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REVIEW

Molecular genetics of myocardial infarction

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Abstract Myocardial infarction (MI) is an important clinical problem because of its large contribution to mortality. The main causal and treatable risk factors for MI include hypertension, hypercholesterolemia or dyslipidemia, diabetes mellitus, and smoking. In addition to these risk factors, recent studies have shown the importance of genetic factors and interactions between multiple genes and environmental factors. Disease prevention is an important strategy for reducing the overall burden of MI, with the identification of markers for disease risk being key both for risk prediction and for potential intervention to lower the chance of future events. Although genetic linkage analyses of families and sib-pairs as well as candidate gene and genome-wide association studies have implicated several loci and candidate genes in predisposition to coronary heart disease (CHD) or MI, the genes that contribute to genetic susceptibility to these conditions remain to be identified definitively. In this review, we summarize both candidate loci for CHD or MI identified by linkage analyses and candidate genes examined by association studies. We also review in more detail studies that have revealed the association with MI or CHD of polymorphisms in *MTHFR*, *LPL*, and *APOE* by the candidate gene approach and those in *LTA* and at chromosomal region 9p21.3 by genome-wide scans. Such studies may provide insight into the function of implicated genes as well as into the role of genetic factors in the development of CHD and MI.

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Abbreviations

SNP	Single nucleotide polymorphism
MI	Myocardial infarction
CHD	Coronary heart disease
ACS	Acute coronary syndrome
CRP	C-reactive protein
GWAS	Genome-wide association study
HDL	High density lipoprotein
LDL	Low density lipoprotein

Introduction

Recent progress in human genetics and genomics research, highlighted by completion of the nucleotide sequence of the human genome by the Human Genome Project (International Human Genome Sequencing Consortium 2004), has provided substantial benefits to clinical medicine, including facilitation of the characterization of disease pathogenesis at the molecular level and the development of panels of genetic markers for assessment of disease risk. In particular, determination of single nucleotide polymorphisms (SNPs) and haplotype blocks and the specification of tag SNPs in each haplotype block for four ethnic groups by the International HapMap Project (The International HapMap Consortium 2007) have led to increasingly effective approaches to the identification of genetic variation associated with various multifactorial diseases, providing new insight into the pathogenesis of these conditions. Furthermore, technological developments such as cDNA microarrays and SNP chips that provide huge

amounts of genetic information have made possible the detection of genetic differences among individuals at the whole-genome level.

Selection of the most appropriate strategies for disease prevention or therapy on the basis of genetic information for a given individual is referred to as personalized or individualized medicine. In conventional medicine, medications are prescribed on the basis of the diagnosis and severity of the disease. However, the efficacy of drugs and the incidence of side effects vary among individuals. The goal of treatment based on genetic or genomic information is to be able to predict therapeutic outcome or side effects in an individual, thereby increasing the effectiveness and safety of therapy. In addition, the clarification of disease etiologies at the molecular level and the identification of genetic variants that confer disease susceptibility are likely to contribute both to disease prevention and to the development of new medicines.

Myocardial infarction (MI) is an important clinical problem because of its large contribution to mortality. In the United States, the total number of individuals affected by coronary heart disease (CHD) was 15.8 million in 2004, with nearly 450,000 patients dying annually from this condition (Rosamond et al. 2007). The annual incidence of MI was 565,000 new attacks and 300,000 recurrent attacks, with an annual mortality of 157,000 (Rosamond et al. 2007). As in the United States, CHD is the most common cause of death in the United Kingdom, where it is responsible for around 101,000 deaths each year (British Heart Foundation; http://www.heartstats.org/homepage.asp). In Japan, the total number of individuals affected by CHD was 910,000 in 2005, and ~50,000 people die annually from MI (Ministry of Health, Labor, and Welfare of Japan).

The main causal and treatable risk factors for MI include hypertension, hypercholesterolemia or dyslipidemia, diabetes mellitus, and smoking. In addition to these risk factors, recent studies have shown the importance of genetic factors and of interactions between multiple genes and environmental factors in this condition (Arnett et al. 2007; Kullo and Ding 2007; Topol et al. 2006). The common forms of CHD and MI are thus thought to be multifactorial and to be determined by many genes, each with a relatively small effect, working alone or in combination with modifier genes or environmental factors (or both). The "common disease, common variants hypothesis" proposes that genetic variants present in many normal individuals contribute to overall CHD risk. In addition, susceptibility to some common diseases may be conferred, in part, by rarer variants (Arnett et al. 2007).

Despite recent advances in therapy, such as drug-eluting stents (Marroquin et al. 2008), for acute coronary syndrome (ACS), CHD remains the leading cause of death in the US and UK and the second leading cause of death in Japan. Disease prevention is an important strategy for reducing the overall burden of CHD and MI, and the identification of biomarkers for disease risk is key both for risk prediction and for potential intervention to reduce the chance of future events.

Linkage analysis of MI, ACS, or CHD

Several genome-wide linkage analyses of families or sib-pairs have identified chromosomal loci linked to or genetic variations that confer susceptibility to MI, ACS, or CHD (Broeckel et al. 2002; Farrall et al. 2006; Francke et al. 2001; Harrap et al. 2002; Hauser et al. 2004; Helgadottir et al. 2004; Pajukanta et al. 2000; The BHF Family Heart Study Research Group 2005; Wang et al. 2003, 2004). The published results of genome-wide linkage analyses for these conditions are summarized in Table 1. Genomic regions identified in the published linkage studies as being correlated with MI or CHD are largely nonoverlapping, suggestive of genetic complexity in which multiple genes are responsible for the development of these conditions, although phenotypic heterogeneity could also have contributed to the nonreplicability of results.

The deCODE Genetics group (Helgadottir et al. 2004) performed linkage analysis with 1,068 microsatellite markers and found a linkage peak (LOD score of 2.86) at chromosomal region 13q12-q13 for 296 Icelandic families (713 individuals) enrolled on the basis of a history of MI. The researchers then genotyped an additional 120 microsatellite markers in this interval in 802 individuals with MI and 837 controls, and they found that a four-marker SNP haplotype spanning the arachidonate 5-lipoxygenase-activating protein gene (*ALOX5AP*) was associated with MI (odds ratio, 1.8) and stroke (odds ratio, 1.7). A subsequent study found that *ALOX5AP* was associated with CHD in British individuals and with stroke in Icelandic and Scottish populations (Helgadottir et al. 2005).

On the basis of the results of the same genome-wide scan, the deCODE Genetics group (Helgadottir et al. 2006) performed fine mapping to determine that a five- to seven-marker SNP haplotype of the leukotriene A4 hydrolase gene (*LTA4H*) accounted for a linkage peak at 12q22. Of particular interest with this haplotype was its ancestry-specific association with the incidence and risk of MI. In European-Americans, the relative risk for MI was only 1.2, with a population attributable risk of 4.6%, whereas among individuals of African ancestry, the relative risk was 3.5 and the population attributable risk was 14% (Helgadottir et al. 2006). Two different genes (*ALOX5AP* and *LTA4H*) in the same inflammation-related pathway of leukotriene B4 production were thus found to be associated with disease in a single genome-wide scan. This pathway had

Table 1 Genome-wide linkage analyses of myocardial infarction (MI), acute coronary syndrome (ACS), or coronary heart disease (CHD)

Chromosomal locus	Marker/gene symbol	Phenotype	References
1p34-p36	D1S1597	MI	Wang et al. (2004)
1q25	D1S518	ACS	Hauser et al. (2004)
2p12-q23.3	D2S2271	CHD	The BHF Family Heart Study Research Group (2005)
2p12-q23.3	D2S2216	MI	The BHF Family Heart Study Research Group (2005)
2q21.1-q22	D2S129, D2S2313	CHD	Pajukanta et al. (2000)
2q36-q37.3	D2S125	ACS	Harrap et al. (2002)
3q13	D3S2460	CHD	Hauser et al. (2004)
3q27	D3S1262, D3S1580	CHD, MI	Francke et al. (2001)
10q23	D10S185	CHD	Francke et al. (2001)
13q12	D13S289/*ALOX5AP*	MI	Helgadottir et al. (2004)
14q	D14S1426	MI	Broeckel et al. (2002)
15q26	D15S120/*MEF2A*	CHD, MI	Wang et al. (2003)
16p13-pter	D16S423	CHD	Francke et al. (2001)
17p11.2-q21	D17S921, D17S787	CHD	Farrall et al. (2006)
Xq23-q26	DXS1072, DXS1212	CHD	Pajukanta et al. (2000)

already been implicated in studies of murine experimental atherosclerosis as well as in human epidemiological and pathological studies (Dwyer et al. 2004; Mehrabian et al. 2002; Spanbroek et al. 2003). In addition, a small-molecule inhibitor of ALOX5AP was shown to reduce both leukotriene production and the plasma concentration of C-reactive protein (CRP), an important biomarker for CHD, in a pilot, placebo-controlled, randomized trial with individuals harboring the risk *ALOX5AP* or *LTA4H* haplotype (Hakonarson et al. 2005). Of note, *LTA4H* was the first MI-linked gene to show an ancestry-specific risk (Damani and Topol 2007; Topol et al. 2006).

Association studies of MI or CHD

Various association studies of unrelated individuals have identified genetic variations that confer susceptibility to MI or CHD. The published results for genes associated with these conditions are summarized in Table 2. Numerous candidate genes have been implicated, but those that show reproducible associations between risk alleles and CHD or MI in replication studies are few. The candidate gene approach has been widely applied to analysis of the possible association between genetic variants and disease, with genes selected on the basis of a priori hypotheses regarding their potential etiologic role. It is characterized as a hypothesis-testing approach because of the biological observation supporting a role for the proposed candidate gene. The candidate gene approach is not able, however, to identify disease-associated polymorphisms in unknown genes. The recent development of high-density genotyping arrays has improved the resolution of unbiased genome-wide scans for common variants associated with multifactorial diseases. Currently, the genome-wide association study (GWAS) makes use of high-throughput genotyping technologies that include about 1 million probes for SNPs and 1 million probes for copy number variations to examine their relation to clinical conditions or measurable traits. Since 2005, nearly 100 loci for as many as 40 common diseases or traits have been identified by GWASs, many in genes not previously suspected of having a role in the condition studied, and some in genomic regions containing no known genes. Although GWASs represent a substantial advance in the search for genetic variants that influence disease, they also have important limitations, including the potential for generating false-positive or false-negative results and for biases related to the selection of study participants and genotyping errors (Pearson and Manolio 2008).

Mendelian randomization

Mendelian randomization analysis is a relatively recent development in genetic epidemiology based on Mendel's second law, which states that the inheritance of one trait is independent of that of other traits (Davey Smith and Ebrahim 2003; Keavney 2002). It relies on common genetic polymorphisms that are known to influence exposure patterns (such as the propensity to drink alcohol) or to have effects equivalent to those produced by modifiable exposures (such as an increased serum cholesterol concentration). Associations between genetic variants and outcomes are not generally confounded by behavioral or environmental exposures, with the result that observational studies of

Table 2 Genes shown to be related to the prevalence of myocardial infarction or coronary heart disease

Chromosomal locus	Gene name	Gene symbol	References
1p36.3	5,10-Methylenetetrahydrofolate reductase	*MTHFR*	Gallagher et al. (1996) and Yamada et al. (2006)
1p36.2	Natriuretic peptide precursor A	*NPPA*	Gruchala et al. (2003)
1p35.1	Gap junction protein, alpha-4	*GJA4*	Yamada et al. (2002)
1p34.1-p32	Proprotein convertase, subtilisin/kexin-type, 9	*PCSK9*	Cohen et al. (2006)
1p34	Low density lipoprotein receptor-related protein 8, apolipoprotein E receptor	*LRP8*	Shen et al. (2007)
1p31.3-p31.2	Cytochrome P450, subfamily IIJ, polypeptide 2	*CYP2J2*	Liu et al. (2007)
1p22-p21	Coagulation factor III	*F3*	Ott et al. (2004)
1p22.1	Glutamate-cysteine ligase, modifier subunit	*GCLM*	Nakamura et al. (2002)
1q21-q23	C-reactive protein, pentraxin-related	*CRP*	Lange et al. (2006)
1q23-q25	Selectin E	*SELE*	Yoshida et al. (2003)
1q23-q25	Selectin P	*SELP*	Tregouet et al. (2002)
1q25	Tumor necrosis factor ligand superfamily, member 4	*TNFSF4*	Wang et al. (2005)
1q25.2-q25.3	Prostaglandin-endoperoxide synthase 2	*PTGS2*	Cipollone et al. (2004)
1q32	Complement factor H	*CFH*	Kardys et al. (2006)
1q42-q43	Angiotensinogen	*AGT*	Katsuya et al. (1995)
1q44	Olfactory receptor, family 13, subfamily G, member 1	*OR13G1*	Shiffman et al. (2005)
2p24	Apolipoprotein B	*APOB*	Hegele et al. (1986)
2p12-p11.2	Vesicle-associated membrane protein 8	*VAMP8*	Shiffman et al. (2006)
2q14	Interleukin 1-beta	*IL1B*	Iacoviello et al. (2005)
2q31	Collagen, type III, alpha-1	*COL3A1*	Muckian et al. (2002)
3pter-p21	Chemokine, CX3C motif, receptor 1	*CX3CR1*	Lavergne et al. (2005)
3p25	Peroxisome proliferator-activated receptor-gamma	*PPARG*	Ridker et al. (2003)
3p21	Chemokine, CC motif, receptor 2	*CCR2*	Ortlepp et al. (2003)
3p21	Chemokine, CC motif, receptor 5	*CCR5*	Gonzalez et al. (2001)
3q13.3-q21	Calcium-sensing receptor	*CASR*	Marz et al. (2007)
3q21-q25	Angiotensin receptor 1	*AGTR1*	Tiret et al. (1994)
3q26.3-q27	Thrombopoietin	*THPO*	Webb et al. (2001)
3q27	Adiponectin, C1Q, and collagen domain containing	*ADIPOQ*	Ohashi et al. (2004)
4q22-q24	Microsomal triglyceride transfer protein, 88-kD	*MTTP*	Ledmyr et al. (2004)
4q26-q28	Annexin A5	*ANXA5*	Gonzalez-Conejero et al. (2002)
4q28	Fibrinogen, B beta polypeptide	*FGB*	Behague et al. (1996)
4q28-q31	Fatty acid-binding protein 2	*FABP2*	Georgopoulos et al. (2007)
4q32.3	Palladin, cytoskeletal associated protein	*PALLD*	Shiffman et al. (2005)
5q13	Thrombospondin IV	*THBS4*	Topol et al. (2001)
5q23-q31	Integrin, alpha-2	*ITGA2*	Moshfegh et al. (1999)
5q31.1	Monocyte differentiation antigen CD14	*CD14*	Hubacek et al. (1999)
5q32-q34	Beta-2-adrenergic receptor	*ADRB2*	Sala et al. (2001)
5q33-qter	Factor XII	*F12*	Endler et al. (2001)
5q34	Potassium channel, calcium-activated, large conductance, subfamily M, beta member 1	*KCNMB1*	Senti et al. (2005)
6p25-p24	Factor XIII, A1 subunit	*F13A1*	Kohler et al. (1998)
6p21.3	Lymphotoxin-alpha	*LTA*	Ozaki et al. (2002)
6p21.3	Tumor necrosis factor	*TNF*	Vendrell et al. (2003)
6p21.2	Kinesin family member 6	*KIF6*	Iakoubova et al. (2008)
6p21.2-p12	Phospholipase A2, group VII	*PLA2G7*	Yamada et al. (1998)

Table 2 continued

Chromosomal locus	Gene name	Gene symbol	References
6p12	Glutamate-cysteine ligase, catalytic subunit	*GCLC*	Koide et al. (2003)
6p12	Vascular endothelial growth factor	*VEGF*	Howell et al. (2005)
6q22	c-Ros oncogene 1, receptor tyrosine kinase	*ROS1*	Shiffman et al. (2005)
6q22-q23	Ectonucleotide pyrophosphatase/phosphodiesterase 1	*ENPP1*	Bacci et al. (2005)
6q23	Arginase, liver	*ARG1*	Dumont et al. (2007)
6q25.1	Estrogen receptor 1	*ESR1*	Shearman et al. (2003)
6q25.3	Superoxide dismutase 2, mitochondrial	*SOD2*	Fujimoto et al. (2008)
6q26	Lipoprotein(a)	*LPA*	Holmer et al. (2003)
6q27	Thrombospondin II	*THBS2*	Topol et al. (2001)
7p21	Interleukin 6	*IL6*	Georges et al. (2001)
7q21.3	Paraoxonase 1	*PON1*	Serrato and Marian (1995)
7q21.3-q22	Plasminogen activator inhibitor 1	*PAI1*	Eriksson et al. (1995) and Yamada et al. (2002)
7q36	Nitric oxide synthase 3	*NOS3*	Shimasaki et al. (1998)
8p22	Lipoprotein lipase	*LPL*	Jemaa et al. (1995) and Yamada et al. (2006)
8p12	Plasminogen activator, tissue	*PLAT*	Ladenvall et al. (2002)
9p21.3	Cyclin-dependent kinase inhibitor 2A/B	*CDKN2A/B* (?)	Helgadottir et al. (2007), McPherson et al. (2007), Samani et al. (2007) and Wellcome Trust Case Control Consortium 2007
9q22-q31	ATP-binding cassette, subfamily A, member 1	*ABCA1*	Tregouet et al. (2004)
9q32-q33	Toll-like receptor 4	*TLR4*	Edfeldt et al. (2004)
10q24-q26	Beta-1-adrenergic receptor	*ADRB1*	Iwai et al. (2003)
11q22-q23	Matrix metalloproteinase 1	*MMP1*	Pearce et al. (2005)
11q23	Apolipoprotein A-V	*APOA5*	Talmud et al. (2004)
11q23	Apolipoprotein C-III	*APOC3*	Olivieri et al. (2002)
11q23	Matrix metalloproteinase 3	*MMP3*	Yamada et al. (2002) and Ye et al. (1995)
12p13.2	Taste receptor, type 2, member 50	*TAS2R50*	Shiffman et al. (2008)
12p13	Guanine nucleotide-binding protein, beta-3	*GNB3*	Naber et al. (2000)
12p13-p12	Low density lipoprotein, oxidized, receptor 1	*OLR1*	Mango et al. (2005)
12q22	Leukotriene A4 hydrolase	*LTA4H*	Helgadottir et al. (2006)
13q12	Arachidonate 5-lipoxygenase-activating protein	*ALOX5AP*	Helgadottir et al. (2004)
13q12.1	Insulin promoter factor 1	*IPF1*	Yamada et al. (2006)
13q14.11	Carboxypeptidase B2, plasma	*CPB2*	Juhan-Vague et al. (2002)
13q34	Factor VII	*F7*	Iacoviello et al. (1998)
13q34	Collagen, type IV, alpha 1	*COL4A1*	Yamada et al. (2008)
14q13	Proteasome subunit, alpha-type, 6	*PSMA6*	Ozaki et al. (2006)
15q15	Thrombospondin I	*THBS1*	Zwicker et al. (2006)
15q21-q23	Lipase, hepatic	*LIPC*	Dugi et al. (2001)
16p13.3	Deoxyribonuclease I	*DNASE1*	Kumamoto et al. (2006)
16p13	Major histocompatibility complex, class II, transactivator	*MHC2TA*	Swanberg et al. (2005)
16p11.2	Vitamin K epoxide reductase complex, subunit 1	*VKORC1*	Wang et al. (2006)
16q13	Matrix metalloproteinase 2	*MMP2*	Vasku et al. (2004)
16q21	Cholesteryl ester transfer protein, plasma	*CETP*	Kuivenhoven et al. (1998)
16q24	Cytochrome b(-245), alpha subunit	*CYBA*	Inoue et al. (1998)
17pter-p12	Glycoprotein Ib, platelet, alpha polypeptide	*GP1BA*	Murata et al. (1997)
17p13	Chemokine, CXC motif, ligand 16	*CXCL16*	Lundberg et al. (2005)
17q11.1-q12	Solute carrier family 6, member 4	*SLC6A4*	Fumeron et al. (2002)

Table 2 continued

Chromosomal locus	Gene name	Gene symbol	References
17q11.2-q12	Chemokine, CC motif, ligand 2	*CCL2*	McDermott et al. (2005)
17q21.1-q21.2	Chemokine, CC motif, ligand 11	*CCL11*	Zee et al. (2004)
17q21.32	Integrin, beta-3	*ITGB3*	Weiss et al. (1996)
17q23	Angiotensin I-converting enzyme	*ACE*	Cambien et al. (1992)
17q23	Platelet-endothelial cell adhesion molecule 1	*PECAM1*	Elrayess et al. (2004)
19p13	Purinergic receptor P2Y, G protein-coupled, 11	*P2RY11*	Amisten et al. (2007)
19p13.3-p13.2	Intercellular adhesion molecule 1	*ICAM1*	Podgoreanu et al. (2006)
19p13.2	Zinc finger protein 627	*ZNF627*	Shiffman et al. (2005) and Yamada et al. (2008)
19q13.1	Transforming growth factor, beta 1	*TGFB1*	Yokota et al. (2000)
19q13.2	Apolipoprotein E	*APOE*	Wilson et al. (1994)
19q13.2	Heterogeneous nuclear ribonucleoprotein U-like 1	*HNRPUL1*	Shiffman et al. (2006)
19q13.4	Glycoprotein VI, platelet	*GP6*	Croft et al. (2001)
19q13.4	Fc fragment of IgA, receptor for	*FCAR*	Iakoubova et al. (2006)
20p11.2	Thrombomodulin	*THBD*	Wu et al. (2001)
20q11.2-q13.1	Matrix metalloproteinase 9	*MMP9*	Zhang et al. (1999)
20q13.11-q13.13	Prostaglandin I2 synthase	*PTGIS*	Nakayama et al. (2002)
21q21.2	ADAM metallopeptidase with thrombospondin type 1 motif, 1	*ADAMTS1*	Sabatine et al. (2008)
22q11.2	Catechol-O-methyltransferase	*COMT*	Eriksson et al. (2004)
22q12	Heme oxygenase 1	*HMOX1*	Ono et al. (2004)
22q12-q13	Lectin, galactoside-binding, soluble, 2	*LGALS2*	Ozaki et al. (2004)

genetic variants have similar properties to intention-to-treat analyses in randomized controlled trials. The simplest way of appreciating the potential of Mendelian randomization analysis is to consider applications of the underlying principles. The inferences that can be drawn from Mendelian randomization studies depend on the different ways in which genetic variants can serve as a proxy for environmentally modifiable exposures (Davey Smith and Ebrahim 2005).

The relations of polymorphisms of the CRP gene (*CRP*) to circulating CRP concentrations and the prevalence of CHD or MI have been examined by Mendelian randomization analysis. Pooled data from 4,659 Caucasian men in six studies revealed that individuals homozygous for the *T* allele of the 1444C→T polymorphism of *CRP* had a higher circulating CRP concentration than carriers of the *C* allele. However, men with the *TT* genotype were not at increased risk of nonfatal MI (Casas et al. 2006). This unbiased and nonconfounded estimate of the effect of *CRP* genotype on coronary events was smaller than estimates provided by previous studies. In two independent prospective cohort studies of 32,826 women and 18,225 men in the US, the minor alleles of 1919A→T and 4741G→C polymorphisms of *CRP* were associated with higher plasma CRP levels, and those of 2667G→C and 3872C→T polymorphisms of *CRP* were associated with lower plasma CRP levels. Two of the five common haplotypes of *CRP* were associated with lower CRP levels. However, neither the individual SNPs nor the common haplotypes were associated with risk of CHD in the direction that would be predicted by their association with CRP levels (Pai et al. 2008). These data suggest that the underlying inflammatory processes that predict coronary events cannot be captured solely by variation in *CRP*. The CRP CHD Genetics Collaboration is a consortium of investigators generating and pooling analyses of data on genetic determinants of circulating CRP levels and CHD. These data should help to clarify the likelihood and magnitude of any causal association between circulating CRP concentration and CHD. The collaboration is likely to advance understanding of the relevance of low-grade inflammation to CHD and indicate whether or not CRP itself should be prioritized as a therapeutic target for long-term prevention strategies (CRP CHD Genetics Collaboration 2008).

Candidate gene association studies for MI or CHD

Association studies based on the candidate gene approach have revealed many polymorphisms to be associated with the prevalence of MI or CHD (Table 2). In this section, we

discuss the association of polymorphisms in *MTHFR*, *LPL*, and *APOE* with MI or CHD.

MTHFR

Homocysteine is a sulfur-containing amino acid that plays a pivotal role in methionine metabolism. 5,10-Methylenetetrahydrofolate reductase (MTHFR) catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, a reaction that provides a substrate for the methylation of homocysteine to methionine catalyzed by methionine synthase. Individuals with the 677C→T (Ala222Val) substitution of *MTHFR* manifest reduced MTHFR activity and higher plasma homocysteine levels compared with those without it (Deloughery et al. 1996; Ma et al. 1996; Schwartz et al. 1997). Association of the 677C→T (Ala222Val) polymorphism of *MTHFR* with CHD or MI has been described by several groups, with the *TT* genotype being a risk factor for these conditions (Gallagher et al. 1996; Kluijtmans et al. 1996; Mager et al. 1999; Morita et al. 1997; Yamada et al. 2006). Other studies, however, did not support such an association (Folsom et al. 1998; Schwartz et al. 1997). These apparently contradictory results are attributable, at least in part, to differences in intake of folate and other B vitamins (Verhoef et al. 1998). A meta-analysis of the association of the 677C→T (Ala222Val) polymorphism of *MTHFR* with the risk of CHD in 11,162 cases and 12,758 controls from 40 studies revealed that individuals with the *TT* genotype had an odds ratio of 1.16 for CHD compared with those with the *CC* genotype (Klerk et al. 2002). These observations suggest that impaired folate metabolism, resulting in high homocysteine concentrations, is an important determinant of CHD. Another meta-analysis of the association of the 677C→T (Ala222Val) polymorphism of *MTHFR* with CHD in 26,000 cases and 31,183 controls from 80 studies yielded an overall odds ratio of 1.14 for the *TT* genotype versus the *CC* genotype; odds ratios for Europe, Australia, and North America were about 1.0, whereas those for the Middle East and Asia were 2.61 and 1.23, respectively (Lewis et al. 2005). These results indicate that the 677C→T (Ala222Val) polymorphism of *MTHFR* is associated with CHD in the Middle East and Asia, but not in Europe, North America, or Australia, with this geographic variability possibly reflecting higher folate intake in the latter regions (Lewis et al. 2005).

LPL

Lipoprotein lipase (LPL) is the rate-limiting enzyme in lipolysis of triglyceride-rich lipoproteins in the circulation. It is synthesized in parenchymal cells of adipose tissue as well as in skeletal and cardiac muscle, and it is then transferred to heparan sulfate-binding sites of the vascular endothelium (Kastelein et al. 2000). The hydrolytic function of LPL is important for the processing of triglyceride-rich chylomicrons and very low density lipoproteins to remnant particles as well as for the transfer of phospholipids and apolipoproteins to high density lipoproteins (HDLs). LPL also plays an important role in the receptor-mediated removal of lipoproteins from the circulation (Groenemeijer et al. 1997). *LPL* is polymorphic, with amino acid substitutions of the encoded protein affecting triglyceride and HDL-cholesterol levels, which are implicated in atherosclerosis risk (Wittrup et al. 1999). The 1595C→G (Ser447Stop) substitution of *LPL* results in carboxyl-terminal truncation of LPL by two amino acids. This change is thought to increase the binding affinity of the protein for receptors or to facilitate or otherwise affect its formation of dimers (Wittrup et al. 1999). The *G* (Stop) allele of the 1595C→G (Ser447Stop) polymorphism has also been shown to be related to decreased plasma triglyceride or increased HDL-cholesterol levels, or both (Groenemeijer et al. 1997; Jemaa et al. 1995; Kuivenhoven et al. 1997; Wittrup et al. 1999). In addition, the *G* (Stop) allele of this polymorphism was found to be associated with a reduced risk of CHD or MI (Wittrup et al. 1999; Yamada et al. 2006; Yang et al. 2004). Evidence suggests that the catalytic activity and stability of the truncated variant of LPL may be largely normal, but that it may be present at higher concentrations in the circulation, resulting in a higher level of LPL activity (Groenemeijer et al. 1997; Henderson et al. 1999; Humphries et al. 1998; Zhang et al. 1996).

APOE

Apolipoprotein E (ApoE) plays an important role in lipid transport and metabolism. Three common alleles (ε2, ε3, and ε4) of *APOE* encode the three major isoforms (E2, E3, and E4) of ApoE, which differ at amino acid positions 112 and 158. Allelic variation of *APOE* accounts for interindividual variability in total cholesterol and low density lipoprotein (LDL)–cholesterol concentrations, with studies in human populations demonstrating associations of the ε4 and ε2 alleles with increased and decreased LDL-cholesterol levels, respectively (Ehnholm et al. 1986; Sing and Davignon 1985; Xhignesse et al. 1991). The various ApoE isoforms interact differently with specific lipoprotein receptors, ultimately affecting circulating levels of cholesterol (Eichner et al. 2002). ApoE from very low density lipoprotein, chylomicrons, and chylomicron remnants binds to specific receptors on cells in the liver. Carriers of the ε2 allele of *APOE* are less efficient than carriers of the ε3 or ε4 alleles at synthesizing very low density lipoprotein and chylomicrons and at transferring them from plasma to the liver as a result of the binding properties of the ApoE2

isoform. Thus, compared with carriers of the ε3 or ε4 alleles, carriers of the ε2 allele are slower to clear dietary fat from their blood (Weintraub et al. 1987). The difference in uptake of postprandial lipoprotein particles results in differences in regulation of hepatic LDL receptors, which in turn contribute to genotypic differences in total and LDL-cholesterol levels (Davignon et al. 1988; Hallman et al. 1991; Schaefer et al. 1994).

The relation of *APOE* polymorphisms to CHD or MI has been extensively investigated in the last 2 decades. In many studies, the ε4 allele has been associated with CAD or MI (Lahoz et al. 2001; van Bokxmeer and Mamotte 1992; Wilson et al. 1994). A meta-analysis of 15,492 subjects with CHD and 32,965 controls pooled from 48 studies revealed that, compared with individuals with the ε3/ε3 genotype, carriers of the ε4 allele had a higher risk for CHD (odds ratio, 1.42), whereas the ε2 allele was not associated with CHD risk (Song et al. 2004). The ε4 allele of *APOE* is thus an important risk factor for CHD.

The -219G→T SNP of *APOE* has been associated with MI for men in France and Northern Ireland, with the *T* allele representing a risk factor for this condition (Lambert et al. 2000). Consistent with its location in the promoter region of *APOE*, the -219G→T SNP was shown to be associated with the plasma concentration of ApoE, with the *T* allele conferring a reduced ApoE concentration (Lambert et al. 2000). The deleterious influence of the *T* allele on MI therefore cannot be explained by its effect on the circulating level of ApoE. The *T* allele of this SNP was also shown to be a risk factor for CHD in low-risk Japanese men (Hirashiki et al. 2003).

Genome-wide association studies of MI or CHD

GWASs have identified susceptibility genes for various multifactorial diseases, including CHD and MI (Table 3).

LTA

Screening of 65,671 SNPs revealed that two polymorphisms of the lymphotoxin-α gene (*LTA*) were associated with susceptibility to MI in a study with 1,133 MI patients and 1,878 controls (Ozaki et al. 2002). Functional analysis in vitro indicated that the *G* allele of one of these two polymorphisms, 252A→G in intron 1 (rs909253), was associated with an increase in the transcriptional activity of *LTA* and that the *A* (Asn) allele of the second SNP, 804C→A (Thr26Asn) in exon 3 (rs1041981), was associated with increased expression of the genes for vascular cell adhesion molecule 1 and selectin E. Ozaki et al. (2002) thus suggested that variants of *LTA* are risk factors for MI and that they influence the vascular inflammation that underlies this condition. These researchers subsequently showed that the 3279C→T polymorphism in intron 1 of the lectin, galactoside-binding, soluble, two gene (*LGALS2*) was associated with the prevalence of MI (Ozaki et al. 2004). LGALS2 plays a role in the secretion of LTA from smooth muscle cells and macrophages, and the identified polymorphism affects the transcriptional activity of *LGALS2*. These results suggested that an LGALS2–LTA axis is important in the pathophysiology of coronary atherosclerosis and thrombosis.

The relation of seven SNPs (rs2071590, rs1800683, rs909253, rs746868, rs2857713, rs3093543, and rs1041981) distributed throughout *LTA* and of their corresponding haplotypes to risk of MI was examined in the International Study of Infarct Survival (ISIS) case–control study involving 6,928 cases of nonfatal MI and 2,712 unrelated controls (Clarke et al. 2006). The seven SNPs were in strong linkage disequilibrium with each other and formed six common haplotypes. None of the SNPs or haplotypes was associated with risk of MI. A meta-analysis of rs909253 or rs1041981 in six previously published studies and the ISIS study (Clarke et al. 2006) found no association with CHD risk in a recessive model (odds raio, 1.07) and only a moderate association in a dominant model (odds raio, 1.09). Overall, these studies suggest that these common polymorphisms of *LTA* are not associated with susceptibility to CHD or MI. Given that the effect of *LTA* variants on the development of MI might differ among ethnic groups or among individuals exposed to different environmental factors such as smoking, further investigation is warranted with large independent subject panels of different ethnic groups.

Table 3 Genome-wide association studies of myocardial infarction (MI) or coronary heart disease (CHD)

Chromosomal locus	Gene symbol	Phenotype	SNP array	References
6p21.3	*LTA*	MI	Japanese SNP database	Ozaki et al. (2002)
9p21.3	*CDKN2A/B* (?)	CHD	100 K custom array	McPherson et al. (2007)
9p21.3	*CDKN2A/B* (?)	MI	Hap 300 K array (Illumina)	Helgadottir et al. (2007)
9p21.3	*CDKN2A/B* (?)	CHD	GeneChip 500 K array (Affymetrix)	Wellcome Trust Case Control Consortium (2007)
9p21.3	*CDKN2A/B* (?)	CHD	GeneChip 500 K array (Affymetrix)	Samani et al. (2007)

Chromosome 9p21.3

In 2007, independent GWASs based on the use of SNP chips identified four SNPs on chromosome 9p21.3 that were associated with CHD or MI in several white cohorts (Helgadottir et al. 2007; McPherson et al. 2007; Samani et al. 2007; Wellcome Trust Case Control Consortium 2007). McPherson et al. (2007) identified two susceptibility SNPs (rs10757274 and rs2383206) that were located within 20 kbp of each other on chromosome 9p21.3 and were associated with CHD in a Canadian population and five other white cohorts. Helgadottir et al. (2007) described an association between MI and two SNPs (rs2383207 and rs10757278) located in the same 9p21.3 region in an Icelandic population, and they replicated the finding in four white cohorts. The same genetic locus was also identified by a GWAS performed with 1,926 CHD cases and 3,000 controls from a British population (Wellcome Trust Case Control Consortium 2007), and the finding was replicated in a German population (Samani et al. 2007). Association of SNPs on chromosome 9p21.3 was also replicated for MI in an Italian population (Shen et al. 2008b) and for CHD in a Korean population (Shen et al. 2008a). Interestingly, the independent population-based case–control studies also identified several SNPs at 9p21.3 that were significantly associated with type 2 diabetes mellitus in white populations in England (Zeggini et al. 2007), Finland (Scott et al. 2007), and Sweden (Saxena et al. 2007). In addition to MI, SNP rs10757278 at this locus was found to be associated with abdominal aortic aneurysm and intracranial aneurysm (Helgadottir et al. 2008). Schunkert et al. (2008) genotyped a SNP (rs1333049) representing the 9p21.3 locus in seven case–control studies including a total of 4,645 subjects with MI or CHD and 5,177 controls. The risk allele (*C*) of this SNP was uniformly associated with MI or CHD in each study, with pooled analysis revealing the odds ratio per copy of the risk allele to be 1.29. Meta-analysis of rs1333049 in 12,004 cases and 28,949 controls provided further evidence for association of this SNP with MI or CHD, yielding an odds ratio of 1.24 per risk allele.

The prospective Northwick Park Heart Study II analyzed complete trait and genotype information available for 2,057 men (183 CHD events over 10.8 years). For a panel of selected genotypes for *UCP2*, *APOE*, *LPL*, *APOA4*, *IL6*, and *PECAM1*, CHD risk estimates incorporating conventional risk factors (age, triglyceride and cholesterol levels, systolic blood pressure, and smoking) and genetic risk interactions were more effective than those based on conventional risk factors alone (Humphries et al. 2007). In a study of the same cohort involving 2,742 men (270 CHD events over 15 years), although rs10757274 at 9p21.3 was associated with CHD, it did not add substantially to the usefulness of the Framingham risk score based on conventional risk factors alone for predicting future CHD events. However, it did improve reclassification of CHD risk and thus may be of clinical utility (Talmud et al. 2008).

Although this broad replication of the association with chromosome 9p21.3 provides important new information on the molecular genetics of CHD and MI, the underlying mechanism is as yet elusive. The region is defined by two flanking recombination hot spots and contains the coding sequences of genes for two cyclin-dependent kinase inhibitors, *CDKN2A* and *CDKN2B*. These genes play an important role in regulation of the cell cycle and belong to a family of genes that have been implicated in the pathogenesis of atherosclerosis as a result of their contribution to inhibition of cell growth by transforming growth factor-β1. However, the SNPs associated most strongly with MI or CHD lie considerably upstream of these genes, with the nearest being located 10 kbp upstream of *CDKN2B*. Although an effect mediated through one or both of these genes is possible, other explanations for the association of the 9p21.3 region with MI or CHD need to be considered (Schunkert et al. 2008).

The high-risk CHD haplotype at 9p21.3 [T (rs10116277)–T (rs6475606)–G (rs10738607)–T (rs10757272)–G (rs1075-7274)–G (4977574)–G (2891168)–G (1333042)–G (23832-06)–G (2383207)–C (1333045)–G (10757278)–C (1333048)–C (1333049)] was recently shown to overlap with exons 13 to 19 of *ANRIL* (Broadbent et al. 2008) (Fig. 1), a newly annotated gene for a large antisense noncoding RNA that was identified by deletion analysis of an extended French family with hereditary melanoma–neural system tumors (Pasmant et al. 2007). Reverse transcription and polymerase chain reaction analysis showed that *ANRIL* is expressed in atheromatous human vessels (specimens of abdominal aortic aneurysm or carotid endarterectomy), which manifest a cell type profile similar to that of atherosclerotic coronary arteries. *ANRIL* was found to be expressed in vascular endothelial cells, monocyte-derived macrophages, and coronary smooth muscle cells (Broadbent et al. 2008), all of which contribute to atherosclerosis. Little is known of the function of *ANRIL*, as is typical of most genes for noncoding RNAs, which in general are thought to participate in

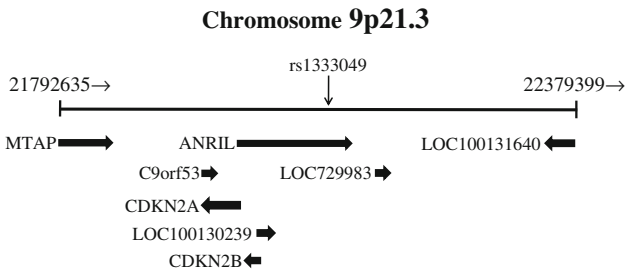

Fig. 1 Genomic region at chromosome 9p21.3

transcriptional control (Mattick and Makunin 2006). A survey of the dbSNP database revealed no SNPs that map within the exons of *ANRIL* that colocalize with the risk haplotype. However, multiple SNPs coupled to the high-risk haplotype map to intronic or downstream sequences of this gene; these variants are plausible candidates for determinants of the level of *ANRIL* expression. The targets of *ANRIL* action remain to be discovered, as do any interactions with neighboring genes (Broadbent et al. 2008). Clarification of the functional relevance of SNPs at 9p21.3 to CHD and MI may provide insight into the pathogenesis of these conditions as well as into the role of genetic factors in their development.

Conclusion

There has been a growing effort to find genetic variants that confer risk for CHD and MI as a means to understand the underlying biological events of these conditions. Such studies may ultimately lead to the personalized prevention of MI (Yamada 2006). It may thus become possible to predict the future risk for MI in each individual on the basis of conventional laboratory examinations and genetic analyses. It should also be possible to assess how the risk level of an individual will decrease if treatable risk factors, including hypertension, diabetes mellitus, hypercholesterolemia or dyslipidemia, and smoking, are ameliorated or eliminated. Furthermore, it may be possible to prevent an individual from undergoing MI by medical intervention based on his or her genotype for specific polymorphisms. In the future, we may have the ability to use specific therapeutic agents individualized on the basis of certain genetic susceptibility factors, thereby increasing the efficacy and limiting the toxicity of treatment (Damani and Topol 2007). Identification of disease susceptibility genes will thus contribute to the prevention, early diagnosis, and treatment of CHD and MI.

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