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Genetic Markers of Myocardial Infarction

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Abstract

Myocardial Infarction (MI) is a complex multifactorial disorder caused by the interaction of environmental and genetic factors. Several types of genetic studies and approaches, such as family studies, linkage analysis, candidate gene approach, and genome wide association studies, have tried to unravel the genetic background of MI. Although it is clear that the genetic component has an important role in the development of MI, in the view of many all these approaches have failed to deliver as expected. It might be due to the fact that beside genetic factors, gene-gene interactions, and epigenetic mechanisms are most probably very much involved in the setting of MI. For clinical use, a clear cut and reliable information should be available from genetic and epigenetic studies to be of help in the decision making in patients with coronary artery disease.

Keywords: Myocardial infarction; Genetic markers; Candidate gene approach; Genome wide association studies

Introduction

Coronary Artery Disease (CAD) and its most important complication, Myocardial Infarction (MI), are among the leading causes of morbidity and death worldwide [1]. It is estimated that in Europe every sixth man and every seventh woman will eventually die from MI [2]. Despite the high prevalence of atherosclerotic coronary disease in the industrialized world, only a small part of patients eventually develop complications, such as acute MI or sudden cardiac death [3].

The underlying mechanism of CAD is atherosclerosis [4]. Atherosclerosis of coronary arteries develops and progresses at different rates, and it may manifest clinically at different stages of coronary stenosis. Thrombus formation within a coronary vessel is the precipitating event in acute coronary syndromes (unstable angina, myocardial infarction or sudden cardiac death), as shown in angiographic and pathologic studies [5,6]. The angiographic severity of coronary stenoses does not adequately predict sites of subsequent acute coronary syndromes. For this reason, rupture of atheromatous plaque in relatively mildly stenosed vessels and subsequent thrombus formation is believed to underlie the majority of acute coronary syndromes [7,8]. The understanding of this complex process of atherothrombosis, leading to MI, evolved in parallel with great advances in the understanding of vascular biology of this process [4] . MI is a complex multifactorial disorder caused by the interaction of environmental factors and hereditary predisposition [9,10]. Due to the influences of gene-environmental interactions, epigenetic mechanisms regulate at least a part of these pathological mechanisms. Epigenetic changes occur without alterations in the DNA sequence and can affect gene transcription in response to environmental changes. Genetic variants that promote coronary atherosclerosis also promote the risk of MI. However, as only a minority of patients with CAD finally develops MI, there should be additional unique genetic factors that facilitate coronary plaque instability, rupture and subsequent thrombosis. According to the results of several genetic studies the genes responsible for plaque rupture and subsequent thrombosis may not be the same as those responsible for the progression of atherosclerotic disease [3].

Several types of genetic studies and approaches (i.e. family studies, linkage analysis, candidate gene approach, genome wide association studies) have been used so far to unravel the genetic background of MI. Family studies were the type of genetic studies that introduced the importance of family history in disease prediction. A positive family history was demonstrated to be an important independent risk factor for CAD/MI [11]. According to the data from the Swedish Twin Study, the relative risk to die from CAD was greater in monozygotic twins than in dizygotic twins and was largely independent of other personal risk factors for CAD [12]. These results evidently suggest a significant genetic contribution to the risk of CAD death. It has been estimated that heritable factors account for 30-60% of the interindividual variation in the risk of CAD [13]. According to several studies the heritability of MI seems to be much more impressive than the heritability of CAD [3]. Family-based linkage studies were successful in identifying rare monogenic Mendelian disorders, but they were less successful to detect common alleles with small effects in complex diseases such as MI [14]. Initial attempts to unravel the genetic architecture of MI were grounded on the established knowledge of the disease process. Candidate gene studies tested the hypothesis that genes coding for proteins with a supposedly known biological role in the pathogenesis of atherosclerosis or plaque rupture carry variants that affect their function and finally the risk of developing CAD/MI [15]. In the last few years, Genome Wide Association Studies (GWAS) have begun to unravel the strong genetic component in the pathogenesis of CAD. Several novel loci that reproducibly associate with CAD and/or MI risk have been identified [16]. However, despite this success, currently identified loci explain only a small part of genetic variability of the disease [16]. In addition, a large part of these associations are located in genomic regions with an unknown functional role in the pathophysiology of the disease [15].

The identified loci may be associated with MI through different pathological processes including those that promote atherosclerosis, precipitate plaque rupture, or facilitate arterial thrombosis [17]. The largest part of available loci seemingly relate to MI simply by way of coronary atherosclerosis rather than having a specific role in plaque

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vulnerability or thrombus formation. In fact, independent studies support this concept for the 9p21 locus. Horne and colleagues have shown that this locus did not predict MI in patients with CAD but was strongly associated with the presence of angiographic CAD versus controls [18].

Candidate Gene Studies

The candidate gene approach is based on the established knowledge of the disease process. It tests the hypothesis that genes coding for proteins with a supposedly known biological role in the pathogenesis of atherothrombosis affect the risk of developing CAD/MI. Candidate gene studies were expected to be successful especially in multifactorial disorders such as MI [14]. In multifactorial disorders such as MI, common alleles with small effects are expected to influence the development of the disorder [14].

The variants were thus selected a priori, on the basis of their localization in genes implicated, for example, in lipoprotein metabolism, hemostasis or inflammatory pathways. In general, only a single or few genetic variants in a given gene were investigated for association with disease, which was a major drawback of these studies. Unless performed in a very large sample size of well-characterized population, the approach was prone to spurious results, particularly for distant phenotypes [19]. Accordingly, despite over 5000 publications on this topic, variants in only a limited number of genes mainly affecting LDL cholesterol were compellingly shown to be associated with the risk of MI [15]. Another disadvantage of candidate gene studies was their inability to identify disease-associated polymorphisms in unknown genes. Overall, the failure of candidate gene approach in unraveling the heritability of MI demonstrates how little of the genetic risk can be clarified by presently known pathways. Additionally, it also partially explains the independency of family history as a risk factor for MI [15].

Thus, it is of no surprise that only some candidate gene studies have succeeded in the identification of reproducible associations with MI. Among them, variants in genes involved in LDL cholesterol metabolism, such as *PCKS9* [20], *Apo E* [20], *Apo B* [21], and *LDLR* [22] genes, have been identified. Additionally, several candidate genes in meta-analyses have been reported so far with modest effect on CAD risk (Table 1). However, [23] have failed to validate the association of 85 putative genetic variants in 70 genes with acute coronary syndrome in a large case-control study of 1461 participants (811 cases and 650 controls) of European ancestry [23]. All the genetic variants were carefully chosen from the available medical literature because of previously reported associations with acute coronary syndrome.

The candidate gene approach conducted in the past was affected by several limitations and was thus only modestly successful in the clarification of MI genes. Genetic variants with rather strong effects at the transcriptional level or variants affecting the functionality of the protein may have escaped the test for association with disease risk. Moreover, frequently too small and too heterogeneous study samples (gender, age, retrospective vs. prospective, low-risk patients vs. high-risk patients; stable angina vs. acute myocardial infarction; ethnic distribution) have seriously questioned the reliability of the results. Other issues include heterogeneity of causality and population stratification [24].

In parallel with candidate gene studies, other strategies were employed to investigate the whole genome without preexisting hypotheses about causal genetic mechanisms of CAD. One of these strategies is genome-wide linkage analysis, which is based in the Mendelian co-segregation of a genetic marker within a family. Although several genome wide linkage studies have been published, the reported associations have seldom been replicated. Thus, only few positional candidate genes-i.e. leukotriene A4 hydrolase (*LTA4H*) [25], arachidonate 5-lipoxygenase-activating protein (*ALOX5AP*) [26], and myocyte enhancer factor-2 (*MEF2A*) [27]-were identified as being possibly involved in CAD/MI.

Genome Wide Association Studies

Genome Wide Association Studies (GWAS) became available with the publication of the International Hap Map Project [28,29] and the development of dense genotyping chips that enabled the investigation of up to one million variants in cases and controls of a given disease or other phenotypic traits. In contrast with candidate gene studies, GWAS provide an unbiased approach that has led to the identification of novel loci associated with MI. Many of the newly discovered loci were not expected on the ground of prior knowledge and have opened new avenues of research into the pathways and processes underlying CAD [24]. Variants discovered at the 9p21 region were the first genetic variants identified as genetic risk factors for CAD and other forms of cardiovascular disease independent of classical risk factors [30-32]. Additionally, locus on chromosome 9p21.3 is the most often replicated locus associated with MI [33]. Current GWAS focus on large populations in order to strengthen the evidence for association and replication [34].

Location	Gene	Polymorphism(s)	Risk genotype	Number of studies (cases)	Size of effect (95% CI)	Reference
1p36.3	*MTHFR* Methylenetetrahydrofolate reductase	C677T	TT	40 (11,162)	1.14 (1.01-1.28)	[70]
1q23	*F5* Factor V Leiden	R506Q	Q+	20 (5,313)	1.10 (0.88-1.36)	[69]
1q42.2	*AGT* Angiotensinogen	Met235Thr (M235T)	TT	21 (4,001)	1.19 (1.10-1.30)	[64]
2p24-p23	*APOB* Apolipoprotein B	Gln4154Lys (Q4154L)	LL	14 (1,796)	1,73 (1.19-2.50)	[75]
2p24-p23	*APOB* Apolipoprotein B	Signal peptide Ins/Del	DD	22 (6,007)	1.19 (1.05-1.35)	[75]
7q21.3	*PON1* Paraoxonase	Q192R	R192	44 (10,106)	1.12 (1.07-1.16)	[65]
7q21.3-q22	*PAI-1* Plasminogen activator inhibitor type 1	5G/4G	4G4G	7 (2,813)	1.20 (1.04-1.39)	[73]
7q36	*NOS3* Nitric oxide synthase 3	Glu298Asp (E298D)	DD	14 (6,036)	1.31 (1.13-1.51)	[74]
8p22	*LPL* Lipoprotein lipase	Ser/Ter (S447X)	X+	4 (2,252)	0.80 (0.7-1.0)	[66]
11p11	F2 Prothrombin	G20210A	A+	19 (4,944)	1.21 (0.99-1.58)	[71]
16q21	*CETP* Cholesteryl ester transfer protein	*Taq*IB	B2B2	7 (7,681)	0.78 (0.66-0.93)	[72]
17q21.32	*ITGB3* Platelet glycoprotein IIIa	PL(A1/A2)	A2+	34 (6,173)	1.13 (1.02-1.26)	[67]
17q23.3	*ACE* Angiotensin I converting enzyme	Insertion/Deletion	DD	43 (14,292)	1.22 (1.11-1.35)	[67]
19q13.2	*APOE* Apolipoprotein E	E2, E3, E4	e4	48 (15,492)	1.30 (1.18-1.51)	[68]

Table 1: List of gene variants with published meta-analysis on CAD risk and more than 2000 cases [76].

The GWA approach is founded on the "common disease-common variant" hypothesis, which posits that common diseases, such as MI, are attributable to frequent genetic variants present in more than 1-5% of the population, each with only a small effect on disease susceptibility. The conferred relative risks, as expressed by odds ratio, usually range between 1.1 and 1.5. The GWAS have been aided by the development of commercial chip arrays that capture most, although not all, common variation in the genome [35]. Further, it is important to recognize that GWAS identify regions of the genome (loci) rather than variants of specific genes. In fact, the specific variant identified by GWAS may simply represent the signal of one or more hidden variants, which are not typed in the arrays used in GWAS. Despite the recent success of the GWAS approach, the ability to identify the genetic basis of complex disease remains rather modest.

GWAS technology is limited by the dependence on HapMap, based on genetic data from a small number of individuals and providing proxies for the majority of SNPs with a minor allele frequency >5%. The Encyclopedia of DNA Elements Projects indicated that >60% of SNPs had a minor allele frequency <0.05. As noted by [36] there is an inverse relationship between minor allele frequency and proportion of SNPs predicted to be damaging [36]. Thus, multiple lower frequency variants are likely to have a cumulatively more important phenotypic effect. Multiple lower frequency common variants (minor allele frequency between 0.5% and 5%) have been shown to contribute importantly to complex phenotypes relevant to MI.

Despite the recent success of GWA approach, several potential limitations should be commented. As the majority of newly discovered loci reside in regions of uncertain biological significance, additional work is needed to establish their specific contribution to disease etiology. In addition, as GWAS provide excellent coverage of common genetic variation, they tend to provide inadequate coverage of less frequent genetic variants encoded in genes with known biological relevance (i.e. "candidate genes"). As GWASs failed to replicate the majority of genetic variants identified in candidate gene studies, it should be stressed that many of these variants were poorly tagged on the GWAS arrays, which clearly fail to cover the full extent of even common variation in particular genes [32].

A rather unanticipated and perplexing finding of GWAS is that the discovered genetic variants account for only a small fraction of phenotypic variation and disease risk. According to [37], a heritability estimate of 40% will encompass the clinical heterogeneity across typical GWAS case series [37]. Further, they estimate that only approximately 8-13% of the total heritability of CAD can be explained by the common variants discovered thus far in GWAS [37]. This difference between estimated and observed variance is termed "missing heritability," the search for which has recently become one of the primary goals for research on MI and other complex conditions [35].

Among the wide array of possible explanations for the missing heritability, the most frequently cited are structural variations, including copy number variations, rare variants with strong effects that are not detected by GWAS, epigenetic inheritance, gene-gene interactions (epistasis), and gene-environment interactions [37]. Lucas et al. have recently addressed the hypothesis that gene-gene interactions (epistasis) contribute to the risk of early-onset MI [38]. Despite performing an extensive search for interactions between SNPs, which are robustly associated with classical cardiovascular risk factors, or with those which show marginal association with MI, they didn't succeed in providing support for the existence of strong interaction effects as a common risk factor for MI. There is mounting evidence that rare variants play an important role in complex disease etiology and may have larger genetic effects than common variants [35]. Contrary to one's expectations, tests of common and rare CNVs of the GWA studies of early onset MI failed to identify additional associations with MI risk [39].

Based on the results from recent large scale studies, several common coronary disease variants have been robustly mapped by GWASs [16,17,32,38-44] or gene-centric SNP arrays [45] (Table 2). These results are mostly based on cases and controls of European descent. GWAS have several limitations and, in the view of many, they failed to fulfill the expectations. First, the identified alleles explain only a small fraction of the heritability of common diseases and traits [35] and have a low predictive value compared with classical risk factors [46]. Second, as GWAS are designed to identify common variants, the existence of rare variants with a large effect has not been addressed [47]. Third, as study size is a crucial determinant to detect a causal variant, these studies need very large samples of cases and controls [48]. Fourth, DNA and data quality control procedures and statistical analysis need to be performed by expert centers [49]. Fifth, GWAS are constrained by cost, ranging from hundreds of thousands to millions of dollars, which is unaffordable for most research groups worldwide [48]. And finally, even after and in spite of all quality control procedures, there is still the chance that the results of GWAS include false-positive results, so that independent replication of the most significantly associated polymorphisms in multiple populations with distinctive genetic backgrounds and lifestyles is particularly important [50].

The rapid development of third generation sequencing technologies will invariably lead to widespread association studies comparing whole exome and finally whole genome sequencing of cases and controls. A tremendous challenge for enabling these "next generation" medical genomic studies is developing statistical approaches for correlating rare genetic variants with disease outcome [51]. The analysis of rare variants is challenging since methods used for common variants are woefully underpowered. As only a fraction of the heritability for most cardiovascular diseases has been explained thus far, forthcoming techniques such as whole-genome sequencing will be important to close the gap of missing heritability.

Complications of MI

A very important topic for clinicians is the prediction of complications in the setting of acute MI. There is convincing evidence for a genetic component to the risk of sudden cardiac death in the setting of acute MI [52]. Ventricular fibrillation accounts for the majority of deaths during the acute phase of MI. Identification of patients at risk for ventricular fibrillation remains challenging, with family history being the key predictor [53]. Recently, Bezzina et al. conducted a GWAS in a set of 972 individuals with a first acute MI, 515 of who had ventricular fibrillation [54]. They found a significant association between a SNP rs2824292 on chromosome 21q21 and ventricular fibrillation (OR 1.78, $p=3.3x10^{-10}$). The susceptibility allele is located near the gene *CXADR*, which encodes the Coxackie virus and adenovirus receptor protein. This transmembrane tight junction protein has been recognized as a modulator of cardiac conduction and has been previously implicated in viral myocarditis and dilated cardiomiopathy [55]. Hopefully, further mechanistic research of this locus will provide new insight into pathophysiology of ventricular fibrillation that may lead to better predictive algorithms and the prevention of sudden cardiac death in patients with acute MI.

β-adrenergic receptor polymorphisms have been associated with differences in heart failure progression and altered pharmacogenetic

Location	*Mapped genes*	SNP(s)	Risk allele frequency - controls	P-value	OR (95% CI)	Gene function (known or probable?)	Disease	References
1p13.3	*CELSR2, PSRC1, SORT1*	rs599849 rs646776 rs599839	0.77 0.81 0.78	4×10^{-9} 8×10^{-12} 3×10^{-10}	1.29 (1.18-1.40) 1.19 (1.13-1.26) 1.11 (1.08-1.15)	LDL	CAD MI CAD	[32] [39] [16]
1p32.2	*PPAP2B*	rs17114046 rs17114036	NR 0.91	2×10^{-7} 4×10^{-19}	NR 1.17 (1.13-1.22)	Lipid phosphate phosphatase-3	CAD CAD	[43] [16]
1p32.3	*PCSK9*	rs11206510 rs11206510	0.81 0.82	1×10^{-8} 9×10^{-8}	1.15 (1.10-1.21) 1.08 (1.05-1.11)	LDL	MI CAD	[39] [16]
1q21.3	*ILR6*	rs2229238	NA	7×10^{-7}	1.45 (NR)	IL-6 receptor		[40]
1q41	*MIA3*	rs17465637 rs17465637 rs17465637	0.71 0.72 0.74	1×10^{-6} 1×10^{-9} 1×10^{-8}	1.2 (1.12-1.30) 1.14 (1.10-1.19) 1.14 (1.09-1.20)	Collagen processing	CAD MI CAD	[32] [39] [16]
2p21	*ABCG8*	rs4299376	0.29		1.09	Lipids	CAD	[45]
2q32.1	*TFP1*	rs7586970	NR	9×10^{-6}	NR	Unknown	CAD	[43]
2q33.2	*WDR12*	rs6725887 rs6725887	0.14 0.15	1×10^{-8} 1×10^{-8}	1.17 (1.11-1.23) 1.14 (1.09-1.19)	Apoptosis	MI CAD	[39] [16]
2q35	*FN1*	rs17458018	NA	7×10^{-6}	1.22 (NR)	Fibronectin		[40]
2q36.3	*KIAA1486*	rs2943634	0.65	2×10^{-7}	1.21 (1.13-1.30)	Unknown	CAD	[32]
2q37.1	*INPP5D*	rs10933436	0.49	7×10^{-6}	1.06 (1.04-1.09)	Hematopoiesis	CAD	[16]
3p25.1	*BTD*	rs7651039	0.54	2×10^{-6}	1.06 (1.04-1.09)	Biotinidase	CAD	[16]
3q22.3	*MRAS*	rs9818870 rs2306374	0.15 0.18	7×10^{-13} 3×10^{-8}	1.15 (1.11-1.19) 1.12 (1.07-1.16)	Adhesion signaling	CAD	[41] [16]
4q31.22	*TTC29 – RPL31P26*	rs1395821	NR	7×10^{-7}	NR	Unknown	CAD	[43]
5q31.1	*IL5*	rS2706399	0.48		1.02	Interleukin 5	CAD	[45]
6p21.1	*VEGFA*	rs6905288	NR	7×10^{-8}	1.23 (NR)	Angiogenesis		[40]
6p21.31	*ANKS1A*	rs17609940	0.75	1×10^{-8}	1.07 (1.05-1.10)	Immune system	CAD	[16]
6p21.33	*HCG27, HLA-C*	rs3869109	NR	1×10^{-9}	1.14 (NR)	Unknown		[40]
6p24.1	*PHACTR1*	rs12526453 rs9349379 rs12526453	0.65 NR 0.67	1×10^{-9} 9×10^{-26} 1×10^{-9}	1.12 (1.08-1.17) NR 1.1 (1.06-1.13)	Coronary calcification	MI CAD CAD	[39] [43] [16]
6q14.1	*FAM46A - IBTK*	rs16893526	0.91	5×10^{-6}	1.13 (1.07-1.21)	Unknown	CAD	[44]
6q16.1	*FHL5*	rs12200560	NR	6×10^{-7}	1.11 (NR)	Transcriptional activation	CAD	[40]
6q23.2	*TCSF21*	rs12190287	0.62	1×10^{-12}	1.08 (1.06-1.10)	Tumor suppressor	CAD	[16]
6q25.1	*MTHFD1L*	rs6922269	0.25	3×10^{-8}	1.23 (1.15-1.33)	Tetrahydrofolate synthesis	CAD	[32]
6q25.3	*LPA*	rs3798220	0.02	3×10^{-11}	1.51 (1.33-1.70)	1.51 (1.33-1.70)	CAD	[16]
6q25.3	*FNDC1*	rs365302	0.24	8×10^{-7}	1.11 (1.06-1.15)	Unknown	CAD	[44]
7q22.3	*BCAP29*	rs10953541	0.80	3×10^{-8}	1.08 (1.05-1.11)	Unknown		[43]
7q31.2	*ASZ1*	rs7808424	0.12	1×10^{-6}	1.1 (1.06-1.14)	Unknown	CAD	[16]
7q32.2	*ZC3HC1*	rs11556924	0.62	9×10^{-18}	1.09 (1.07-1.12)	Unknown	CAD	[16]
8q24.13	*TRIB1*	rs10808546	0.65		1.04	Lipids	CAD	[45]
9p21.3	*ANRIL/CDKN2BAS* *CDKN2A, CDKN2B*	rs1333049 rs4977574 rs4977574 rs4977574 rs1333049	0.47 0.56 NR 0.46 0.49	3×10^{-19} 3×10^{-44} 2×10^{-25} 1×10^{-22} 7×10^{-58}	1.36 (1.27-1.46) 1.29 (1.25-1.34) 1.20 (1.16-1.25) 1.29 (1.23-1.36) 1.27 (1.23-1.31)	Regulatory functions?	CAD MI CAD CAD CA	[32] [39] [43] [16] [44]
9q22.33	*HEMGN – ANP32B*	rs4743150	NR	5×10^{-6}	NR	Unknown	CAD	[43]
9q34.2	*ABO*	rs514659 rs579459	0.37 0.21	8×10^{-9} 4×10^{-14}	1.21 (1.13-1.28) 1.10 (1.07-1.13)	Coronary thrombosis	CAD/MI CAD	[17] [16]
10p11.23	*KIAA1462*	rs3739998 rs2505083	0.44 0.38	1×10^{-11} 4×10^{-8}	1.15 (1.11-1.20) 1.07 (1.04-1.09)	Endothelial cell adhesion	CAD CAD	[42] [43]
10q11.21	*CXCL12*	rs501120 rs1746048 rs1746048	0.87 0.84 0.87	9×10^{-8} 7×10^{-9} 3×10^{-10}	1.33 (1.20-1.48) 1.17 (1.11-1.24) 1.09 (1.07-1.13)	Platelet aggregation?	CAD MI CAD	[32] [39] [16]
10q23.31	*LIPA*	rs1412444 rs1412444	0.42 0.32	3×10^{-13} 4×10^{-8}	1.09 (1.07-1.12) 1.1 (1.07-1.14)	Lipids	CAD	[43] [44]
10q24.32	*CNNM2*	rs12413409 rs12413409	NR 0.89	4×10^{-6} 1×10^{-9}	NR 1.12 (1.08-1.16)	Mg homeostasis?	CAD CAD	[43] [16]
11q22.3	*PDGFD*	rs974819	0.32	2×10^{-9}	1.07 (1.04-1.09)	Smooth muscle cell proliferation	CAD	[43]
11q23.3	*ZNF259*	rs964184	0.13	1×10^{-17}	1.13 (1.10-1.16)	Unknown	CAD	[16]
11q24.2	*ST3GAL4*	rs4937126	0.69	5×10^{-6}	1.06 (1.04-1.09)	Protein glycosylation	CAD	[16]
12q24.12	*SH2B3*	rs3184504	0.44	6×10^{-6}	1.07 (1.04-1.10)	Hematopoiesis	CAD	[16]
12q24.31	*HFN1A*	rs2259816	0.36	5×10^{-7}	1.08 (1.05-1.11)	Transcription factor	CAD	[41]
13q34	*COL4A1-A2*	rs4773144	0.44	4×10^{-9}	1.07 (1.05-1.09)	Type IV collagen	CAD	[16]

14q32.2	*HHIPL1*	rs2895811	0.43	1×10^{-10}	1.07 (1.05-1.10)	Unknown	CAD	[16]
15q22.33	*SMAD3*	rs17228212	0.30	2×10^{-7}	1.21 (1.13-1.30)	Transcriptional modulator	CAD	[32]
15q25.1	*ADAMTS7*	rs1994016 rs43800028 rs3825807	0.60 0.65 0.57	5×10^{-13} 4×10^{-9} 1×10^{-12}	1.19 (1.13-1.24) 1.07 (1.05-1.10) 1.08 (1.06-1.10)	Migration of vascular smooth muscle cells	CAD CAD CAD	[17] [43] [16]
15q24.1	*CYP1A1–CYP1A2*	rs2472299		3×10^{-6}	NR	Lipid synthesis?	CAD	[43]
17q12	*ACCN1*	rs11650066	NR	6×10^{-6}	NR	Sodium channel?	CAD	[43]
17p13.3	*SMG6*	rs216172	0.37	1×10^{-9}	1.07 (1.05-1.09)	Telomerase ribonucleoprotein complex	CAD	[16]
17p11.2	*PEMT*	rs12936587	0.56	4×10^{-10}	1.07 (1.05-1.09)	Choline metabolism	CAD	[16]
17q21.32	*UBE2Z*	rs46522	0.53	2×10^{-8}	1.06 (1.04-1.08)	Apoptosis?	CAD	[16]
17q23.3	*PECAM1*	rs6504218	NR	1×10^{-6}	NR	Angiogenesis?	CAD	[43]
19p13.2	*LDLR*	rs1122608 rs1122608	0.75 0.77	2×10^{-9} 1×10^{-9}	1.15 (1.10-1.20) 1.14 (1.09-1.18)	LDL	MI CAD	[39] [16]
19q13.2	*APOE*	rs2075650	0.14		1.14	LDL	CAD	
21q22.11	*MRPS6, KCNE2*	rs9982601 rs9982601	0.13 0.15	6×10^{-11} 4×10^{-10}	1.20 (1.14-1.27) 1.18 (1.12-1.24)	Voltage gated potassium channel	MI CAD	[39] [16]
Xq23	*CHRDL1*	rs5943057	NR	9×10^{-7}	NR	Angiogenesis?	CAD	[43]

Table 2: Chromosome loci associated with coronary artery disease and myocardial infarction in populations of European descent.

responses to β-adrenergic blockade [52]. In a prospective pharmacogenetic cohort study of 735 patients with acute coronary syndrome, β-blocker therapy was associated with different survival rates according to nonsynonymous coding variants in the β2-adrenergic receptor (*ADRB2*) gene [56]. In a smaller study including 122 patients with acute MI treated with a β1 receptor antagonist, McLean et al. have demonstrated that polymorphisms of the *ADRB1* and *ADRB2* genes are associated with differential LV remodeling [57]. The SNP rs2383207 on chromosome 9p21.3 was associated with a 25% increased risk of MI [30] and a 23% increased risk of sudden cardiac death syndrome [58]. The results have been recently replicated in FinSCDgen Study [59].

Morgan et al. examined 95 polymorphisms in 69 distinct gene regions identified in a GWAS for premature MI for their association with post-ACS mortality among 811 white patients [60]. Positive genetic associations were than replicated in a large, racially diverse cohort of 2.284 patients with MI. Finally, the apparent associations were investigated further in 6.086 additional CAD patients. However, none of the studied genetic variants proved to substantially alter the probability of survival after acute coronary syndrome. The results of the study imply that independent GWAS studies of cohorts of many thousands of acute coronary syndrome patients may be required in order to identify prognostic factors in biological pathways promoting post-ACS mortality.

Clinical Perspective and Personalized Medicine

The wealth of new information on heritable aspects of MI emanating from genetic studies clearly opens several novel possibilities for further scientific research. However, from a clinical perspective, the main focus is on risk prediction and therapy improvement for MI [15]. As clinicians, we hope that the identification of genetic susceptibility traits will allow for more accurate risk stratification of patients than is achievable with current clinical models. Hopefully, this will lead to the improvement of specific interventions that lower the overall risk of CAD and especially MI. Certainly, the information will be available sooner, at an earlier age of an individual patient, so the preventive measures could be applied earlier, and this is the cornerstone of personalized medicine. A still unsolved statistical problem is the appropriate management and integration of information deriving from multiple risk variants to calculate the overall genetic risk [15]. Simply counting and summing the number of risk alleles present in an individual patient may be an oversimplification as various loci might have a fairly different impact on risk, due to different biological mechanisms involved in disease pathogenesis. Rather, a reliable estimation of genetic risk carried by an individual will require sophisticated and complicated algorithms also taking in account gene-gene and gene-environmental interactions [15]. In future, the incidence of cardiovascular diseases is expected to rise. The identification of subjects at risk will hopefully improve, and genetic tests are expected to improve traditional risk factor scoring. Genetic markers may have additional value in primary prevention in subjects with intermediate risk, posing them at higher risk for an acute event [15,38]. As already mentioned, the majority of novel loci are located in genes that modulate disease risk through a so far unknown mechanism. Unraveling so far unknown mechanisms of atherothrombosis might be of great importance for the development of new cardiovascular drugs. In order to make the most of the new genetic information for the treatment and prevention of MI, it is imperative to unravel the functions of the genes at the disease-associated loci and the mechanisms through which they affect MI risk [15].

Another important aspect of personalized medicine in cardiovascular medicine are the results derived from pharmacogenetic studies. Pharmacogenetics is the study of the effect of a medication as it relates to single or defined sets of genes. An important goal of pharmacogenetics in cardiovascular disorders is to integrate the two (drugs plus genes), so that true personalized therapy can be delivered.

Clinical Impact of Genetic Testing

Demonstrating that a genetic test has clinical validity does not necessarily lead to health improvement. A test has clinical utility when its results lead to a measurable improvement in health outcomes. Clinical trials should provide evidence that the use of the test is associated with changes in physician management decisions, patient motivation and long-term behavioral changes, improved health outcomes, and reduced costs to the health care system [61].

Conclusions

The ability to foretell a significant portion of disease risk from genotype will hopefully enable us to intervene earlier and treat better, but overall, to prevent MI and its complications. The identification of a molecular profile would certainly be a helpful tool for the prevention and management of cardiovascular disorders [62]. Despite the successes of various genetic methods and approaches, only a fraction of the heritability for most cardiovascular diseases has been explained

thus far. Forthcoming techniques, such as whole-genome sequencing, will be important to close the gap of missing heritability. Through the use of these methods in future studies, a better understanding of the disease and improved clinical outcomes are feasible [63].

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