risk for MI. The increased incidence of MI associated with blood groups A, B, or AB is presumably the prolonged half-life of vWF8 complex and increased thrombosis. Individuals of blood groups A or B exhibit increased blood levels of the vWF8 complex.[35] This raises the question in the future as to whether individuals of blood groups A, B, or AB, or individuals with CAD, should receive prophylactic antiplatelet therapy or anticoagulants if undergoing procedures such as angioplasty with stents or cardiac surgery. It will require clinical trials to assess the magnitude of this problem and whether it can be reversed by such treatment. It is of note that nearly 60% of the Caucasian population is of blood groups A, B, or AB. This is certainly a worthy challenge and an opportunity for the immediate future. It remains to be determined which, if any, of the other genetic risk variants relate to MI.

Clinical Implications for Genetic Testing and Management of Coronary Artery Disease

Are we ready to perform routine genetic testing? The simple answer is no. Some would argue, rightfully so, that until we alter management, there is no reason for genetic screening. It is reasonable to acknowledge that we are on the cusp of genetic screening for CAD. There are multiple risk variants occurring in the majority of population that act independently of known risk factors. Second, comprehensive prevention of CAD is unlikely without modifying genetic predisposition. It will require more information and time to explore these genetic risk variants, and perhaps function will have to be determined before implementation.

However, 9p21 compares favorably with conventional risk factors. The 9p21 variant in individuals with early onset of CAD has a 2-fold increase risk in homozygotes and a 50% increase risk in heterozygotes.[7,8] This risk is equivalent to the 2-fold increased risk of smoking,[36] the 30% increased risk of a SD increase in low-density lipoprotein cholesterol (LDL-C) or decrease in high-density lipoprotein cholesterol,[37] or the 40% increased risk associated with a 10-mm increase in blood pressure.[38] The technical barrier to testing for hundreds of genetic risk factors has promptly been overcome using either blood or saliva as the source of DNA. One approach that could be considered currently is using the independent risk factor of 9p21 for more aggressive treatment in lowering LDL-C. Currently, according to the guidelines, LDL-C should be decreased to 160 mg/dL if 1 risk factor is present, to 140 mg/dL if 2 risk factors are present, and to <100 mg/dL if more risk factors are present. The recommendation in an individual with elevated LDL-C, with no other conventional risk factors but having ≥1 genetic risk factors such as 9p21, could be to categorize the individual into a higher risk category, resulting in more intensive treatment of LDL-C. This approach could be adopted before the development of specific therapy for the treatment of genetic predisposition. It would of course require recommendation from authorities such as Adult Treatment Panel III.

Conclusion

In only 5 years, GWAS have confirmed that genetics plays a role in predisposition toward CAD. The genetic risk variants are very common, with some occurring in >75% of the population (Table). The major finding that is likely to have the greatest impact on treatment of CAD is the observation that 23 of the 36 genetic risk variants act through as yet unknown mechanisms. This has the potential to provide new targets for drug development. It will also elucidate new knowledge of the biology of atherosclerosis and MI. The 23 variants acting through unknown mechanisms may act through only 1 or 2 pathways. A major pathway such as the cholesterol pathway is likely waiting to be discovered. The technology barrier for rapid (<60 min) genotyping of hundreds of genes simultaneously on a single blood sample has already been eliminated. The application of routine genetic testing will occur gradually, and perhaps appropriately so, as laws will

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have to evolve to protect privacy and it will require some time to educate physicians and society of the implications of genetics in medical management.

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