Published in final edited form as:

Curr Atheroscler Rep. 2013 June ; 15(6): 328. doi:10.1007/s11883-013-0328-6.

Nutrigenetics and Nutrigenomics of Atherosclerosis

Aksam J. Merched and

Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, USA.
INSERM U1034, 33600 Pessac, France

Lawrence Chan

Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, USA

Aksam J. Merched: amerched@bcm.edu; Lawrence Chan: lchan@bcm.edu

Abstract

The latest genome-wide association studies (GWAS) have re-energized our effort to understand the genetic basis of atherosclerotic cardiovascular disease. Although the knowledge generated by GWAS has confirmed that mediators of inflammation and perturbed lipid metabolism are major players in cardiovascular disease (CVD) development, much of individual disease heritability remains unexplained by the variants identified through GWAS. Moreover, results from interventions that aim at the pharmaceutical modification of lipid parameters fall short of expectation. These elusive treatment goals based on heritability studies highlight a key supportive, and perhaps even primary, role of nutritional therapy to achieve better health outcomes. Nonetheless, effective and specific interventions for CVD prevention using principles of “personalized” nutrition require a better knowledge of gene-diet interactions, an area that remains poorly explored. Dietary fatty acids such as omega-3 polyunsaturated fatty acids (PUFAs) are an excellent example of a widely studied “environment” that interacts with the genetic makeup in relation to CVD. A thorough exploration of the nutrigenomics and nutrigenetics of omega-3 PUFAs is key to understanding the etiology, and developing effective preventive measures. In this review, we will summarize the current state of knowledge of genetic interactions with omega-3 PUFAs in modulating lipid metabolism and inflammation, and defining health outcomes. Nutrigenetics and nutrigenomics are still in their infancy with respect to CVD prediction and therapy. Integration of the progress in the omics, including metabolomics, lipidomics, transcriptomics, and proteomics, coupled with advances in nutrigenomic and nutrigenetic research will move us towards personalized medicine as the ultimate paradigm of responsible clinical practice.

Keywords

Polyunsaturated fatty acids; Docosahexaenoic acid; Lipoxygenase; Inflammation; Lipid metabolism

© Springer Science+Business Media New York 2013

Correspondence to: Aksam J. Merched, amerched@bcm.edu; Lawrence Chan, lchan@bcm.edu.

Conflict of Interest Aksam Merched declares that he has no conflict of interest.

Lawrence Chan declares that he has no conflict of interest.

This article is part of the Topical Collection on *Genetics*

Introduction

Genome-wide association studies (GWAS) that were developed and popularized in the last decade have advanced our understanding of the genetic basis of cardiovascular diseases. The GWAS approach has identified dozens of novel genes and/or loci for atherosclerosis and related quantitative phenotypes, many of which have been confirmed by numerous independent studies. However, the identified susceptibility alleles so far explained only a small fraction (up to ~30 %) of the estimated overall heritability variance, with typical odds ratios of 1.3 or lower and limited predictive values. The missing heritability are likely attributed to several factors, including missing power to detect rare susceptibility allelic variants and lacking the context of interaction between genes and the environment including nutritional habits. Indeed, how genetic makeup interacts with dietary and other environmental factors is an area of cardiovascular research area that remains poorly explored. Nonetheless, many of the identified loci are mapped to genes associated with lipids traits (total cholesterol, low density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol (HDL-c) and triglyceride (TG) concentration) and network analysis of associated biological pathways are mainly linked to lipid metabolism and inflammation [1].

Inflammation and perturbed lipid metabolism are major players in atherosclerosis development. The relationship between elevated circulating lipids and atherosclerosis and cardiovascular diseases has been clearly established. High LDL cholesterol remains one of the major risk factors for this disease, while the presumed protective aspect of HDLc is not as straightforward. Although lipid-lowering interventions e.g., using statin treatment, have been proved successful in lowering coronary artery disease (CAD) risk, compelling benefit of statin therapy on all-cause mortality in a high-risk primary prevention trial has not been demonstrated [2]. Moreover, the side effects and the lack of response in some patients to the treatment underline the need of additional and alternative treatment options for controlling hyperlipidemia and other risk factors to ameliorate CAD risk. In the meantime, interventional studies aiming at improving the levels of HDL have not been shown to produce any benefit [3, 4]. These elusive objectives underscore the important supportive and perhaps even primary role of nutritional therapy to achieve better health outcomes.

Indeed, better nutrition remains the cornerstone to metabolic homeostasis and atherosclerosis prevention. Optimization of lipid metabolism depends on interplay of complex biochemical pathways involving numerous enzymes, receptors, activators, and other factors. Genetic variability of these players is a key modulator of the final lipid phenotype. Unfortunately, much of the traditional nutritional research-based recommendations on reference values and guidelines to the general population have not paid sufficient attention to individual genetic variability; a much more nuanced approach towards such recommendations is warranted.

The integration of the human genome project with nutritional, genetic research and health outcomes studies have led to the emergence of nutrigenetics and nutrigenomics. These disciplines investigate in a systematic fashion the effect of genetic makeup on individual

dietary response and the role of dietary factors and bioactive nutrient products in gene expression, and stability respectively [5•]. This review will focus on the nutrigenetics of atherosclerosis using polyunsaturated fatty acids (PUFA) as an example. We will be incorporating the latest discoveries from GWAS of large human populations and will also discuss selected aspects of nutrigenomics.

Genetics of Atherosclerosis: The Candidate Gene and Unbiased Hypothesis-Free Approaches

Conventional risk factors of atherosclerosis were based on evidences from epidemiological studies leading to defining different risk factors such as gender, age, hypertension, hyperlipidemia, obesity, and diabetes. Genetic roots of this disease were validated by many epidemiological, family and twin studies, where heritability estimates for atherosclerosis exceeds 50 % in many investigations. The development of mouse models using over-expression and gene-knockout technology has identified and/or validated the potential involvement of, and the possible mechanisms of action of numerous candidate gene products thought to be important in atherosclerosis development (reviewed in Ref [6•]). The advent of the era of genome-wide association studies (GWAS) in atherosclerosis research enabled the scanning of the whole genome in an unbiased fashion in large human populations that has unearthed many new loci significantly associated with CAD [7].

Five years after the discovery of the most robustly replicated genetic signal for CAD around the world e.g. the 9p21.3 locus, 46 other loci have been identified by the Wellcome Trust Case Control Consortium; the Ottawa Heart Study; German Myocardial Infarction Family Studies I, II, and III; deCode; the Myocardial Infarction Genetics Consortium in Wang et al. in a Han Chinese population, Gretarsdottir et al. in the DAB2IP gene and the meta-analyses by the Coronary ARtery Disease Genome-Wide Replication Meta-Analysis (CARDIoGRAM) consortium, the International Consortium for Coronary Artery Diseases (C4D) and the CARDIoGRAMplusC4D Consortium (reviewed in Refs [1, 8]), in addition to a multivariate genome-wide association analysis that combines SNP data and serum metabolomic profiles [9]. It is noteworthy that all these identified loci contributed with very modest effects and limited predictive value on disease. Meanwhile, several of the CAD loci are significantly associated with lipid phenotype related mainly to LDL cholesterol levels, whereas most of the genes and/or loci were completely novel and were not previously suspected to be involved in atherosclerosis or myocardial infarction. Twelve loci were significantly associated with the concentrations of blood lipids (total cholesterol, LDL cholesterol (LDL-c), high-density lipoprotein (HDL) cholesterol (HDL-c) and triglyceride concentration), and five were associated with blood pressure. Network analysis revealed relevant biological pathways that underlie the pathogenesis of CAD linked to lipid metabolism and inflammation [1].

Functional Implications of Genetic Variants to Disease Risk

Several loci are related to CAD risk factors mainly LDL metabolism (Table 1), whereas the vast majority of the loci were not previously reported to be associated with CAD.

The functional implications of these associations can be translated at different levels. The variant of the leading SNP at 9p21.3 locus linked to CAD was shown to enhance vascular cell proliferation, leading to excessive aortic smooth muscle cell proliferation and predisposing to atherosclerosis. The neighboring genes in this locus include cyclin-dependent protein kinase (CDK) inhibitory genes; *CDKN2A* and *CDKN2B*. The *CDKN2A* locus encodes two isoforms: p16INK4A and p19ARF, and the *CDKN2B* gene encodes p15INK4B. We were the first to implicate cell cycle proteins and tumor suppressors in atherogenesis. We have demonstrated that tumor suppressor gene p53 has protective role in the development of atherosclerosis in apolipoprotein E (ApoE) and LDL receptor knockout (KO) mice [10, 11] by affecting both cell proliferation and apoptosis in plaques. Meanwhile, we showed that the tumor suppressor gene p21Waf1 is involved in promoting atherogenesis in ApoE-KO mice [12]. Interestingly, p21Waf1-deficient macrophages present high expression level of *CDKN2A* and exhibit higher protective housekeeping function of phagocytosis, underscoring the important role of these CDKs in inflammation. However, studies in human tissue and cell culture have failed to demonstrate a consistent relationship between the levels of the genes flanking 9p21, the noncoding transcript ANRIL (*CDKN2BAS*), and the 9p21 risk alleles [13–16]. Moreover, knockout and gain-of-function studies in different mouse models provided additional insight into this relationship [17–20], which may be related to significant compensatory regulation in this region. Furthermore, cell and tissue specificity of gene expression may underlie differences in phenotype, e.g., examination of tissue-specific expression in macrophages, smooth muscle cells, and endothelial cells will be needed to address the subtle cell-specific effects on phenotype.

SORT1 regulates hepatic lipoprotein production and affect the level of LDL cholesterol and very low density lipoprotein secretion. The *MRAS* locus (3q22.3) plays a role in neuronal differentiation, in osteogenesis, in the osteoblastic determination, differentiation, and transdifferentiation under p38 mitogen-activated protein kinase 1 and mitogen-activated protein kinase 8, also known as JNK regulation. However, the mechanistic implication of the association of the variant to CAD is not clear. *SMG6* 17p13.3 is known to be involved in nonsense-mediated mRNA decay. *SRR*, a gene in the region of the 17p13.3 risk locus, was previously shown to be associated with cardiac structure and function (aortic root size). The *RASD1* gene mapped to the 17p11.2 locus, which encodes a member of the Ras superfamily of small GTPases and is thought to play a role in dexamethasone-induced alterations in cell morphology, growth, and cell–extracellular matrix interactions. *PPAP2B* is known to actively hydrolyze extracellular lysophosphatidic acid and short-chain phosphatidic acid. GIP is thought to induce insulin secretion and to have significant effects on fatty acid metabolism. *SERPINA1* encodes alpha 1-antitrypsin, a protease inhibitor that protects surrounding tissues at sites of inflammation, a process involved in atherosclerosis. *AQP9* encodes aquaporin 9, a liver glycerol channel involved in gluconeogenesis. No functional implications have been identified for the remaining loci.

Replication and validation of the GWAS findings in additional population samples is often necessary to corroborate whether these are reproducible association signals. As mentioned earlier, the GWAS approach is characterized by its limited power to identify gene-

environment interactions. Finally, animal studies and systems-based approaches are needed to further identify and validate the pathways and mechanisms leading to disease [7].

Nutrigenomics and Nutrigenetics of Omega-3 Polyunsaturated Fatty Acids

Fatty acids are classified in different groups: saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), or polyunsaturated fatty acids (PUFAs), based on the number of double bonds present in the hydrocarbon backbone structure. Saturated fatty acids lack double bonds, MUFAs have one and PUFAs two or more double bonds per molecule. The number and position of double bonds within the hydrocarbon chain give PUFA their name and is the basis of their physiochemical properties and physiological reactivity. A different nomenclature such as omega (w)–3 or omega–6 reflects the locations of the double bond closest to the methyl end of the hydrocarbon chain. In the omega–3 fatty acids, the terminal double bond is on the third carbon away from the methyl end.

A growing number of epidemiologic data attributed atheroprotective properties to fish and fish oil rich in omega–3 PUFA, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Cardioprotection conferred by this PUFA species can be attributed to different mechanisms, including regulation of lipid metabolism and blood pressure, stabilization of atherosclerotic plaques, anti-arrhythmic and anti-inflammatory actions. Treatment with omega-3 fatty acids has slowed down the development of atherosclerosis in different animal models.

We have uncovered the anti-inflammatory and anti-atherosclerotic properties of omega–3 PUFA in multiple animal and cellular models. We demonstrated that their bioactive end product produced by the 12/15 lipoxygenases (*ALOX*) exert proresolution functions both at the cellular level involving macrophages and endothelial cells in vitro, and in mouse models engineered to express different levels of *ALOX-15* in vivo [21••]. The pro-resolution arm of the inflammation homeostatic process is mediated by the eicosanoids resolvins, protectins and maresins, which counteract the potent proinflammatory mediators derived from the omega–6 PUFA arachidonic acid.

Dietary fatty acids such as omega–3 PUFAs are an excellent example of a widely studied “environment” that interacts with the genetic makeup in correlation with cardiovascular disease and many other human diseases. Understanding the nutrigenomics and nutrigenetics of omega–3 PUFAs is key to understanding the etiology, as well as developing effective preventive measures, for CVD.

Extensive reports have shown cardioprotective effects of dietary fish, fish oil or a combination of EPA/DHA used in nutritional supplementation. However, many of these studies observed large variation in lipid phenotype e.g. levels of LDL-c, triglycerides and HDL-c. We will highlight the growing knowledge of the interactions between these nutrients and individual characteristics, which may help us better understand what the diet response for each individual could be. Individual gene variations in apolipoprotein (apo)AI [22], apoA5 [23], apoE [24], TNFalpha [25], PPAR alpha [26], NOS3 [27], ALOX5 and 12/15 genes [21••, 28–30] and their interactions with omega-3PUFA intake in modulating lipid metabolism and cardiovascular outcome are summarized in Fig. 1. There are recent review

articles that deal with nutrigenetics studies focused on lipid metabolism [31], and other aspects of nutrigenetic involvement of PUFA in CVD [32].

Interaction of PUFA with HDL-c Metabolism Modulated by ApoAI and TNF α Polymorphisms

ApoA-I is a major structural constituent protein of HDL, and plays a pivotal role in their metabolism. We and others have shown that HDL-cholesterol (HDL-c) is a protective factor for both cardio and cerebrovascular diseases. Plasma levels of HDL-c and apoAI were positively correlated with cognitive functions in patients with Alzheimer's disease [33]. Using an animal model and gene therapy approach, we found that apoAI gene delivery retards atherosclerosis progression, and remodels the lesions to a more stable-appearing phenotype [34].

Associations between plasma apoAI concentrations and circulating HDL-c levels have been somehow conflicting. Inconsistencies between studies could be attributed to the complex genetic and dietary contribution to the control of HDL level. Indeed, the Framingham Study has reported significant interaction in women between a common genetic polymorphism in the promoter region of the *APOA1* gene, the -75G/A SNP and PUFA intake in determining plasma HDL-c concentration [22]. Carriers of the A allele at the -75 G/A polymorphism show an increase in HDL-c concentrations with increased intakes of PUFA, whereas those of the more common G allele have the opposite effect by displaying lower HDL-c levels as the intake of PUFA increases.

Tumor necrosis factor- α (TNF- α) is a proinflammatory cytokine that can have an impact on lipid metabolism by modulating the expression of lipoprotein lipase (LPL); proliferator activated receptors (PPARs); apolipoprotein (apo) A-I, apo A-IV, and apo E; and lecithin: cholesterol acyltransferase. TNF- α itself is also known to be modulated by dietary PUFAs. Two common genetic polymorphisms in the promoter region of the TNF- α gene were known to alter the transcriptional activity of the cytokine gene in vitro. The potential role of these TNF- α genotypes on the association between dietary PUFA intake and serum lipid concentrations was investigated among individuals with type 2 diabetes in the Canadian trial of dietary Carbohydrate in Diabetes study [25]. PUFA intake was positively associated with serum HDL-c and apoA-I level in carriers of the -238A allele, but negatively associated in those with the -238GG genotype. PUFA intake was inversely associated with HDL-c level in carriers of the -308A allele, but not in those with the -308GG genotype. A stronger nutrigenetic effect was observed when the polymorphisms at the two positions (-238/-308) were combined.

These are classic examples of how a nutrient-gene interaction can affect the association between a particular genotype and a biological risk marker, which may underlie inconsistencies in reported study outcomes. In the meantime, it is prudent to suggest that subjects with low levels of HDL-c, carriers of the A allele at the *APOA1* -75 G/A and the alleles -238A, 308GG at the TNF- α -238G/A and -308G/A polymorphisms may benefit from diets containing higher percentages of PUFA.

Interaction of PUFA with Triglyceride Metabolism Modulated by ApoA5, NOS3 and PPARA Polymorphisms

Apolipoprotein A-V (ApoA-V) is a component of lipoproteins including HDL and chylomicrons and is involved in postprandial lipoprotein metabolism. By activating LPL, a key enzyme in the metabolism of TG, apoA-V is an important determinant of plasma TG concentrations. In the Framingham study, authors demonstrated a significant interaction between -1131T/C SNP, which is associated with greater TG concentrations in carriers of the C allele and PUFA intake [23]. The -1131C allele was associated with an increased fasting TG and remnant-like particle-TG concentrations only in subjects consuming 46 % of energy from PUFA.

Nitric oxide synthase (NOS3) is responsible for the production of nitric oxide (NO), which is involved in the regulation of vascular function and blood pressure. SNPs in the NOS3 gene were found to be associated with a number of CVD risk markers, including dyslipidemia and inflammation. The effects of NOS3 polymorphisms were investigated in a cohort of 450 patients with metabolic syndrome from the LIPGENE study who participated in a 12-week dietary intervention to alter dietary fatty acid composition and amount [27]. The study demonstrated that carriers of the minor allele for rs1799983 SNP showed a negative correlation between plasma TG concentrations and plasma omega-3 PUFA status compared with subjects homozygous for the major allele. Following omega-3 PUFA supplementation, subjects with the minor alleles had a better response to changes in plasma omega-3 PUFA than major allele homozygous carriers. This highlights the potential benefit for individual carriers of the minor allele at rs1799983 in NOS3 in omega-3 PUFA supplementation to achieve reduction of plasma TG concentrations.

Peroxisome proliferator-activated receptor α (PPAR- α) is a ligand-dependent transcription factor that is a key regulator of lipid homeostasis. Because of its strong involvement in activating LPL, clearance of plasma triglycerides and upregulation of HDL-c, PPARA has been a drug target for pharmaceutical companies. The most frequently studied polymorphism of the PPARA gene was the Leu162Val variant, in which the minor allele was associated with lipid metabolism and atherosclerosis. However, there was controversy on the potential effect of this SNP on plasma TG and apoC-III concentrations. Subsequent studies showed that dietary PUFA intake can modulate the effects of this SNP on lipid metabolism [26]. The 162 V allele was associated with higher TG and apoC-III levels only in subjects consuming a low-PUFA diet. Conversely, high consumption of PUFA diet in 162 V subjects was related with the opposite effect on apoC-III [26].

Nutrigenetics and Nutrigenomics of PUFA Bioactive Mediators of Inflammatory Resolution Generated by Lipoxygenase Pathways

One important mechanistic aspect of cardioprotective functions of PUFA may have to do with curtailing inflammation, returning to homeostasis and preserving tissue integrity. The omega-6 PUFA arachidonic acid can be converted into different families of lipid mediators: prostaglandins (PGs) and leukotrienes (LTs), which are mostly proinflammatory molecules,

and lipoxins (LXs) such as LXA4, an anti-inflammation mediator. The omega-3 PUFAs, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), generate different types of proresolution mediators, including resolvins, protectins and maresins (Fig. 2). Lipoxygenases are key enzymes involved in the conversion of these PUFAs to their respective bioactive mediators. However, they have multi-enzymatic activities regulating different metabolic pathways.

We have conducted extensive studies of the putative role of murine 12/15-LOX in atherosclerosis development by observations on multiple models of enzyme overproduction and deficiency [21]. The simultaneous examination of cell and mouse models that exhibit high, normal, and reduced 12/15-LOX expression allowed us to modulate the metabolism of LOX-derived mediators e.g. LXA, RvD, PD1 and Mar1 [21], and to demonstrate their active involvement in the resolution of inflammation. Macrophage overexpressing the 15LOX were better metabolizers of DHA and enriched the metabolic products (DHA metabolome) of RvD1, PD1 and Mar1 (Fig. 2). DHA is a source of a wide range of bioactive products involved in many pathways [35]. We conducted nutrigenomic analysis of the effect of bioactive metabolome of resolution and demonstrated a wide range of targets. It stimulated the reduction of multiple inflammatory cytokines, chemokines, and adhesion molecules in macrophages and endothelial cells, improved the phagocytic potential of macrophages and the elimination of apoptotic cells and downregulated the accumulation of modified lipids, effectively putting the brakes on atherosclerosis progression (Fig. 3). As part of their mechanism of action, these mediators exert their potent actions via activating specific pro-resolving G-protein coupled receptors [36••]. Taken together, these findings suggest that a failure of local endogenous resolution mechanisms may underlie the unremitting inflammation that fuels atherosclerosis.

Interestingly, however, results from animal experiments by different groups show a range of responses with the 12/15-lipoxygenase pathways in atherosclerosis. We recently uncovered key nutrigenetic interactions between the lipoxygenase and dietary intervention. Importantly, when we switched mice from a normal chow to a western type diet, we found that the inflammatory responses and 12/15-lipoxygenase effect on atherosclerosis disappeared or, in some cases, were actually reversed; such responses were actually supported by congruent results observed with high lipids on cells in vitro [30]. The observation of the nutrigenetic disruption of inflammation-resolution homeostasis and on the process of atherogenesis may explain much of the conflicting data on the role of the putative pro- and anti-atherogenic effects of lipoxygenase in vivo. In addition, the multifunctional involvement of these enzymes and their complex regulation in vivo could have amplified the diversity of data related to their physiopathological effects in human populations.

Genetic studies on the role of 12/15-lipoxygenases in human atherosclerosis suggest that on balance the *ALOX15* locus is more commonly associated with either a relatively neutral or an atheroprotective effect [29] than the converse. On the other hand, these human genetic studies did not consistently show an association of functional variants in *ALOX15* with clinical end points of atherosclerosis.

Given the potent actions of lipoxins, resolvins, protectins and maresins in models of human disease, deficiencies in resolution pathways may contribute to many diseases including atherosclerosis. These lipid mediators represent potential new therapeutic agents that limit the damage incurred by inflammatory disease via heightened resolution. Lipidomic and metabolomic analysis of these bioactive lipid mediators provide a powerful approach to investigate the nutrigenetic and nutrigenomic effect of omega-3 PUFAs in health and disease.

Conclusions

Evidence of interaction between genetic markers and dietary components has helped shed light on the inconsistencies that have been reported between diet-related studies and sometimes genetic analyses among different populations. The knowledge from gene-environment (diet) interactions will enable more effective and specific interventions for CVD prevention based on “personalized” nutrition. It is important to emphasize, however, that although many published investigations often indicated strong nutrient-gene interactions that underlie variability of phenotypes, with nutrient intake potentially modulating risk factors of CVD, it is difficult at this time to apply these data to clinical practice. Indeed each of these nutrigenetic studies considered individually only one or at most two gene variants, neglecting the possible global interactions between a wide array of gene variants with different nutritional interactions. Nutrigenetics and nutrigenomics are still in their infancy with respect to cardiovascular disease prediction and therapy!

The road of personalized medicine requires much more robust and sophisticated characterization of the functional implications of a growing set of new polymorphisms and CVD risk factors, supported by well-controlled dietary intervention studies that yield highly consistent results. Atherosclerotic CVD is as much a metabolic as it is an inflammatory disease. The power of nutrigenetics and nutrigenomics can be further enhanced with the coapplication of metabolomics, another rapidly emerging discipline.

Management and prevention of CVD will benefit tremendously from personalized medicine including individualized nutritional therapy. The public health implications of nutritional therapy are enormous. Integration of the progress in the omics, such as metabolomics, lipidomics, transcriptomics, and proteomics, coupled with advances in nutrigenomic and nutrigenetic research will make personalized medicine a reality. In the meantime, nutritionists, medical practitioners and genetic counselors need to embrace the new nutrigenetics/nutrigenomics revolution to help bring the nutritional component of preventive medicine from the dangerous stage of “generalization” toward the new era of “personalized medicine”.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Deloukas P, Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TLWC, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet.* 2013; 45(1):25–33. [PubMed: 23202125]
2. Ray KK, Seshasai SR, Erqou S, Sever P, Jukema JW, Ford I, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. *Arch Intern Med.* 2010; 170(12):1024–31. [PubMed: 20585067]
3. Lavigne PM, Karas RH. The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression. *J Am Coll Cardiol.* 2013; 61(4):440–6. [PubMed: 23265337]
4. Gotto AM Jr, Moon JE. Recent clinical studies of the effects of lipid-modifying therapies. *Am J Cardiol.* 2012; 110(1 Suppl):15A–26.
5. Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French TA, Tai ES, et al. Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. *J Nutrigenet Nutrigenomics.* 2011; 4(2):69–89. A nice overview of different aspects of nutrigenetics and nutrigenomics in nutrition research, in optimizing well being and control, management and treatment of diseases including cancer, metabolic syndrome and cardiovascular diseases. [PubMed: 21625170]
6. Stylianou IM, Bauer RC, Reilly MP, Rader DJ. Genetic basis of atherosclerosis: insights from mice and humans. *Circ Res.* 2012; 110(2):337–55. A comprehensive review of the genetic basis of atherosclerosis, summarizing data on more than a hundred genes affecting pathogenesis in mouse models and the latest data from genome wide association studies. [PubMed: 22267839]
7. Lusis AJ. Genetics of atherosclerosis. *Trends Genet.* 2012; 28(6):267–75. [PubMed: 22480919]
8. Maouche S, Schunkert H. Strategies beyond genome-wide association studies for atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2012; 32(2):170–81. [PubMed: 22258900]
9. Inouye M, Ripatti S, Kettunen J, Lyytikäinen LP, Oksala N, Laurila PP, et al. Novel Loci for metabolic networks and multi-tissue expression studies reveal genes for atherosclerosis. *PLoS Genet.* 2012; 8(8):e1002907. [PubMed: 22916037]
10. Guevara NV, Kim HS, Antonova EI, Chan L. The absence of p53 accelerates atherosclerosis by increasing cell proliferation in vivo. *Nat Med.* 1999; 5(3):335–9. [PubMed: 10086392]
11. Merched AJ, Williams E, Chan L. Macrophage-specific p53 expression plays a crucial role in atherosclerosis development and plaque remodeling. *Arterioscler Thromb Vasc Biol.* 2003; 23(9):1608–14. [PubMed: 12842843]
12. Merched AJ, Chan L. Absence of p21Waf1/Cip1/Sdi1 modulates macrophage differentiation and inflammatory response and protects against atherosclerosis. *Circulation.* 2004; 110(25):3830–41. [PubMed: 15596565]
13. Holdt LM, Beutner F, Scholz M, Gielen S, Gabel G, Bergert H, et al. ANRIL expression is associated with atherosclerosis risk at chromosome 9p21. *Arterioscler Thromb Vasc Biol.* 2010; 30(3):620–7. [PubMed: 20056914]
14. Holdt LM, Sass K, Gabel G, Bergert H, Thiery J, Teupser D. Expression of Chr9p21 genes CDKN2B (p15^{INK4b}), CDKN2A (p16^{INK4a}), p14^(ARF) and MTAP in human atherosclerotic plaque. *Atherosclerosis.* 2011; 214(2):264–70. [PubMed: 20637465]
15. Jarinova O, Stewart AF, Roberts R, Wells G, Lau P, Naing T, et al. Functional analysis of the chromosome 9p21.3 coronary artery disease risk locus. *Arterioscler Thromb Vasc Biol.* 2009; 29(10):1671–7. [PubMed: 19592466]
16. Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Mohlke KL, et al. INK4/ARF transcript expression is associated with chromosome 9p21 variants linked to atherosclerosis. *PLoS One.* 2009; 4(4):e5027. [PubMed: 19343170]
17. Fuster JJ, Molina-Sanchez P, Jovani D, Vinue A, Serrano M, Andres V. Increased gene dosage of the Ink4/Arf locus does not attenuate atherosclerosis development in hypercholesterolaemic mice. *Atherosclerosis.* 2012; 221(1):98–105. [PubMed: 22226369]
18. Gonzalez-Navarro H, Abu Nabah YN, Vinue A, Andres-Manzano MJ, Collado M, Serrano M, et al. p19^(ARF) deficiency reduces macrophage and vascular smooth muscle cell apoptosis and aggravates atherosclerosis. *J Am Coll Cardiol.* 2010; 55(20):2258–68. [PubMed: 20381282]

19. Kim JB, Deluna A, Mungrue IN, Vu C, Pouladar D, Civelek M, et al. Effect of 9p21.3 coronary artery disease locus neighboring genes on atherosclerosis in mice. *Circulation*. 2012; 126(15): 1896–906. [PubMed: 22952318]
20. Kuo CL, Murphy AJ, Sayers S, Li R, Yvan-Charvet L, Davis JZ, et al. Cdkn2a is an atherosclerosis modifier locus that regulates monocyte/macrophage proliferation. *Arterioscler Thromb Vasc Biol*. 2011; 31(11):2483–92. [PubMed: 21868699]
21. Merched AJ, Ko K, Gotlinger KH, Serhan CN, Chan L. Atherosclerosis: evidence for impairment of resolution of vascular inflammation governed by specific lipid mediators. *Faseb J*. 2008; 22(10):3595–606. In a comprehensive series of experiments using overproduction and deficiency murine models 12/15-LOX, this study demonstrates that PUFAs are metabolized by the lipoxygenases to generate lipid mediators with potent proresolution and anti-inflammation effects both at the cell level and in vivo. [PubMed: 18559988]
22. Ordovas JM. The quest for cardiovascular health in the genomic era: nutrigenetics and plasma lipoproteins. *Proc Nutr Soc*. 2004; 63(1):145–52. [PubMed: 15070444]
23. Lai CQ, Corella D, Demissie S, Cupples LA, Adiconis X, Zhu Y, et al. Dietary intake of n-6 fatty acids modulates effect of apolipoprotein A5 gene on plasma fasting triglycerides, remnant lipoprotein concentrations, and lipoprotein particle size: the Framingham Heart Study. *Circulation*. 2006; 113(17):2062–70. [PubMed: 16636175]
24. Lovegrove JA, Gitau R. Nutrigenetics and CVD: what does the future hold? *Proc Nutr Soc*. 2008; 67(2):206–13. [PubMed: 18412994]
25. Fontaine-Bisson B, Wolever TM, Chiasson JL, Rabasa-Lhoret R, Maheux P, Josse RG, et al. Genetic polymorphisms of tumor necrosis factor- α modify the association between dietary polyunsaturated fatty acids and fasting HDL-cholesterol and apo A-I concentrations. *Am J Clin Nutr*. 2007; 86(3):768–74. [PubMed: 17823444]
26. Tai ES, Corella D, Demissie S, Cupples LA, Coltell O, Schaefer EJ, et al. Polyunsaturated fatty acids interact with the PPARA-L162V polymorphism to affect plasma triglyceride and apolipoprotein C-III concentrations in the Framingham Heart Study. *J Nutr*. 2005; 135(3):397–403. [PubMed: 15735069]
27. Ferguson JF, Phillips CM, McMonagle J, Perez-Martinez P, Shaw DI, Lovegrove JA, et al. NOS3 gene polymorphisms are associated with risk markers of cardiovascular disease, and interact with omega-3 polyunsaturated fatty acids. *Atherosclerosis*. 2010; 211(2):539–44. [PubMed: 20409549]
28. Dwyer JH, Allayee H, Dwyer KM, Fan J, Wu H, Mar R, et al. Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. *N Engl J Med*. 2004; 350(1):29–37. [PubMed: 14702425]
29. Hersberger M. Potential role of the lipoxygenase derived lipid mediators in atherosclerosis: leukotrienes, lipoxins and resolvins. *Clin Chem Lab Med*. 2010; 48(8):1063–73. [PubMed: 20441482]
30. Merched AJ, Serhan CN, Chan L. Nutrigenetic disruption of inflammation-resolution homeostasis and atherogenesis. *Journal of Nutrigenet Nutrigenomics*. 2011; 4(1):12–24.
31. Garcia-Rios A, Perez-Martinez P, Delgado-Lista J, Lopez-Miranda J, Perez-Jimenez F. Nutrigenetics of the lipoprotein metabolism. *Mol Nutr Food Res*. 2012; 56(1):171–83. [PubMed: 22121097]
32. Allayee H, Roth N, Hodis HN. Polyunsaturated fatty acids and cardiovascular disease: implications for nutrigenetics. *Journal of Nutrigenet Nutrigenomics*. 2009; 2(3):140–8.
33. Merched A, Xia Y, Visvikis S, Serot JM, Siest G. Decreased high-density lipoprotein cholesterol and serum apolipoprotein AI concentrations are highly correlated with the severity of Alzheimer's disease. *Neurobiol Aging*. 2000; 21(1):27–30. [PubMed: 10794845]
34. Belalcazar LM, Merched A, Carr B, Oka K, Chen KH, Pastore L, et al. Long-term stable expression of human apolipoprotein A-I mediated by helper-dependent adenovirus gene transfer inhibits atherosclerosis progression and remodels atherosclerotic plaques in a mouse model of familial hypercholesterolemia. *Circulation*. 2003; 107(21):2726–32. [PubMed: 12742997]
35. Shinohara M, Mirakaj V, Serhan CN. Functional metabolomics reveals novel active products in the DHA metabolome. *Front Immunol*. 2012; 3:81. [PubMed: 22566962]

- 36••. Serhan CN, Krishnamoorthy S, Recchiuti A, Chiang N. Novel anti-inflammatory--pro-resolving mediators and their receptors. *Curr Top Med Chem*. 2011; 11(6):629–47. A review of state-of-the-art approaches to identify and profile lipid mediators, including specialized pro-resolving mediators such as resolvins, protectins and maresins that are produced by phagocytes in inflammatory exudates. [PubMed: 21261595]

Fig. 1.

Nutrigenetic of omega 3 PUFAs in cardiovascular disease and related traits. See text for more details

Fig. 2.

Dietary bioactive compounds of DHA generated by macrophages expressing different levels of 12/15 Lipxygenase. *A.* Adherent peritoneal macrophages from 15 lipoxigenase transgenic (TG) and wild type (WT) mice incubated with 1 mg of DHA in PBS for 30 minutes at 37 °C. *B.* Metabolic pathway of DHA by 12/15LOX. *C.* MS/MS spectrum of 14HDHA. *D.* amount of prostaglandin E2 (PGE2), protectin D1 (PD1), and other intermediate of DHA metabolism. *Below detection limit

Fig. 3.

Nutrigenomics of DHA bioactive lipidome. The specialized pro-resolving lipid mediators generated from DHA via the lipoxygenase pathways prevent excessive inflammation and modified lipid accumulation and promote removal of apoptotic cells, thereby expediting resolution, return to tissue homeostasis and protecting the cardiovascular system. RvD1: ResolvinD1 (7*S*,8*R*,17*S*-trihydroxy-4*Z*,9*E*,11*E*,13*Z*,15*E*,19*Z* - docosahexaenoic acid), Mar1: Maresin1 (7,14-dihydroxy-docosa-4*Z*,8,10,12,16*Z*,19*Z* - hexaenoic acid), PD1: Protectin D1 (10*R*,17*S*-dihydroxy-4*Z*,7*Z*,11*E*,13*E*,15*Z*,19*Z*-docosahexaenoic acid), EC: endothelial cell, Mφ: macrophage

Table 1

Genome-wide association with known coronary artery disease (CAD) risk factors

Loci and associated genes	CAD risk factors
9q34.2 <i>ABO</i>	total cholesterol and LDL
10q24.32 <i>CYP17A1/CNNM2/NT5C2</i>	hypertension
11q23.3 <i>ZNF259/APOA5/4/1/APOC3</i>	LDL, HDL, and total cholesterol
1p13.3 <i>CELSR2/PSRC1/SORT1</i> , 1p32.3 <i>PCSK9</i> , 9q34.2 <i>ABO</i> , 11q23.3 <i>ZNF259/APOA5/4/1/APOC3</i> , and 19p13.2 <i>LDLR/SMARCA4</i>	LDL-c
11q23.3 <i>ZNF259/APOA5/4/1/APOC3</i> , 17p13.3 <i>SMG6/SRR</i> , and 19p13.2 <i>LDLR/SMARCA4</i>	HDL-c
1p13.3 <i>CELSR2/PSRC1/SORT1</i> , 9q34.2 <i>ABO</i> , 11q23.3 <i>ZNF259/APOA5/4/1/APOC3</i> , and 19p13.2 <i>LDLR/SMARCA4</i>	total cholesterol
6p21.31 <i>ANKS1A</i> and 17q21.32 <i>UBE2Z/GIP/ATP5G1/SNF8</i>	body mass index
11q23.3 <i>ZNF259/APOA5/4/1/APOC3</i>	triglyceride
1p13.3 <i>CELSR2/PSRC1/SORT1</i>	blood lipid trait
6p21.31 <i>ANKS1A</i> , 6q23.2 <i>TCF21</i> and 7q22.3 <i>BCAP29</i>	obesity
1q41 <i>MIA3</i>	adiposity
6p21.31 <i>ANKS1A</i>	alcoholism
9q34.2 <i>ABO</i> and 15q25.1 <i>ADAMTS7</i>	smoking behavior
12q24.12 <i>SH2B3</i> and 17q21.32 <i>UBE2Z/GIP/ATP5G1/SNF8</i>	diastolic blood pressure
10q24.32 <i>CYP17A1/CNNM2/NT5C2</i> and 12q24.12 <i>SH2B3</i>	systolic blood pressure

LDL low density lipoprotein; *LDL-c* low density lipoprotein cholesterol; *HDL* high-density lipoprotein; *HDL-c* high-density lipoprotein cholesterol

Data in this Table were derived from Ref [8].