Genetic Basis of Atherosclerosis: Part I
New Genes and Pathways

Aldons J. Lusis, PhD; Alan M. Fogelman, MD; Gregg C. Fonarow, MD

Atherosclerosis, the primary cause of coronary heart disease (CHD), involves numerous cell types and organs and a number of disparate physiological processes (see Figure 1).[1–3] It is not surprising, then, that the genetic basis of CHD is complex. This complexity is clearly illustrated by studies of rodent models; for example, experiments with transgenic and gene-targeted mice have revealed >100 genes that can influence the development of atherosclerotic lesions. The purpose of this review is to provide a brief overview of our current understanding of the genetic factors that contribute to susceptibility to atherosclerosis in human populations (Part I) and then to examine the clinical implications of this knowledge (Part II).

Rare and Common Genetic Differences Contributing to Susceptibility to Atherosclerosis

Single-gene (mendelian) disorders with large effects are the most dramatic examples of the genetic contributions to atherosclerosis.[4,5] However, most forms of the disease are the product of many genes with small effects that are modified by the environment and the effects of other genes, rather than of a single highly penetrant gene. Studies of identical twins are particularly informative because these twins share all of their genes, and such studies consistently indicate that genetic effects powerfully influence heart disease as well as most of its risk factors (Table). Estimates of the heritability of CHD—the proportion of variance of the disease that correlates with genetic differences—are mostly in the range of 40% to 60%.[6,7] A detailed discussion of the many genes that have been identified as candidates for susceptibility to atherosclerosis is beyond the scope of this review, but Figure 1 summarizes some of the currently known pathways and the molecular interactions that are involved.

The classic genetic trait in heart disease is familial hypercholesterolemia (FH). Carl Miller, a physician at Oslo County Hospital, Norway, first described the disorder ≈70 years ago. He noted that the triad of elevated cholesterol, tendon xanthomas, and early heart disease segregated together in families, providing strong evidence for an association between blood lipids and atherosclerosis. Joseph Goldstein and Michael Brown further examined the disease in the early 1970s, and over the last 3 decades, their landmark studies have fostered many insights in the control of cholesterol levels and the etiology and treatment of CHD. Along the way, they discovered receptor-mediated endocytosis and novel mechanisms for transcriptional regulation by lipids. Their studies revealed that FH is the result of mutations that destroy the ability of the LDL receptor to mediate the binding, internalization, or degradation of LDL (Figure 2). Individuals carrying 2 mutant copies have extremely high levels of cholesterol (>600 mg/dL), whereas heterozygotes with 1 mutant copy have levels of ≈400 mg/dL. The penetrance of CHD in FH varies widely, dependent on modifier genes and the same lifestyle environmental risk factors that determine risk in noncarriers, including diet, smoking, and activity level.[8] The frequency of heterozygotes in most populations is surprisingly high for a lethal disease, ≈1 in 500.[9] Because a significant fraction of heterozygous individuals are unaware that they carry a lethal dominant gene that is shared by half of their first-degree relatives, it would seem that DNA screening of the disease would be worthwhile, particularly because effective treatments for the heterozygous disease are available.[10] Unfortunately, FH is heterogeneous in most populations, the exception being founder populations such as French Canadians and Afrikaners, involving hundreds of different mutations of the LDL receptor gene. Nevertheless, rapid-mutation screening methods for FH have been developed.[11]

Familial defective apolipoprotein B (apoB), another relatively common hypercholesterolemia (≈1 in 800), is the result of the mutations of apoB, the major protein of LDL, which prevent its binding to the LDL receptor. In contrast to FH, this disorder is homogeneous, with most cases resulting from a single nucleotide substitution at codon 3500. Although the cholesterol levels of these patients are somewhat lower than are those with FH, they are still highly elevated. Like FH, the disorder exhibits dominant inheritance; therefore, half of the first-degree relatives of an individual with familial defective apoB will be affected.

Most other single-gene traits associated with CHD are rare and of lesser clinical significance.[5] As was the case with FH, studies of rare disorders have led to many novel insights into

(*Circulation.* **2004;110:1868-1873.**)

Circulation is available at http://www.circulationaha.org   DOI: 10.1161/01.CIR.0000143041.58692.CC
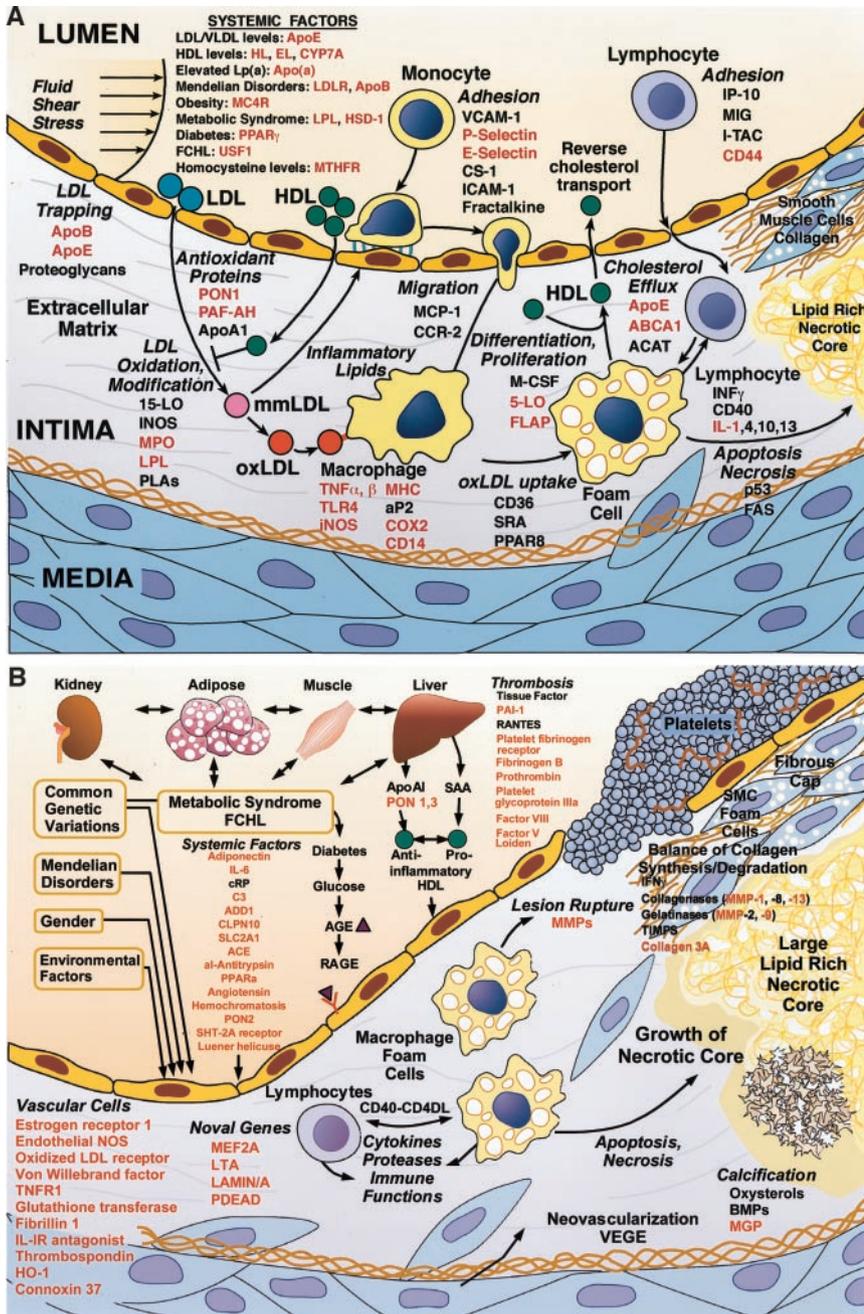
Figure 1. Candidate genes for genetic susceptibility to CHD and some pathways thought to be involved in development and rupture of atherosclerotic lesions. A, Early stages of lesion formation; B, later stages. Many genes shown here have been examined in population-association studies, but only a fraction have been convincingly confirmed as playing role in CHD or genetic susceptibility to its risk factors. Genes with preliminary evidence of association with CHD are shown in red. (For detailed discussion of pathways based largely on transgenic studies in mice, see references 1 through 3.) 5-HT2A receptor indicates serotonin 2A receptor; ACE, angiotensin-converting enzyme; ADD1, adducin 1; AGE, advanced glycosylation end product; aP2, fatty acid–binding protein; BMPs, bone morphogen proteins; C3, complement component 3; CCR2, chemokine receptor 2; CLPN10, calpain 10; COX2, cyclooxygenase-2; CRP, C-reactive protein; CYP7A, cholesterol 7α-reductase; EL, endothelial lipase; GPIIIA, glycoprotein IIIA; HL, hepatic lipase; HO-1, heme oxygenase-1; HSD-1, 11β-hydroxysteroid e reductase-1; IL, interleukin; INF, interferon; MC4R, melanocortin 4 receptor; MCP-1, monocyte chemoattractant protein-1; MGP, matrix gla protein; MHC, major histocompatibility complex; MMPs, metalloproteinases; MPO, myeloperoxidase; NOS, nitric oxide synthase; RAGE, receptor for AGE; SAA, serum amyloid A; SLC 2A1, solute carrier family 2, glucose transporter, membrane 1; sPLA2, secretory phospholipase; TIMPs, tissue inhibitors of metalloproteinasese; TLR4, toll-like receptor 4; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule-1; and VEGF, vascular endothelial growth factor. Other abbreviations as in text.

the pathways involved in atherogenesis. For example, our understanding of cholesterol transport and the control of lipoprotein levels has been transformed recently by the identification of ABC transporters as the cause of Tangier disease and sitosterolemia. Similarly, Lifton's studies[12] of rare mendelian forms of hypertension have identified key processes in the control of blood pressure.

During the past 20 years, the study of human genetics has been revolutionized by positional cloning, a combination of genetic and physical mapping that allows genetic differences to be identified solely on the basis of their locations in the genome. At present, ≈2000 different mendelian disease genes have been identified by positional cloning. Unfortunately, the complex etiology of common diseases, involving many different genetic factors as well as important environ-

mental influences, has made it difficult to apply positional cloning. Thus, in contrast to the great success achieved in identifying single-gene disorders for atherosclerosis, our understanding of the common, complex forms remains limited.

Most of our success in understanding the genetic basis of common forms of atherosclerosis has come from studies of "candidate genes," genes identified by biochemists and subsequently examined for genetic differences and associations in populations. A good example of a candidate gene is apolipoprotein E (apoE). ApoE has been studied intensively as a central player in plasma lipid metabolism, in which it mediates the uptake of chylomicron and VLDL remnants by the LDL receptor and its cousin, LDL receptor-related protein (LRP) (Figure 2). Common genetic differences (polymor-

Genetic and Environmental Risk Factors for CHD

Risk factors with a significant genetic component (heritability)

    Elevated LDL and VLDL cholesterol (40%–60%)

    Low HDL cholesterol (45%–75%)

    Elevated triglycerides (40%–80%)

    Increased body mass index (25%–60%)

    Elevated systolic blood pressure (50%–70%)

    Elevated diastolic blood pressure (50%–65%)

    Elevated lipoprotein(a) levels (90%)

    Elevated homocysteine levels ($\approx$45%)

    Type 2 diabetes mellitus (40%–80%)

    Elevated fibrinogen (20%–50%)

    Elevated C-reactive protein ($\approx$40%)

    Gender

    Age

    Family history

Environmental risk factors

    Smoking

    Diet

    Exercise

    Infection

    Fetal environment

    Air pollution (particulates)

Risk factors for CHD can be subdivided into those that are determined significantly by genetic differences and those that are largely environmental. Heritabilities of genetic risk factors are in parentheses.[1]

phisms) of apoE were identified by Utermann and colleagues[13] in the 1970s, and subsequent studies by many laboratories revealed clear associations with plasma cholesterol levels and type III hyperlipidemia (and later, Alzheimer disease). As compared with the E3 allele (population frequency $\approx$60%), the E4 allele (frequency $\approx$30%) increases plasma cholesterol levels, whereas the E2 allele (frequency $\approx$10%) decreases plasma cholesterol levels. In the US population, these common variations of apoE explain $\approx$5% of the genetic variation in cholesterol levels.[14] Type III hyperlipidemia is an interesting example of a genetic interaction. Almost all individuals with this uncommon (1 in several thousand) hyperlipidemia are homozygous for the E2 allele, but most individuals who are homozygous for the E2 allele do not have the disorder.[15] Thus, other genetic or environmental interactions are required to produce hyperlipidemia in addition to homozygosity for the E2 allele.

Our knowledge of genetic differences contributing to CHD risk is greatest in lipid metabolism (Figure 2). In addition to apoE, convincing evidence suggests that common variations of hepatic lipase influence levels of HDL,[16] that variations of the apoAI-CIII-AIV-AV locus contribute to plasma triglyceride levels,[17] and that variations of the apo(a) gene determine $\approx$90% of the population variance of Lp(a) levels.[18] Both hepatic lipase and the apoAI-CIII-AIV-AV cluster appear to influence LDL particle size, a predictor of CHD risk.[19] However, these genetic differences together explain only a small fraction of the total variance of plasma lipid phenotypes.

More than 2 dozen studies have revealed significant associations between polymorphisms of paraoxonase-1 (PON1) and measures of CHD (although about an equal number of studies have been negative).[20,21] PON1 is a serum esterase bound to HDL, first recognized for its ability to hydrolyze a metabolite of the insecticide parathion. PON1 was identified as a candidate gene for CHD because of its ability to inhibit the oxidation of LDL (Figure 1A), and transgenic studies in mice have confirmed that PON1 is antiatherogenic in vivo.[22] The studies with PON1 are especially significant in providing support for the oxidation hypothesis of atherosclerosis.[23]

Many other candidate genes have been examined in population-association studies (Figure 1). Common variations in some of these genes have been convincingly associated with CHD or its risk factors (see Part II of this review). Most associations, however, require confirmation, and many are likely to prove to be false positives.[24]

A clustering of atherosclerotic risk factors termed the "metabolic syndrome" (MetSyn) is an especially common contributing factor to CHD (Figure 1B). MetSyn is characterized by visceral adiposity, insulin resistance, low HDL cholesterol, hypertriglyceridemia, a systemic proinflammatory state, and small dense LDL, and it is a strong predictor of both CHD and type 2 diabetes mellitus.[25] At present in the United States, $\approx$25% of people >20 years old and $\approx$45% of people >50 years old exhibit MetSyn. The assessment and treatment of MetSyn have yet to be effectively integrated into clinical practice.[25] MetSyn, like atherosclerosis, clearly is complex, with a host of genetic and environmental contributions. Genetic differences in the nuclear receptor peroxisome proliferator-activator receptor-γ (PPARγ) appear to play a key role in MetSyn and type 2 diabetes mellitus.[26] Interestingly, PPARγ agonists are effective in correcting a number of features of MetSyn. Recent studies also have implicated common variations of the lipoprotein lipase (LPL) gene in MetSyn.[27] LPL is an enzyme in capillary surfaces that hydrolyzes the triglyceride in plasma chylomicrons and VLDL, releasing free fatty acids for uptake by peripheral tissues (Figure 2). Human studies that suggest a role for PPARγ and LPL in MetSyn are strongly supported by studies with transgenic mice.

Recent Progress

In 2001, the complete sequence of the human genome was published, and with it came a powerful ability to identify genes, particularly for complex traits. Since that time, the trend has been a tremendous acceleration in the discovery of genes for complex traits, and this trend is likely to continue. The "HapMap" is an ongoing effort to identify all of the major haplotypes (specific combinations of genetic differences in blocks on chromosomes) throughout the genome, and this is expected to greatly simplify association studies. Also, the ability to rapidly and efficiently survey gene expression for most genes will help to identify disease gene pathways.[28] One interesting example is the identification of the role of the oxidative phosphorylation pathway in type 2 diabetes mellitus.[29]
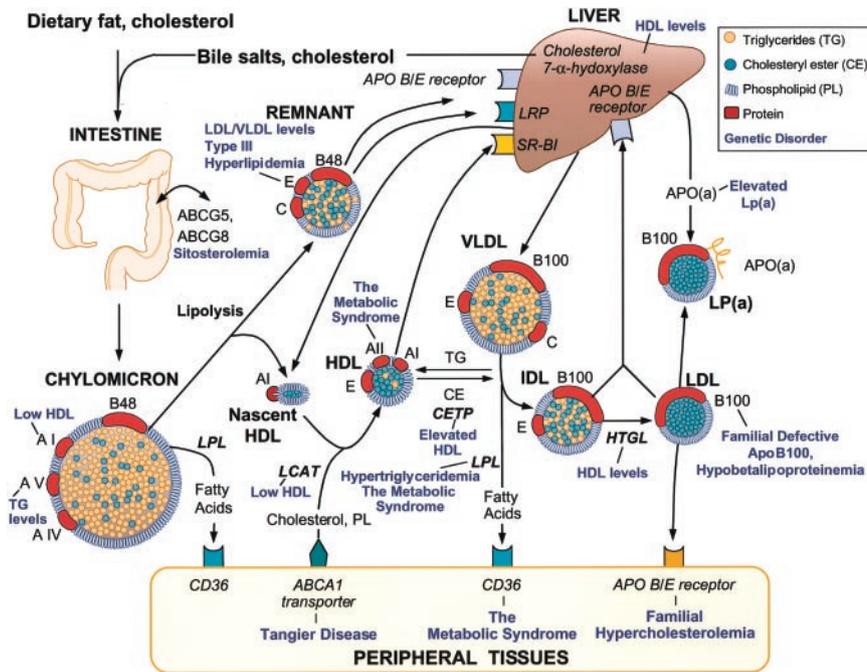
Figure 2. Candidate genes in lipoprotein metabolism. Lipids are transported through the circulation as complexes with various apolipoproteins that package lipids and act as cofactors for enzymes or ligands for uptake by cellular receptors. Dietary lipids are absorbed in intestine, packaged into chylomicrons, and secreted into lymph. On entering circulation, triglycerides are hydrolyzed through action of LPL and the resulting remnants taken up by interaction of apoE with LDL receptor (apoB, E receptor) or LRP. During lipolysis, surface phospholipids and chylomicron proteins slough off to give rise to HDL precursors. Liver cells package triglycerides and cholesterol esters into VLDL particles. LPL acts on them to produce intermediate-density lipoproteins (IDL), which can be taken up by B, E-receptor, or further lipolyzed, partly through hepatic lipase (HL) action, to produce LDL. LDL retains a single major protein, apoB100, and is removed from circulation by the apoB, E receptor. Because of slow kinetics of LDL uptake, LDL particles constitute major cholesterol-carrying particle in most individuals. LDL can complex with apo(a) protein to form Lp(a) particles, which appear par-ticularly atherogenic. HDLs are formed largely in the circulation from apoAI and AII secreted by liver and intestine and from chylomicrons' surface and VLDL during their lipolysis. HDL precursors take up cholesterol from various tissues through interaction with ABCA1 transporter, and cholesterol is esterified by lecithin:cholesterol acyl transferase (LCAT) action. Lipids can be transferred between lipoproteins through the actions of cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP).

An intriguing example of a disorder that results in early-onset heart disease independent of any known risk factors is Hutchinson-Gilford progeria. This rare mendelian disorder possesses many of the symptoms of extremely rapid aging, and death usually results from myocardial infarction (MI) at an early age (median age 13). Atherosclerosis is a rather specific feature of this disease because it does not result in many other disorders that are associated with aging such as dementia or cancer. Recent studies have revealed that the disorder is the result of a specific mutation of the lamin A gene, which culminates in an in-frame alternate splice transcript that encodes a peptide with a 50–amino acid deletion in the carboxyl terminus.[30] Interestingly, different lamin A gene mutations result in a variety of different disorders including dilated cardiomyopathy, familial partial lipodystrophy, and muscular dystrophy.[31]

A large case-control study in which many candidate genes for CHD were examined for premature MI suggested the involvement of multiple members of the thrombospondin family of genes.[32] These studies still require confirmation, but it is intriguing that 3 different but related genes exhibited significant evidence of association.

Genetic studies of a large family exhibiting dominant inheritance of early-onset CHD resulted in the identification of the transcription factor myocyte enhancer factor 2A (MEF2A) as the underlying gene.[33] MEF2A is expressed in endothelial cells as well as in myocytes, but how it contributes to CHD is unknown.

Association studies provide a means of testing the possible involvement of genes in a complex trait, but until recently the approach has been restricted to candidate genes previously recognized through biochemical studies. With the identification of hundreds of thousands of genetic differences, particularly single-nucleotide polymorphisms (SNPs), throughout the human genome, it has become possible to perform whole genome-association studies, in which polymorphisms of many of the ≈35 000 genes in the genome are queried for possible association with a complex trait. Ozaki et al[34] performed such a whole genome-association study on populations in Japan and concluded that the most significant association with MI occurred with genetic differences of the lymphotoxin-α (LTA) gene. LTA is involved in inflammatory responses and the control of immunoglobulin levels. Schreyer and colleagues[35] showed that a null mutation of the LTA gene in mice has a significant although modest effect on atherosclerotic lesion development in mice.

On the basis of the findings with LTA, Ozaki and colleagues searched for proteins that interact with LTA, and using a yeast 2-hybrid system they showed that galectin-2 regulates LTA secretion. They then tested for an association between an SNP of the galectin-2 gene and susceptibility to MI in a Japanese population and observed a highly significant relationship.[36] This study nicely illustrates the concept that pathway members can serve as covariates in genetic studies.

One powerful approach to the identification of genes for complex traits is the study of genetic isolates (ie, populations derived from a relatively small number of "founders"). Such populations tend to have reduced heterogeneity (a smaller number of disease-causing alleles) and other features that simplify positional cloning. Using the population of Iceland,

a genetic isolate founded by the Vikings, workers at deCODE identified the gene encoding phosphodiesterase-4D (PDE4D) in ischemic stroke.[37] They first used linkage analysis of families to map the gene to the long arm of chromosome 5 and then saturated the region with genetic markers to test for association. By far the strongest association was observed with the PDE4D gene, and the genetic differences were shown to influence PDE4D expression. At present, the role of PDE4D in ischemic stroke, which results largely from atherosclerosis, is unknown, but it is interesting to note that cyclic adenosine monophosphate, a signaling molecule in the inflammatory responses of endothelial cells to oxidized lipids, is a substrate of PDE4D.

Familial combined hyperlipidemia (FCHL) is the most common discrete hyperlipidemia (population frequency ≈2%) and is a common cause of "early" CHD (≈20% of middle-aged MI patients have FCHL). It was first recognized in 1973 by Goldstein and coworkers[38] in studies of families that were enriched for early CHD. FCHL is characterized by elevated levels of plasma triglycerides or cholesterol or both, as well as by early CHD, and it exhibits an apparent dominant pattern of inheritance. Although the disorder was recognized >30 years ago, the major genes for FCHL have proved elusive. In studies of the Finnish isolate, Pajukanta and coworkers mapped the first major locus of FCHL to chromosome 1q21–23, and recently they provided strong evidence (based on association) that the gene underlying the linkage is the upstream transcription factor-1 (USF-1) gene.[39] If confirmed, these studies are likely to have important implications for diagnostic testing and for a more complete understanding of the genetic basis of FCHL. USF-1 is known to regulate many important genes in plasma lipid metabolism, including certain apolipoproteins and hepatic lipase. Linkage of type 2 diabetes mellitus as well as FCHL to the region harboring the USF-1 gene has been observed in several different populations worldwide,[40] raising the possibility that USF-1 also may contribute to MetSyn and type 2 diabetes.

Another useful approach to the identification of genes for common disease is to use animal models, particularly the mouse.[41] Mehrabian and colleagues[42] recently identified the gene for 5-lipoxygenase (5-LO) as a contributor to susceptibility to atherosclerosis in mice. Hypothesizing that polymorphisms of this gene also may contribute to susceptibility to CHD in human populations, Mehrabian et al subsequently demonstrated that a common promoter polymorphism of the 5-LO gene was associated with carotid intimal-medial thickness, a measure of atherosclerosis.[43] 5-LO is a key enzyme in the production of leukotrienes, inflammatory mediators derived from the oxidation of arachidonic acid. Because the enzyme is expressed primarily in leukocytes, including monocyte-macrophages, it may affect the growth and survival of leukocytes in the vessel wall. Workers at deCODE reported that genetic differences in another gene in the leukotriene pathway, 5-LO–activating protein, confer the risk of MI and stroke in the Icelandic isolate. They also showed that a separate haplotype of 5-LO–activating protein is associated with MI in patients in the United Kingdom.[44]

A number of genome scans have provided strong evidence for novel loci segregating with measures of CHD or MI.[45–47]

Thus, it is likely that additional novel genes will be identified in the near future.

Conclusion

In recent years we have witnessed some dramatic advances in our understanding of genetic factors in CHD. It is clear that genetic factors acting directly on vascular cells or blood cells contribute importantly to susceptibility to CHD. In fact, studies of genetic susceptibility to atherosclerosis in mice suggest that such factors may be more important than those influencing the traditional risk factors.[41] It is also clear that novel highly penetrant genetic differences, some rare and some common, exist in the population, predisposing individuals to CHD (Figure 1B). The identification of these genetic factors is expected to provide an understanding of novel pathways and to lead to new treatments and new diagnostic tests for CHD (see Part II of this review).

Acknowledgments

Disclosure
Dr Alan M. Fogelman is a principal in Bruin Pharma.

References

1. Lusis AJ. Atherosclerosis. *Nature*. 2000;407:233–241.
2. Glass CK, Witztum JL. Atherosclerosis. The road ahead. *Cell*. 2001;104:503–516.
3. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868–874.
4. Milewicz DM, Seidman CE. Genetics of cardiovascular disease. *Circulation*. 2000;102:IV-103–IV-111.
5. Nabel EG. Cardiovascular disease. *N Engl J Med*. 2003;349:60–72.
6. Lusis AJ, Weinreb A, Drake TA. Genetics of atherosclerosis. In: Topol EJ, Califf RM, Isner J, et al, eds. *Textbook of Cardiovascular Medicine*. Philadelphia, Pa: Lippincott Williams & Wilkins;1998:2389–2413.
7. Motulsky AG, Brunzell JD. Genetics of coronary artery disease. In: King RA, Rotter JI, Motulsky AG, eds. *The Genetic Basis of Common Disease*. 2nd ed. New York, NY: Oxford University Press; 2002:105–126.
8. Sijbrands EJ, Westendorp RG, Defesche JC, et al. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study. *BMJ*. 2001;322:1019–1023.
9. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science*. 1986;232:34–47.
10. Thorsson B, Sigurdsson G, Gudnason V. Systematic family screening for familial hypercholesterolemia in Iceland. *Arterioscler Thromb Vasc Biol*. 2003;23:335–338.
11. Heath KE, Humphries SE, Middleton-Price H, et al. A molecular genetic service for diagnosing individuals with familial hypercholesterolaemia (FH) in the United Kingdom. *Eur J Hum Genet*. 2001;9:244–252.
12. Lifton RP. Molecular genetics of human blood pressure variation. *Science*. 1996;272:676–680.
13. Utermann G, Pruin N, Steinmetz A. Polymorphism of apolipoprotein E. III. Effect of a single polymorphic gene locus on plasma lipid levels in man. *Clin Genet*. 1979;15:63–72.
14. Sing CF, Davignon J. Role of the apolipoprotein E polymorphism in determining normal plasma lipid and lipoprotein variation. *Am J Hum Genet*. 1985;37:268–285.
15. Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science*. 1988;240:622–630.
16. Cohen JC, Vega GL, Grundy SM. Hepatic lipase: new insights from genetic and metabolic studies. *Curr Opin Lipidol*. 1999;10:259–267.
17. Talmud PJ, Hawe E, Martin S, et al. Relative contribution of variation within the APOC3/A4/A5 gene cluster in determining plasma triglycerides. *Hum Mol Genet*. 2002;11:3039–3046.

18. Boerwinkle E, Leffert CC, Lin J, et al. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. *J Clin Invest*. 1992;90:52–60.
19. Lusis AJ, Ivandic B, Castellani LW. Lipoprotein and lipid metabolism. In: Rimoin DL, Conner JM, Pyeritz RE, et al, eds. *Emery and Rimoin's Principles and Practice of Medical Genetics*. 4th ed. London, England: Churchill Livingstone; 2002:2500–2537.
20. Durrington PN, Mackness B, Mackness MI. Paraoxonase and atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2001;21:473–480.
21. Shih DM, Reddy S, Lusis AJ. CHD and atherosclerosis: human epidemiological studies and transgenic mouse models. In: Costa LG, Furlong CE, eds. *Paraoxonase (PON1) in Health and Disease: Basic and Clinical Aspects*. Boston, Mass: Kluwer Academic Publishers; 2002:93–117.
22. Tward A, Xia YR, Wang XP, et al. Decreased atherosclerotic lesion formation in human serum paraoxonase transgenic mice. *Circulation*. 2002;106:484–490.
23. Navab M, Ananthramaiah GM, Reddy ST, et al. The oxidation hypothesis of atherogenesis: the role of oxidized phospholipids and HDL. *J Lipid Res*. 2004;45:993–1007.
24. Lohmueller KE, Pearce CL, Pike M, et al. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet*. 2003;33:177–182.
25. Reilly MP, Rader DJ. The metabolic syndrome: more than the sum of its parts? *Circulation*. 2003;108:1546–1551.
26. Altshuler D, Hirschhorn JN, Klannemark M, et al. The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet*. 2000;26:76–80.
27. Goodarzi MO, Guo X, Taylor KD, et al. Lipoprotein lipase is a gene for insulin resistance in Mexican Americans. *Diabetes*. 2004;53:214–220.
28. Schadt EE, Monks SA, Drake TA, et al. Genetics of gene expression surveyed in maize, mouse and man. *Nature*. 2003;422:297–302.
29. Mootha VK, Lindgren CM, Eriksson KF, et al. PGC-1alpha–responsive genes involved in oxidative phosphorylation are coordinately down-regulated in human diabetes. *Nat Genet*. 2003;34:267–273.
30. Eriksson M, Brown WT, Gordon LB, et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature*. 2003;423:293–298.
31. Hegele RA. Lamin mutations come of age. *Nat Med*. 2003;9:644–645.
32. Topol EJ, McCarthy J, Gabriel S, et al. Single nucleotide polymorphisms in multiple novel thrombospondin genes may be associated with familial premature myocardial infarction. *Circulation*. 2001;104:2641–2644.
33. Wang L, Fan C, Topol SE, et al. Mutation of MEF2A in an inherited disorder with features of coronary artery disease. *Science*. 2003;302:1578–1581.
34. Ozaki K, Ohnishi Y, Iida A, et al. Functional SNPs in the lymphotoxin-alpha gene that are associated with susceptibility to myocardial infarction. *Nat Genet*. 2002;32:650–654.
35. Schreyer SA, Vick CM, LeBoeuf RC. Loss of lymphotoxin-alpha but not tumor necrosis factor-alpha reduces atherosclerosis in mice. *J Biol Chem*. 2002;277:12 364–12 368.
36. Ozaki K, Inoue K, Sato H, et al. Functional variation in LGALS2 confers risk of myocardial infarction and regulates lymphotoxin-alpha secretion in vitro. *Nature*. 2004;429:72–75.
37. Gretarsdottir S, Thorleifsson G, Reynisdottir ST, et al. The gene encoding phosphodiesterase 4D confers risk of ischemic stroke. *Nat Genet*. 2003;35:131–138.
38. Goldstein JL, Schrott HG, Hazzard WR, et al. Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest*. 1973;52:1544–1568.
39. Pajukanta P, Lilja HE, Sinsheimer JS, et al. Familial combined hyperlipidemia is associated with upstream transcription factor 1 (USF1). *Nat Genet*. 2004;36:371–376.
40. Allayee H, Krass KL, Pajukanta P, et al. Locus for elevated apolipoprotein B levels on chromosome 1p31 in families with familial combined hyperlipidemia. *Circ Res*. 2002;90:926–931.
41. Allayee H, Ghazalpour A, Lusis AJ. Using mice to dissect genetic factors in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2003;23:1501–1509.
42. Mehrabian M, Allayee H, Wong J, et al. Identification of 5-lipoxygenase as a major gene contributing to atherosclerosis susceptibility in mice. *Circ Res*. 2002;91:120–126.
43. Dwyer JH, Allayee H, Dwyer KM, et al. Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. *N Engl J Med*. 2004;350:29–37.
44. Helgadottir A, Manolescu A, Thorleifsson G, et al. The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. *Nat Genet*. 2004;36:233–239.
45. Lusis AJ, Mar R, Pajukanta P. Genetics of atherosclerosis. *Annu Rev Genet Genom*. In press.
46. Wang Q, Rao S, Shen GQ, et al. Premature myocardial infarction novel susceptibility locus on chromosome 1P34-36 identified by genomewide linkage analysis. *Am J Hum Genet*. 2004;74:262–271.
47. Fox CS, Cupples LA, Chazaro I, et al. Genomewide linkage analysis for internal carotid artery intimal medial thickness: evidence for linkage to chromosome 12. *Am J Hum Genet*. 2004;74:253–261.

Genetic Basis of Atherosclerosis: Part I: New Genes and Pathways

Aldons J. Lusis, Alan M. Fogelman and Gregg C. Fonarow

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circ.ahajournals.org/content/110/13/1868