Coronary artery disease (CAD) remains the number one cause of death in industrialized countries despite our collective efforts to minimize attributable risk from known contributors to CAD such as hypertension, dyslipidemia, and smoking. In addition, clinical trials have consistently demonstrated a family history of coronary disease to be predictive for future cardiovascular events beyond that which would be explained by traditional risk factors. These findings support and have prompted widespread investigation into the genomic basis of CAD and myocardial infarction (MI). Recent advances in genotyping technology have allowed for easier identification and confirmation of susceptibility genes for complex traits across different cohorts via increased power of studies stemming from faster accrual of cases and control subjects and more precise genetic mapping. These technological advances have resulted in defining the genes contributing to a substantial or even majority of population-attributable risk for type 2 diabetes and age-related macular degeneration (AMD) cases. Similar progress in replicating novel susceptibility genes for CAD and specifically MI is now rapidly occurring, with a recent gene marker on chromosome 9p21 representing a highly significant and common variant susceptibility factor. With improved resequencing technology and better phenotypic characterization of our CAD cases and control subjects, we should achieve successes in gene identification and confirmation similar to diabetes and AMD, thereby allowing us to better quantify CAD risk earlier in life and institute more effective therapy reducing the individual propensity to develop CAD. (J Am Coll Cardiol 2007;50:1933–40) © 2007 by the American College of Cardiology Foundation

G.M. is a 53-year-old woman recently diagnosed with coronary artery disease (CAD) via coronary angiography. Her evaluation was prompted by progressive breathlessness. She is a nonsmoker, and her only risk factor is a significant family history with a brother and father having myocardial infarctions (MIs) in their 40s. She was found by angiography to have 60% and 70% stenoses in her midleft anterior descending artery and a diagonal branch, respectively.

What is G.M.’s risk for having a future MI? What is the risk for MI in her other siblings? Her offspring? How might we target prevention and therapy specifically for G.M.? Answers to these critical questions will eventually rely on our ability to establish the genomic basis of MI and CAD. The purpose of this review is to summarize the conceptual progress that has been made in this field, both with respect to the genomics of CAD, and related complex traits that are further along and hopefully foretell what the landscape will ultimately look like for atherosclerotic coronary disease.

Dissecting the Human Genome

Before embarking on a further discussion of genomics, it is important to understand heritability of traits. “Simple” Mendelian traits are relatively infrequent and deterministic, segregating in an autosomal dominant, recessive, X-linked, or mitochondrial basis (1). Examples include familial hypertrophic cardiomyopathy, Marfan’s syndrome, and the long QT syndromes. Complex traits such as MI, type 2 diabetes mellitus (DM), and age-related macular degeneration (AMD) involve multiple gene–gene and gene–environmental interactions. These traits are relatively common, do not segregate in Mendelian fashion, and are probabilistic with respect to inducing susceptibility (1).

Even though the draft of the human genome was announced in 2000, and published the following year, there has been an appreciable gap from having a map of where genes are located to understanding which genes play a role in health and disease. The human genome consists of 3.1 billion base pairs (bps) but fewer than 24,000 genes, and although it may seem to be difficult to pinpoint the principal genes that underlie the biological basis of a particular disease, there have been great strides in recent years in defining “blocks” or “bins” of the units of the genome that are in linkage disequilibrium, that is, inherited as a block without recombination (Fig. 1). This major advance can be likened to zip codes for facilitation of locating an area of interest within the genome, thereby providing us an opportunity to study haplotypes or linkage disequilibrium bins or blocks to simplify the search for a location in the genome that is associated with a medical condition.
Previous methods for determining genetic linkage of a complex trait relied chiefly upon the technique of genome-wide scanning with microsatellites (short tandem repeat sequences). This required the laborious accrual of hundreds of families, particularly sibling pairs of MI or CAD (or both). Using 400 microsatellite markers distributed evenly across the genome every 10 centimorgan (approximately 1 million bps), the genomes were systematically assessed to search for a “linkage peak” or an extensive allele sharing locus among affected siblings and family members as compared with unaffected individuals. A significant linkage peak is defined by a logarithm of odds ratio score ≥3.5 corresponding to a p < 10^{-6} (2). Such a linkage peak would indicate a gene that is in linkage disequilibrium near or even within a microsatellite region. However, identifying disease-causing genes interspersed between microsatellites, or 1 million bps, has proved to be quite difficult (2). This is illustrated by the relatively limited success of the 9 genome-wide linkage scans that have been performed to date identifying only 4 genes and only 1 locus that has been replicated from one study to the next: 2p11 British Heart Foundation and in the studies by Wang et al. (3–14).

A more contemporary approach in genotyping involves the use of ultra-high throughput assessment of single nucleotide polymorphisms (SNPs) across the genome to establish association (Fig. 2). Of the 3.1 billion bps in our genome, our interindividuality is determined by only 0.1% or approximately 3 million of those base pairs (15,16). These are referred to as SNPs. Fortunately there is an even smaller number of “tag” SNPs (approximately 250,000 in those of European ancestry to 500,000 in those of African ancestry) that identify the various haplotypes (collections of SNPs inherited together) present within a population. Thus, essentially less than 0.01% of all nucleotides comprising the human genome can be used to codify each individual (17).

When assessing these vital tag SNPs in high throughput genotyping, we are able to utilize sporadic cases of MI and CAD in a cohort instead of sibling-pairs or “multiplex” families. This allows for rapid accrual of a large number of sporadic cases for independent genomic studies and a corresponding increase in power of these studies to detect haplotypes that are in linkage disequilibrium with disease-causing genes (Table 1). For example, this technology has been used in the discovery of complement factor H (CFH) as the basis for AMD, the leading cause of adult blindness (18–22). Several other notable susceptibility loci and genes for complex traits have also been discovered or validated via this process including type 2 DM, systemic lupus erythematosus, inflammatory bowel disease, obesity, prostate cancer, rheumatoid arthritis, acute lymphoblastic leukemia, and MI (23–40) (Table 2).

Very recently, genome-wide association studies have identified and widely replicated a common variant of the genome associated with MI and CAD (38–40). Many additional, parallel studies are currently in progress. However, it is important to note that genetic contribution to complex traits can be a combination of common sequence variants with a small effect (low odds ratio), or rare sequence variants with a large effect. Traditionally, searches for rare variants in large-scale population-based studies have been of prohibitive cost secondary to the need for resequencing entire nucleotide sequences of genes in thousands of individuals. However, recent advances in technology have significantly reduced costs for resequencing making these searches possible (41). Using this technology, Cohen et al. (42–44) have had remarkable success in identifying rare variants in quantitative metabolic traits with known contribution to atherosclerosis by resequencing candidate genes in populations presenting on either extreme of a distribution.
Most recently, Romeo et al. (45) were the first to use resequencing technology in a large population to demonstrate that rare variants in ANGPTL4, a gene with known effects on lipid metabolism in mice, influenced the level of plasma triglycerides in individuals of European-American ancestry.

The greatest strides in defining and quantifying genetic predisposition to complex traits have come with recent breakthroughs in type 2 DM and AMD using genome-wide association studies. Common variants in 2 genes implicated in the complement pathway and 1 gene whose product has yet to be determined have shown to contribute to over half of the heritability of AMD. These findings have been confirmed in multiple independent studies (18–22,46,47). In addition, carriers of these same genetic mutations are now demonstrating more rapidly progressive disease in comparison with their counterparts without the mutations (48). This homozygous variant of CFH implicated in AMD has now also been demonstrated to increase susceptibility for MI (49,50). This is not surprising given the similarity of known epidemiologic risk factors for AMD and CAD: smoking, high fat diet, hypertension, and high C-reactive protein.

Similar findings to AMD are now unfolding with type 2 DM. Grant et al. (24) first reported on a variant of the gene TCF7L2, which has been linked to reduced beta cell function and poor insulin response to oral glucose loads (51). Since its first discovery, this gene has been widely confirmed in independent studies as a pivotal susceptibility marker for type 2 DM (23,25–28,40). Recently, 6 genome-wide SNP association studies have identified and replicated in separate stages several additional novel genes conferring susceptibility to type 2 DM (23,25–28,40) (Table 2). Interestingly, these loci primarily include genes involved in pancreatic beta cell development and function as opposed to insulin resistance—the current accepted mechanism for type 2 DM. This development casts doubt on our traditional pathophysiological modeling of the type 2 diabetic patient and underscores the need for genomic studies to further define pathobiological processes of complex traits.

### Identifying Major Pathways

Through genomics research, we have thus far identified 4 distinct biological pathways contributing to CAD and specifically MI. These include disturbances in lipoprotein handling, vulnerability of endothelial integrity, altered arterial inflammation, and thrombosis. The following is a brief overview of the key genes implicated in each pathway (Table 3).

#### Altered lipoprotein handling.

The classic example is the extensively studied polymorphism in the apolipoprotein (apo) E gene. Amino acid substitutions at residues 112 and 158 are responsible for 3 variants: apo E2 (cysteine, cysteine), apo E3 (cysteine, arginine), and apo E4 (arginine, arginine). Song et al. (52) demonstrated an increased risk for MI and CAD with the E4 allele in their meta-analysis of 48 studies. The functional genomics of this polymorphism is incompletely understood. However, these patients have been shown to have a predisposition to elevated low-density lipoprotein (LDL) and an exquisite sensitivity to statins (53).

### Table 1 Differences Between Genome-Wide Linkage Scans and SNP Association Studies

<table>
<thead>
<tr>
<th>Genome-Wide Linkage Scans</th>
<th>SNP Association Studies</th>
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<tr>
<td>Affected and unaffected sibling pairs of “multiplex” families</td>
<td>Sporadic cases and controls</td>
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<tr>
<td>Utilizes microsatellite markers</td>
<td>Utilizes SNPs</td>
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<td>Laborious accrual of families</td>
<td>Rapid accrual of cases and control subjects</td>
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<tr>
<td>Less power to detect common genotypic variants</td>
<td>Increased power to detect common genotypic variants</td>
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<td>Easier replication in independent studies</td>
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SNP = single nucleotide polymorphism.
Two mutations have recently been described in a cholesterol-regulated gene encoding, proprotein convertase subtilisin/kexin type 9 (PCSK9), which is a serine protease that modulates LDL receptor levels (42,43,54,55). Variants in this gene have shown direct correlation with both high and low LDL cholesterol. In the ARIC (Atherosclerosis Risk In Communities) study, nonsense mutations in PCSK9 were associated with a striking reduction in LDL levels, MI, CAD-related death, and repeat revascularization in patients of African descent. This finding further reinforces the concept that lifelong LDL cholesterol reduction may be associated with a dramatic lowering of cardiovascular events.

Recently, Mani et al. (56) described a mutation in the LRP6 gene, which encodes a coreceptor in the Wnt signaling pathway. Functional studies showed a missense mutation in this gene at a normally highly conserved residue impaired Wnt signaling in vitro and clinically led to hyperlipidemia, hypertriglyceridemia, and early onset CAD. Whether other Wnt pathway genes will be implicated in more common forms of CAD remains to be seen.

Disruption in endothelial integrity. The thrombospondin (TSP) family of matrix proteins are associated with premature MI (57). The proline for alanine substitution in the TSP 4 variant resulted in a near 2-fold risk for MI. This gain-of-function mutation causes increased calcium binding of the TSP 4 variant and is associated with a dramatic reduction in endothelial proliferation, or otherwise stated, inability for appropriate endothelial repair. The risk for premature MI with this variant has been replicated in multiple studies (58–61). Yamada et al. (61) noted a polymorphism in the connexin 37 gene, an endothelial gap-junctional protein preventing diapedesis of inflammatory cells and LDL cholesterol, to be associated with MI after adjustment for risk factors.

Wang et al. (62) identified a 21-bp deletion in the transcription factor myocyte enhancer factor 2a (MEF2A) and low LDL cholesterol. In the ARIC (Atherosclerosis Risk In Communities) study, nonsense mutations in PCSK9 were associated with a striking reduction in LDL levels, MI, CAD-related death, and repeat revascularization in patients of African descent. This finding further reinforces the concept that lifelong LDL cholesterol reduction may be associated with a dramatic lowering of cardiovascular events.

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in a family with an autosomal dominant inheritance pattern of MI. Functional studies demonstrated the mutant MEF2A's inability to localize in the nucleus of arterial endothelial cells and virtual shutdown of transcription. Missense point mutations in the same gene have also been noted to be associated with MI in over 400 cases and control subjects (63). Weng et al. (64) challenged these findings with the same 21-bp deletion noted in control subjects without CAD, but potential methodological flaws were noted in their study. Incomplete penetrance of the rare deletion mutation may also explain this discrepancy (65).

**Arterial inflammation.** Perhaps the most substantial progress to date has been made in identifying genes with a role in inflammation and MI. Helgadottir et al. (5,12) identified 2 genes in the same inflammation pathway of leukotriene production—a pathway that has been unequivocally associated with atherosclerosis (66). Both haplotype variants of 5-lipoxygenase activating protein (FLAP) and leukotriene A4 hydrolase (LTA4H) were found to be associated with MI. Of note, LTA4H was the first gene linked to MI that showed ancestry-specific risk with a relative risk (RR) of 1.2 for European Americans and RR of 3.5 in those with African ancestry. These findings led to the first gene-specific cardiovascular clinical development program with a FLAP blocker in a phase 2 placebo-controlled, crossover, double-blind clinical trial, showing leukotriene production and C-reactive protein were reduced (67,68).

Ozaki et al. (68,69) performed the first whole-genome association study of over 90,000 SNPs in over 13,000 genes. A 5-SNP haplotype of the lymphotixin-alpha gene (LTA) was shown to be associated with MI. Functional studies demonstrated a gain-of-function effect by increasing vascular cell adhesion molecule expression thereby inducing proinflammatory and proatherogenic effects. Subsequently, a critical ligand to LTA, galectin 2 (LGALS2) from the galactose-binding lectin family, was also found to be highly significant for MI (RR 0.4, p = 2.6 × 10^{-6}) with the TT allele conferring protection and the CC allele vulnerability. Thus, for the first time, genes for both a ligand and a receptor have been associated with MI.

Other genes implicated in the inflammatory pathway and MI include stromelysin 1, a matrix metalloproteinase (61), Ox40L (70), a cytokine from the tumor necrosis factor family, and multihistocompatibility factor (MHC2TA) promoter A168G SNP, which was significantly associated with not only MI, but 2 other diseases associated with inflammation—rheumatoid arthritis and multiple sclerosis (71). Most recently from a prior linkage peak, Wang et al. (13) demonstrated the KALRN gene, belonging to the Rho GTPase-signaling pathway, to have a significant association with early onset CAD cases among individuals of European ancestry.

**Thrombosis.** Genes modifying the normal process of clot and thrombus formation have also been implicated in multiple studies. Shiffman et al. (72) identified a VAMP8 variant, a gene modulating platelet degranulation, correlating with early onset MI. A polymorphism in the plasminogen activator inhibitor-1 gene has also been implicated in women with MI (61). Two variants described in the coagulation pathway are in factor V (1691A) and prothrombin (20210A), which were both shown to have increased risk for MI in a comprehensive meta-analysis (73).

**Challenges to Progress**

Unlike conditions such as AMD and diabetes where genomic findings have been extensively replicated and very large phenotypic effects of gene variants have been defined, we are only now beginning to demonstrate this with CAD. A significant source of difficulty has been from poor phenotypic characterization of cases and control subjects (74). Unlike AMD and type 2 DM where a well-accepted phenotype and a standard definition of disease exist, atherosclerotic CAD has a wide range of clinical manifestations, from asymptomatic disease to acute MI to sudden cardiac death. This contributes substantially to the genotypic heterogeneity of cohorts that have been assessed to date. Myocardial infarction, however, is a relatively infrequent phenomenon and has discrete manifestations demonstrated by electrocardiogram and positive biomarkers indicating myocardial necrosis. Hence, MI is a more “restrictive” phenotype allowing better standardization across independent studies with documented success in identifying novel genes (5,38–40,57,58). Support for this concept is demonstrated by MI showing much greater heritability in independent studies to date and the lack of this demonstration using atherosclerotic CAD as a marker (7,38–40,57).

The lack of a clear definition for control subjects is also a significant confounder. The “ideal” control would be a 90-year-old individual with completely normal coronary arteries on angiography and no prior history of MI. However, this is unrealistic for multiple reasons. First, atherosclerotic CAD is nearly pervasive in our population—even in many younger patients (75). Second, performing invasive studies in all normal control subjects to establish lack of disease is not feasible, and there exists a distinct possibility that age-matched control subjects may, later in life, become cases. Therefore, useful parameters in selecting control subjects include age >20 years older than cases, documented absence of traditional risk factors, and lack of other forms atherosclerotic disease. In addition, functional non-invasive testing or use of multidetector computed tomography to ensure accurate phenotyping may be necessary (74).

Other specific factors contributing to genotypic heterogeneity and thus making replication of findings in independent studies of MI more challenging than other complex traits are ancestry specific risk for CAD, age of onset of disease with premature CAD showing greater heritability than late onset disease (38,76,77), and inadequately of power of studies to detect genes with rare sequence variants contributing potentially large phenotypic effect. In addition, attributable risk from a single genetic polymorphism may be
magnified or offset by the presence or absence of various genetic and epigenetic modifiers. Hence, multiple genetic variants may only confer attributable risk for disease when considered in aggregate. This would weaken the value of any test that searches for a single genetic variant contributing substantial risk for CAD.

Finally, a logistic challenge we must confront when most MI susceptibility genes are implicated is the potential of exorbitant cost associated with genetic testing. This would potentially stem from licensing of patents or acquiring rights for commercial use of discovery of key genes.

**Our Current State and Future Directions**

Despite the vast number of challenges present in establishing the genomic basis of MI, we have made substantial progress in further defining this disease. For the first time, 3 separate whole-genome association studies with replication in 7 independent study populations, involving over 40,000 patients of European descent identified and validated a single susceptibility locus on chromosome 9p21 that contributes a large attributable risk for MI in those of European descent (38–40). Over 20% of individuals are homozygous for allele G of the SNP rs10757278, which is near tumor suppressor genes CDKN2A/B. The population-attributable risk of this SNP marker is 21% for MI at any age, and 31% for premature MI, with an odds ratio of 1.4 to 2.0, respectively. Interestingly, this SNP marker is also very close to an SNP near CDKN2B recently identified as a susceptibility factor for type 2 DM (28,40). Furthermore, the Oxford investigators (40) have identified many additional SNPs of significance (p < 10^{-5} to 10^{-6}), albeit not of genome-wide significance, that if replicated may be an important contributor to CAD risk. These 3 studies are similar in quality to those performed in AMD, type 2 DM, and other diseases where more significant progress has been made in defining their genetic architecture.

Through genome-wide linkage scans and SNP association studies we have been able to implicate specific genes and loci involved in the intricate biological pathways of MI that would otherwise have not been appreciated such as with LTA, FLAP, LTA4, and now a common variant on 9p21, the functional genomics of which still needs elucidation. Furthermore, these genes have already served as a potential source for a targeted medicine approach to CAD (therapy specifically chosen to match one’s genetic profile), with the ongoing trial of the FLAP receptor blocker as a prime example. The apo E4 gene variant also requires our further attention. Apo E4 has been widely replicated in independent studies consistently demonstrating increased risk for CAD (52,78). A compelling argument can be made to initiate routine screening for this allele in our high-risk CAD patients, especially considering the striking reduction in mortality demonstrated with statin use in apo E4 carriers with prior MI (53). However, before widespread acceptance of this testing, we must first address the unique ethical implications present with identifying those with the apo E4 gene given its link to Alzheimer’s disease susceptibility (79).

A recent study has raised questions about whether genotyping of currently validated genes would be fruitful for assessing susceptibility risk (80). However, this study, which questioned replication of 85 genes implicated in CAD, is difficult to interpret. The control subjects used were not assessed for coronary disease, and the cases combined various subtypes of acute coronary syndrome altogether. The statistical power was also remarkably low to detect any effect of uncommon variants.

Our patient, G.M., is relatively young with a strong family history for premature MI and has an otherwise low-risk profile. Based on her family history, she is at increased risk for future MI not explained by traditional risk factors. However, at this time we are unable to specifically quantify this risk. Ultimately, our ability to better define our predisposition to MI depends on our enhancing our understanding of the complexities of the human genome. This will require better phenotypic characterization of CAD cases and control subjects in well-designed clinical trials and subsequently confirming any findings in independent cohorts. By doing so, we will minimize the potential for false-positive associations between genetic variants and CAD susceptibility, a problem that has provided a serious impediment to the widespread replication of genomic findings in the past (Table 3). The recent breakthrough studies widely replicating the common genetic variant on 9p21 in multiple large populations should serve as a reference standard when designing future genomic studies to determine cardiovascular risk (38–40). Furthermore, the concept that the genome per se will not be sufficient, and that

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**Figure 3 AMD Composite Genomic Risk**

Relative risk plotted as a function of the genetic load of the 5 variants that influence risk of age-related macular degeneration (AMD). Two variants are in the CFH gene on chromosome 1: Y402H and rs1410996. Another common variant (A69S) is in the hypothetical gene LOC387715 on chromosome 10. Two relatively rare variants are observed in the C2 and BF genes on chromosome 6. There was no evidence for interaction between any of the variants, suggesting an independent mode of action. Reprinted with permission from Maller et al. (18).
ancillary information will be required from proteomics, epigenomics, and metabolomics is unarguable (81).

Hopefully, in the future, patients such as G.M. will undergo rapid genotyping to search for a key panel of genes that will specifically quantify her risk for future coronary events similar to what now exists with AMD (Fig. 3). More importantly, at some point in the future, we may have the ability to use specific agents personalized for certain genetic susceptibility factors, thereby increasing efficacy and limiting toxicity of treatment. In summary, we are just now entering an age where rapid genomic delineation of the susceptibility for MI is becoming possible.

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