Human Genetics of Atherothrombotic Disease and its Risk Factors

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The pace of discovery in the application of human genetics to atherothrombotic disease and its risk factors has been accelerating. A large number of genetic loci have been identified in association with myocardial infarction (MI), coronary artery disease (CAD), thrombotic events, lipid traits, and other circulating biomarkers related to atherothrombotic disease. Several articles in ATVB during 2013 and 2014 were related to these discoveries and the underlying biology and functional genomics of these loci. In this article, we review these reports in the broader context of the rapid progress in this field.

Functional Biology of Genes at Novel Loci Associated With Coronary Artery Disease

Genome-wide association studies (GWAS) have identified ≈50 discrete genetic loci that are significantly associated with MI/CAD.1 One of the biggest challenges in the field is to identify the causal gene at each of the novel loci and to elucidate the molecular and physiological mechanisms by which these causal genes influence the development, progression, and clinical outcomes of CAD.

Chromosome 9p21.3 Coronary Heart Disease–Associated Region

The first GWAS locus discovered to be associated with MI/CAD was a locus on chromosome 9p21.3 spanning an ≈60-kilobase region, which has come to be called the chromosome 9p21.3 coronary heart disease (CHD)–Associated Region (C9CAR). This locus remains the most robustly associated with CAD, accounts for ≈20% of the attributable risk for CAD, and is also associated with other vascular traits, such as aneurysms. However, the mechanism linking this locus to CAD remains to be elucidated. Two of the closest genes encode CDKN2A and 2B, cyclin-dependent kinase inhibitors that interact with CDK4 and CDK6 and are involved in cell cycle regulation. Gene expression studies have suggested that variants at C9CAR associated with increased CAD are associated with reduced expression of CDKN2B in atherosclerotic plaque and vascular smooth muscle cells, but relatively little is known about the effect of CDKN2B on vascular disease in model systems. Kim et al2 had reported that Cdkn2b knockout mice had no difference in atherosclerotic lesion burden compared with controls. Leeper et al3 reported in ATVB the use of Cdkn2b knockout mice to explore the effects of Cdkn2b deficiency on the response to vascular injury. Two vascular injury models were used, complete carotid artery ligation to induce negative remodeling and pancreatic elastase infusion to generate abdominal aortic aneurysms (AAAs). Surprisingly, although they had the expected increased vascular smooth muscle cell proliferation in response to injury, the Cdkn2b deficient mice had smaller neointimal lesions and larger aortic aneurysms because of increased vascular smooth muscle cell apoptosis. This effect was not mediated through hematopoietic cells, as it was not reproduced by bone marrow transplantation from Cdkn2b deficient donors. The effect on apoptosis was found to be because of a reduction in mouse double minute 2 homolog and an increase in p53 signaling, and it could be reversed by simultaneously inhibiting p53. The same authors then went on to show that Cdkn2b-deficient mice developed increased atherosclerosis with advanced plaques and large necrotic cores accompanied by impaired efferocytosis of apoptotic bodies by macrophages, increased foam cell formation, and increased inflammatory responses.4 Although much work remains to be done, these findings implicate CDKN2B as potentially causally involved vascular diseases associated with genetic variation at C9CAR, suggesting that regulation of vascular smooth muscle cell apoptosis may be an important mediator, and also implicate the potential for p53 involvement in vascular disease.

CXCL12–CXCR4 Pathway

One of the earliest novel loci found to be associated with MI/CAD was the CXCL12 gene locus encoding the chemokine CXCL12, or stromal-derived factor 1. Variation at the CXCL12 locus is also associated with endothelial progenitor cell numbers. There has been intense interest in understanding the functional biology underlying these robust genetic associations. Several articles in ATVB during the past 2 years have addressed the biology of CXCL12 and its major receptor CXCR4 in atherosclerosis and vascular biology.

The laboratory of Christian Weber has made several important observations about the role of this pathway in vascular disease, particularly with regard to its role in the mobilization of smooth muscle cell progenitors from the bone marrow, neointimal hyperplasia after injury. More recently, Noels et al5 investigated the role of endothelial CXCR4 in neointima formation using the endothelial-specific Bmx-CreER(T2) CXcr4-floxed mice crossed onto the apolipoprotein E–deficient background.

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ARTERIOSCLEROSIS THROMBOSIS VASCULAR BIOLOGY. 2015;35:741-747. DOI: 10.1161/ATVBAHA.115.305492.

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DOI: 10.1161/ATVBAHA.115.305492
After carotid wire-injury, the mice deficient in endothelial Cxcr4 displayed significantly increased neointima formation accompanied by more macrophages, reduced vascular smooth muscle cells and extracellular matrix, and impaired endothelial cell proliferation. Interestingly, endothelial staining of Cxcl12 was significantly reduced in the injured carotids. The endothelial-deficient Cxcr4 mice had reduced mobilization of endothelial progenitor cells after vascular injury, although there were no differences in plasma concentrations of Cxcl12 or other cytokines involved in mobilization of progenitor cells. Studies in human aortic endothelial cells showed that CXCL12 treatment enhanced wound-healing capacity. These studies strongly suggest that the CXCL12–CXCR4 pathway is vasculoprotective after endothelial injury.

Another vascular protective effect of this pathway, namely that of promoting endothelial barrier function, was demonstrated by Kobayashi et al. Using bovine aortic endothelial cells in vitro, the authors showed that treatment with CXCL12 inhibited thrombin-induced dextran hyperpermeability through stimulating CXCR4 in a process that required phosphoinositide 3-kinase activation and involved Rac1 activation. Using an in vivo croton oil–induced vascular leakage model, the authors confirmed that CXCL12 administration reduced leakage and that this effect was dependent on CXCR4 activation. Whether this effect of the CXCL12–CXCR4 pathway on endothelial permeability is related to atherosclerosis is unknown, but it is biologically plausible. These data, together with other previous data, are consistent with a model in which this pathway is vasculoprotective and atheroprotective.

However, not all data support a vascular protective effect of this pathway. Michineau et al. investigated the expression of CXCL12 and CXCR4 in aortic aneurysms in mice and humans and the effects of inhibition of this pathway on AAA in mice. They found that CXCL12 and CXCR4 are increased in both mouse and human AAA wall in proportion to the aortic diameter. In the mouse CaCl2–induced model of AAA, CXCL12 is rapidly induced and plays a key role in the recruitment of bone marrow–derived macrophages to the aorta. Inhibition of the CXCR4 pathway using AMD3100 reduced the recruitment of macrophages and slowed the development and expansion of AAA. Thus, these studies suggest that the CXCL12–CXCR4 pathway helps to promote the development of AAA.

Finally, epidemiological studies of plasma CXCL12 and relationship with cardiovascular events have further clouded the picture with regard to the directionality. One report in patients with chronic kidney disease indicated that plasma levels of CXCL12 were positively associated with risk of incident cardiovascular disease (CVD). In ATVB, Subramanian et al. examined the association of plasma CXCL12 levels to endothelial progenitor cells and CVD-related outcomes in the Framingham Heart Study. CXCL12 levels were inversely associated with lower CD34+ endothelial progenitor cells. On the basis of a median follow-up of 9.3 years and after adjusting for clinical risk factors, CXCL12 levels were not associated with MI or CVD events but were positively associated with incident heart failure and all-cause mortality. This study brings into question the putatively protective role of this pathway, but as an observational study does not directly address causality. Clearly substantial additional work is required to better understand the relationship of the CXCL12–CXCR4 pathway to vascular disease.

**Histone Deacetylase 9**

One of the most interesting new GWAS loci associated with atherosclerotic cardiovascular disease is HDAC9 that has been associated with both CAD and ischemic stroke. Histone deacetylases (HDACs) modulate gene expression by deacetylation of histone and nonhistone proteins. Thus, this genetic finding suggests the potential of a direct link between epigenetic modification by HDAC9 and atherosclerotic vascular disease. Two articles in *ATVB* during the past 2 years addressed the biology of HDAC9 related to vascular biology and atherosclerosis.

Kaluza et al. analyzed the function of HDAC9 in angiogenesis. The authors showed that silencing of HDAC9 in vitro reduces endothelial cell tube formation and sprouting and that genetic deletion of HDAC9 in vivo impairs blood flow recovery after hindlimb ischemia and reduces retinal vessel outgrowth. They suggested that this effect was at least in part through transcriptional repression of the miR-17 to 92 cluster by HDAC9. In an accompanying editorial, Sato pointed out that HDAC9 may directly affect histone deacetylation of the miR-17 to 92 cluster in endothelial cells or alternatively, HDAC9 may affect transcription factors that regulate the miR-17 to 92 cluster, or may recruit other classes of HDACs which can influence the expression of miRNA-17 to 92 cluster.

In another article in *ATVB* more directly related to atherosclerosis, Cao et al. used genetic deletion of HDAC9 in mice to assess the effects on atherosclerosis. The authors crossed HDAC9-deficient mice onto the low-density lipoprotein (LDL) receptor–deficient background and fed a western diet to induce atherosclerosis. Interestingly, HDAC9-deficient mice had significantly decreased atherosclerotic lesions despite relatively minimal effects on plasma cholesterol distribution. Bone marrow transplantation studies confirmed that mice receiving bone marrow lacking HDAC9 reproduced the atheroprotective phenotype, identifying hematopoietic cells as the source of HDAC9 responsible for affecting atherosclerosis. Aortas from mice lacking HDAC9 showed increased expression of ABCA1, ABCG1, and arginase-1 and reduced expression of interleukin-1β and MCP1, and macrophages lacking HDAC9 had increased ABCA1 and ABCG1 expression, increased cholesterol efflux, and increased expression of markers for alternatively activated M2 macrophages. These studies suggest that HDAC9 promotes atherosclerosis, and its deficiency protects against atherosclerosis, at least in part through resulting in macrophage M2 polarization and improved macrophage cholesterol efflux. This article was accompanied by an editorial by Smith, who pointed out that this study raises the provocative question as to whether HDAC9 inhibitors, currently in development for cancer, might be effective in reducing the risk of cardiovascular disease.

**Lipid Phosphate Phosphatase 3 (PPAR2B)**

Lyosphosphatidic acid (LPA) and sphingosine-1-phosphate are bioactive lipids that act through G-protein–coupled...
receptor-mediated pathways and have increasingly been implicated in vascular biology and even atherosclerosis. Lipid phosphate phosphatase 3 (LPP3), encoded by the PPAP2B gene, dephosphorylates and inactivates the signaling actions of LPA and sphingosine-1-phosphate. The PPAP2B locus has been identified as genome-wide significantly associated with CAD independent of other traditional risk factors. Data using expression quantitative trait locus analysis suggest that the allele associated with increased CAD risk is associated with reduced leukocyte expression of PPAP2B. Panchatcharam et al used mouse models with cell-specific LPP3 deficiency in endothelial and hematopoietic cells to better understand the role of this enzyme in vascular phenotypes. Induced LPP3 deficiency in adult mice resulted in increased inflammatory responses. Endothelial cell LPP3 deficiency resulted in increased in vascular permeability and enhanced sensitivity to inflammation-induced vascular leak that was prevented by inhibition of LPA production or LPA-G-protein-coupled receptor signaling. These findings suggest that the enzymatic activity of LPP3 in terminating LPA and sphingosine-1-phosphate signaling inhibits vascular inflammation, maintains endothelial integrity, and protects vessels from inflammation-induced vascular leak. Whether these observations are directly relevant to atherosclerotic vascular disease remains to be determined.

**Genetics of Circulating Biomarkers Associated With CAD**

There is increasing interest in discovery of genetic variation influencing variation in concentrations of circulating biomarkers associated with cardiovascular disease. This approach has the advantage of potentially identifying genetic tools that can be used to address questions of causality through the approach of Mendelian randomization.

**Lipoprotein(a)**

Plasma lipoprotein(a) (Lp(a)) levels are highly genetically determined and have been associated with increased risk of CVD in multiple observational studies. Lp(a) has emerged in the past few years as a poster child for Mendelian randomization, in that plasma levels are strongly associated with incident cardiovascular events and genetic variants at the LPA gene locus specifically associated with plasma Lp(a) levels are themselves strongly associated with cardiovascular events. Nevertheless, important questions remain unanswered. One key question has been whether Lp(a) levels are associated with incident cardiovascular events in people with overt CAD at the time of baseline measurement. Nestel et al addressed this important question making use of the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, a randomized controlled trial in subjects with a previous coronary event of pravastatin versus placebo with a primary end point of major cardiovascular events. The positive relationship between the Lp(a) level at the time of randomization and incident recurrent cardiovascular events during a median follow-up of 6 years was highly statistically significant. This result suggests that elevated Lp(a) could be causal for promoting progression and destabilization of coronary plaques even in patients who already have overt CAD.

Genetic variation in the LPA gene results in a highly polymorphic protein that includes multiple copies of the kringle domain and is a major factor affecting plasma Lp(a) levels. However, some of the variations in Lp(a) levels attributed to the LPA gene are independent of kringle copy number variation. Kyriakou et al addressed the relationship of a relatively common (minor allele frequency, 3%) null allele of LPA (rs41272114) with Lp(a) levels and prevalent CAD in the Precocious Coronary Artery Disease (PROCARDIS) study. This single-nucleotide polymorphism results in alternative splicing and premature truncation, generating an apoA protein that cannot covalently bind to apoB to form a mature Lp(a) particle. Carriers of the null allele were found to have significantly lower Lp(a) levels; importantly, they also had a significantly reduced risk of CAD. This finding adds to the growing body of data supporting a causal role for Lp(a) in CAD and refines our understanding of this relationship by indicating that it extends beyond genetic factors that influence Lp(a) levels solely through isoform size.

**Tissue-Type Plasminogen Activator**

Tissue-type plasminogen activator (tPA) is a glycoprotein enzyme made by endothelial cells that cleaves plasminogen to form plasmin, itself an active enzyme that lysed fibrin-containing clots. Circulating tPA is mostly found to be associated with its inhibitor plasminogen activator inhibitor-1 as part of an inactive complex. Plasma tPA levels are, somewhat counterintuitively given that tPA promotes clot lysis, positively associated with the risk of incident cardiovascular events. Factors regulating plasma levels of tPA are incompletely understood, but one source of variation is, as with most circulating proteins, genetic in nature. Huang et al reported in *ATVB* the first GWAS of circulating tPA levels; this report was accompanied by an editorial by Chasman. The authors performed a meta-analysis of 14 studies that had both genome-wide genotype data and plasma tPA quantification, involving a total of $\approx 27,000$ subjects. One genome-wide significant locus included the PLAT gene, which encodes tPA itself, serving as a useful positive control for the experiment and potentially providing new insight into the transcriptional regulation of the PLAT gene. The other 2 loci included the genes STXBP5 (which encodes the protein syntaxin-binding protein 5) and STX2 (which encodes the protein syntaxin 2), both are novel findings. Each locus harbored a strong expression quantitative trait locus for the respective gene but not for other genes at the loci, suggesting that these may be the causal genes.

Syntaxins are members of a family of membrane-integrated soluble N-ethylmaleimide-sensitive factor attachment protein receptor proteins that participate in exocytosis. Provocatively, siRNA studies in vascular endothelial cells revealed that silencing of STXBP5 decreased tPA release, whereas silencing of STX2 increased the tPA release. Previously-reported GWAS for von Willebrand factor had also identified the STXBP5 and STX2 loci as genome-wide significantly associated with levels of von Willebrand factor. Syntaxin-4, another member of the syntaxin family, is required for the release of von Willebrand factor from intracellular endothelial Weibel–Palade vesicles.
Combined, these data suggest a broad role for syntaxins in the release of circulating hemostatic factors by endothelial cells.

Mendelian randomization is based on the concept that inherited random genetic variation influences lifelong exposure to a biomarker, and thus, that genetic variants can be used as instruments to assess potential causality of circulating proteins. The authors were unable to find evidence of association between variants at their 3 loci and cardiovascular disease using large databases. Thus, the causal relationship between tPA and cardiovascular events remains uncertain.

**Soluble CD14**

CD14 is a glycosylphosphatidylinositol-anchored membrane glycoprotein expressed on neutrophils, monocytes, and macrophages. On binding of many proinflammatory ligands, it participates in the activation of intracellular proinflammatory signaling pathways. As with many cell surface receptors, CD14 can be enzymatically cleaved to generate a soluble form (sCD14), and this cleavage is induced by inflammatory stimuli, leading to increased sCD14 levels in the setting of acute and chronic inflammatory conditions. Thus, sCD14 is a circulating biomarker of potential interest in the setting of atherothrombotic disease. Reiner et al measured the baseline levels of sCD14 in the Cardiovascular Health Study (CHS) involving >5000 subjects aged >65 years. Plasma levels of sCD14 were higher in people of European ethnicity and female sex and were positively correlated with smoking, hypertension, diabetes mellitus, and other inflammatory biomarkers (C-reactive protein, interleukin-6, and fibrinogen). They were associated with ankle-brachial index and carotid intimal-medial thickness and strongly predicted incident cardiovascular events and all-cause mortality. A genome-wide association analysis of sCD14 levels identified 2-genome-wide significant loci. One was the CD14 structural locus on chromosome 5q21, including a novel African ancestry–specific allele of CD14 associated with lower sCD14. The second locus included the gene **PIGC**, which encodes an enzyme required for the first step in glycosylphosphatidylinositol–anchored biosynthesis. A missense variant of **PIGC**, Pro266Ser, was noted for the first time to be significantly associated with higher plasma sCD14 levels. This finding suggests that defective glycosylphosphatidylinositol–anchored synthesis may result in increased release of sCD14 in the setting of acute and chronic inflammatory conditions. Thus, sCD14 is a circulating biomarker of potential interest in the setting of atherothrombotic disease.

**Protein C pathway**

The protein C (PC) pathway is critical in preventing inappropriate blood coagulation. Circulating protein C is activated on the surface of vascular endothelial cells after binding to its endothelial PC receptor (EPCR) and being presented to the thrombin–thrombomodulin complex. Activated PC, in conjunction with its cofactor protein S, reduces thrombin generation by degrading the coagulation cofactors Va and VIIIa. Genetic variation in this pathway can influence the risk of venous thromboembolism (VTE). Navarro et al investigated the association of a missense variant (Ala455Val) in the **THBD** gene encoding thrombomodulin with plasma soluble thrombomodulin, activated PC levels, and VTE. In cultured endothelial cells, the A455V allele was associated with increased cellular thrombomodulin, reduced soluble thrombomodulin in media, and increased PC activation. Subjects carrying the A455V allele had reduced soluble thrombomodulin levels, increased circulating activated PC levels, and importantly reduced VTE risk. These results established that a missense variant in thrombomodulin modulates its activity, the generation of activated PC, and the risk of VTE.

In a follow-up study, Medina et al studied common haplotypes H1 and H3 in **PROC**, the gene encoding the EPCR, for their association with EPCR expression and risk of VTE. Studies in cultured endothelial cells showed that the H1 haplotype was associated with increased membrane-bound EPCR, increased PC activation, and reduced soluble EPCR in the media. Subjects carrying the H1 haplotype were found to have increased plasma activated PC levels, reduced plasma soluble EPCR levels, and most notably, reduced VTE risk. In contrast, the H3 haplotype was associated with reduced membrane-bound EPCR, reduced PC activation, and increased soluble EPCR in media. Subjects with the H3H3 genotype had reduced plasma activated PC levels, increased plasma soluble EPCR levels, and an increased VTE risk. These results indicate that genetic variation at the **PROC** locus influences the activity of the EPCR and thus the risk of VTE.

Wu et al performed targeted gene sequencing of exon 3 of **PROC** (encoding PC) and exons 2 and 3 of **PROC** (encoding EPCR) in 653 patients with VTE and 627 healthy controls. Three subjects were found to have private mutations in **PROC** that affected the protein sequence (Arg-1Cys, Arg9Cys, and Val34Met), and all had decreased synthesis, with 2 also showing reduced ability to be activated. Two subjects had private missense mutations in **PROC** (Arg96Cys and Val170Leu) that demonstrated reduced affinity for fluorescently labeled PC. Although the overall numbers were small, these findings suggest that private mutations in **PROC** or **PROC** that impair PC–EPCR interactions may be associated with an increased risk of VTE.

**Human Genetics of Triglyceride Metabolism**

**Identify New Therapeutic Targets**

Elevated triglyceride levels are associated with increased CAD risk, but the causal nature of this relationship has been uncertain. A gain-of-function variant in the **LPL** gene, S447X, is associated with reduced triglyceride and reduced risk of cardiovascular disease, consistent with a protective effect of lipoprotein lipase (LPL) in not only reducing triglyceride levels but also reducing the risk of CVD. Common genetic variants that influence triglyceride levels are significantly associated with CAD risk even after adjusting for their effects on other lipid traits. Loss-of-function mutations in **APOC3** that reduce plasma levels of apoC-III (an inhibitor of LPL) are associated with lower triglyceride and decreased risk of...
coronary calcification and clinical CAD. In contrast, loss-of-function mutations in APOA5 (which encodes apoA-V, an activator of LPL) are associated with elevated triglycerides and in some cases with increased CAD risk. Remarkably, in a hypothesis-free exome sequencing experiment in people with early MI compared with older controls without MI identified a significant enrichment of rare APOA5 mutations in early MI cases. These findings establish that disruption of apoA-V protein function increases the risk of cardiovascular disease and makes it imperative to better understand the normal physiology of apoA-V and the effect of structural mutations on its function.

**Apolipoprotein A-V**

In this regard, the work of Sharma et al has been highly informative. Sharma et al used a recombinant adeno-associated virus serotype 8 to express human apo-A-V in the livers of hypertriglyceremic apo-A-V–deficient mice. Expression of human apo-A-V protein substantially reduced plasma triglyceride levels, establishing this approach as one that can be used to test in vivo the function of other naturally occurring mutants of apo-A-V. Indeed, the same investigators went on to use this approach to study the Gly162Cys mutation in apo-A-V that has been associated with hypertriglyceridemia in people of East Asian descent. Adeno-associated virus was used to express the Gly162Cys variant of human apo-A-V in comparison with wild-type apo-A-V in the livers of apo-A-V–deficient mice. The Gly162Cys variant was less effective than wild-type apo-A-V in reducing plasma triglyceride levels. Unlike wild-type apo-A-V, >50% of Gly162Cys was recovered in the lipoprotein-free fraction because of the free cysteine that forms disulfide bonds with other plasma proteins. More work on natural variants of apo-A-V and their relationship with triglyceride metabolism and CAD risk is needed.

**Angiopoietin-Like Proteins 3 and 4**

Angiopoietin-like proteins (ANGPTLs) are secreted proteins characterized by key structural motifs, and several of which play roles in triglyceride metabolism. ANGPTL3 and ANGPTL4 are the 2 members of the family that have been most extensively studied, and for which human genetic data exist, supporting a causal role in modulating the metabolism of triglyceride-rich lipoproteins. ANGPTL3 reversibly inhibits and ANGPTL4 irreversibly inhibits LPL. In mice, overexpression of ANGPTL3 or ANGPTL4 causes elevated triglycerides and depletion of ANGPTL3 or ANGPTL4 results in a decrease in triglyceride levels. Common variants at the ANGPTL3 and ANGPTL4 loci are associated with triglyceride levels, and nonsynonymous loss-of-function variants in both proteins are associated with lower triglyceride levels. Exome sequencing in a family with decreased triglyceride, LDL cholesterol (LDL-C), and high-density lipoprotein cholesterol identified loss-of-function mutations in ANGPTL3. Mehta et al determined plasma ANGPTL3 and ANGPTL4 levels in 1770 subjects and assessed their association with lipids and metabolic traits. Plasma ANGPTL3 levels were positively associated with LDL-C and high-density lipoprotein cholesterol levels but not triglyceride levels. In contrast, plasma ANGPTL4 levels were negatively associated with LDL-C and high-density lipoprotein cholesterol and positively associated with triglycerides. In addition, ANGPTL4, but not ANGPTL3, levels were positively associated with fasting blood glucose and metabolic syndrome. Thus, although ANGPTL3 and ANGPTL4 both inhibit LPL, their in vivo physiology is complex and additional studies of their plasma levels incorporating genetic data are needed.

One approach is to take advantage of individuals with loss-of-function mutations for further deep phenotyping. Robciuc et al recruited homozygotes and heterozygotes with the S17X loss-of-function mutation in ANGPTL3 and age- and sex-matched noncarrier controls. Postheparin plasma LPL mass and activity were significantly higher, and plasma free fatty acid, insulin, and glucose were significantly lower in S17X homozygotes when compared with S17X heterozygotes and controls. No changes in hepatic lipase or endothelial lipase activities were noted, even in homozygotes. These results suggest that ANGPTL3 may influence insulin sensitivity and glucose metabolism, in addition to its role in lipid metabolism.

**Genetic Risk Scores and Prediction of Incident Cardiovascular Events**

The plethora of genome-wide studies identifying novel loci associated with cardiovascular disease and its risk factors have paved the way for the use of this information in the clinical prediction of future risk of cardiovascular disease. Indeed, this topic has been of substantial interest as one major way that genomic information can be applied to clinical practice. Three articles in the same issue of ATVB addressed different ways of approaching this problem and were accompanied by an editorial putting them all in perspective.

Tikkkanen et al set out to construct a genetic risk score (GRS) and evaluate its ability to predict incident cardiovascular disease events. They genotyped 28 genetic variants in >24000 participants in several Finnish population-based, prospective cohorts and developed a multilocus GRS. After taking into account conventional risk factors and family history, adding the GRS significantly improved prediction of CHD and other cardiovascular outcomes. They concluded that application of a GRS in patients at intermediate risk for CHD would reclassify 12% into a high-risk category.

Ganna et al developed GRSs and evaluated their potential for clinical use in predicting CHD. They genotyped >10000 participants free of CHD at baseline in several Swedish prospective cohorts. An overall GRS was developed on the basis of 395 variants associated with cardiovascular traits, and a CHD-specific GRS was developed on the basis of 46 variants associated with CHD itself. Both risk scores significantly improved risk classification for incident CHD beyond established risk factors and resulted in net reclassification improvement of 4% to 5%.

Isaacs et al took a more focused approach and developed risk scores on the basis of common genetic variants for lipid traits and tested their relationship with incident CHD using Dutch prospective cohorts. The total cholesterol and LDL-C GRSs, but not the high-density lipoprotein cholesterol risk score, were significantly associated with incident CHD. These
results are consistent with the concept that the lifelong benefit of genetically reducing LDL-C is substantially greater than that seen in shorter-term pharmacological trials. A practical consequence of this conclusion would be to initiate LDL-lowering therapy earlier in life.

In their editorial accompanying the 3 articles, Thanassoulis et al. were optimistic about the use of GRSs for screening and risk prediction in intermediate-risk individuals. “A major advantage of a GRS is that because genetics are immutable through life, this risk information is available (and potentially actionable) starting at birth… Even more encouraging is the fact that current GRS captures only a fraction of the total genetic risk, and future iterations of a GRS based on larger discovery samples are expected to better discriminate risk.” The authors conceded, however, that more data are needed before the use of GRS for predicting future CHD becomes a part of standard clinical practice and also pointed out that randomized controlled trials will be needed to test the benefits and risks of interventions based on an analysis of GRS.

Disclosures

None.

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Arterioscler Thromb Vasc Biol. 2015;35:741-747
doi: 10.1161/ATVBAHA.115.305492

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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