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Adaptive genetic variation and heart disease risk

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Abstract

Purpose of review—Obesity, dyslipidemia and cardiovascular disease are complex and determined by both genetic and environmental factors and their inter-relationships. Many associations from genome-wide association studies and candidate gene approaches have described a multitude of polymorphisms associating with lipid and obesity phenotypes but identified genetic variants account for only a small fraction of phenotypic variation.

Recent findings—That many genotype–phenotype associations involve variants under positive selection and that those variants respond to environmental cues together suggest prominent roles for both genetic adaptation and their interactions with the environment. Adaptive genetic variations interacting with environment modulate disease susceptibility but the level to which those variants contribute to dyslipidemia and obesity and how environmental factors, especially diet, alter the genetic association is not yet completely known.

Summary—It is evident that genetic variants under positive selection make important contributions to obesity and heart disease risk. Advances in resequencing the entire human genome will enable accurate identification of adaptive variants. Considering interactions between environmental factors and genotypes will empower both genome-wide association studies and characterization of the relationship between positive selection and the obese and dyslipidemic conditions.

Keywords

dyslipidemia; gene–environment interaction; obesity; positive selection

Introduction

Advances in genome-wide genotyping technology, genome-wide association studies (GWAS) and improved statistical methods to detect natural selection in human populations facilitate discovery of links between genetic variants under positive selection and disease. Drawing on recently reported putative adaptive genetic variants from genome-wide scans and associations, we discuss the importance of genetic variants under positive selection, which contribute to the risk of, and understanding of, genetic architecture of dyslipidemia, heart disease and obesity in human populations.

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Adaptation of the genome and its implications

Over the past 100 000 years, humans have experienced diverse adaptation to changes in the local environment, including food resources, geography, climate, culture and pathogens. Such adaptation driven by natural selection has been imprinted in the genome as fixation, or changes of frequency of variant alleles or linkage disequilibrium patterns [1–4]. Advantageous adaptive genetic variants are functional variants underlying the diversity of phenotypes observed in contemporary populations, including skin color, body composition, metabolic rate and disease risk. For instance, variants at the *lactase* locus, which permit carriers to tolerate dietary lactose into adulthood, have been driven to high frequency in many European and some African populations in response to dairy farming over the past 10 000 years [5]. Well established theories in population genetics and new methods of analysis to detect natural selection enabled genome-wide screens for genetic signatures of old and recent positive selection [2–4]. However, it remains to be illustrated the extent to which variants under putative positive selection are linked to risk of disease.

Diet may influence both health and genome adaptation

Lipid homeostasis, obesity and coronary heart disease (CHD) are complex conditions influenced by combinations of genetic, dietary, behavioral and social factors [6]. The dramatic, recent increase in the prevalence of obesity in many populations as well as the status of heart disease as America's number one killer suggest prominent consideration of gene–environment interactions because the rate of environmental change has been much more rapid than adaptation of any human genome [7–9]. In response to prolonged exposure to periods of famine, natural selection favored energy storage for survivability. However, in many present-day societies with food over-abundance and sedentary lifestyles, alleles selected for thriftiness may now confer risk of obesity, dyslipidemia and heart disease [10].

Statistical methods for detecting selection

The primary statistical methods to detect positive selection based on population genetics algorithms are amino acid substitution rate, haplotype and linkage disequilibrium, site frequency spectrum (SFS) and population subdivision tests [11]. The integrated haplotype score (iHS) detects positive selection for variants that have not reached fixation (<30 000 years ago) based on differential levels of linkage disequilibrium surrounding a positively selected allele as compared with the background allele [1,12]. Extended haplotype homozygosity (EHH) detects positive selection based on high frequencies of long haplotypes. SFS tests, such as Tajima's D and Fay and Wu's H, detect selection from about 80 000 or 250 000 years ago to recent by use of allele frequencies in individuals segregating nucleotide sites. Fst statistics can describe the partitioning of genetic diversity within and among populations [13]. These methods have been reviewed in detail [11]. On the basis of HapMap phase II data, use of Haplotter, (http://hg-wen.uchicago.edu/selection/haplotter.htm) provides test statistics of *P* values for 2 501 050, 2 366 655 and 2 795 352 single-nucleotide polymorphisms (SNPs) from European, Asian and African populations, respectively [12]. To identify SNPs subjected to putative positive selection based on Tajima's D and Fay and Wu's H method, we have selected those SNPs, which associate with lipid, obesity and heart disease phenotypes and are within the upper 5% of the empirical *P* values. Haplotter data based on iHS and other positive selection data [14] were also mined to identify disease loci under positive selection.

Adaptive genetic variants and risk of dyslipidemia and heart disease

As modern human populations adapted to local surroundings, diet was likely key in driving changes in frequency of specific, selected genetic variants. Fat intake in the ancestral diet

would certainly have played a crucial role in adaptation, as this is a calorie-dense energy source to survive times of low food supply. Thus, it is expected that in the past 100 000 years, positive selection acted upon polymorphic sites in genes important in lipid metabolism. Today, individuals who carry these adaptive variants in an environment of high-fat meals and low physical activity could be at increased risk for dyslipidemia and heart disease. The last few years have seen many candidate genes affecting blood lipids and heart disease risk identified from GWAS and candidate gene studies. These lipid traits include LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), triglyceride and total cholesterol measured in serum. Although many such genes and polymorphisms have been described, it is important to note that some genetic variants are under positive selection (Table 1 [15–21,22•• ,23,24•,25–38]).

Results from GWAS have uncovered only a small proportion of genetic variation. In particular, although the Framingham Heart Study identified 30 loci contributing to polygenic dyslipidemia [20], seven of those (23%) show strong likelihood to be adaptive variants (Table 1). The European Network for Genetic and Genomic Epidemiology (ENGAGE) study [16] of 16 European countries with 22 562 participants identified 22 loci contributing to variation in blood lipid levels and six (27%) are likely under positive selection (Table 1). The White-hall II Study [24•] of 5592 European participants reported 195 SNPs in 16 genes/ regions associated with three major lipid fractions and two apolipoprotein components, with seven of those genes under positive selection. However, it is puzzling that these studies, and others, show concordance at a few major loci but still only define at most 15% of the genetic variation for such traits as LDL-C, HDL-C and triglyceride [24•].

Proprotein convertase subtilisin-like kexin type 9 (*PCSK9*) encodes a serine protease that mediates LDL receptor degradation by a post-transcriptional mechanism [39]. Many functional variants have been identified at this locus. Missense mutations that increase PCSK9 activity are associated with hypercholesterolemia [40], whereas loss-of-function mutations associate with lower LDL-C concentrations [41••]. Sequencing 28 kbp of the *PCSK9* gene in 24 African–Americans and 23 European Amer-icans allowed detection of significant signals of positive selection based on Fay and Wu's H, Tajima's D, Fst and long-range haplotype methods in both populations [41••]. In particular, according to the relative EHH (REHH) test after correction for background distribution, three potentially functional SNPs, rs2479409, rs562556 (I1470V) and rs505151 (E670G), displayed strong evidence of positive selection.

The *APOA1*/*C3*/*A4*/*A5* cluster has demonstrated association with both fasting and postprandial plasma lipid concentrations of triglyceride, HDL-C and LDL-C in directed studies [42] and in GWAS [15–18,20,28,29] and contributes to risk of heart disease [43,44]. This gene cluster is likely under selective adaptation [12]. SNP rs2548861 at gene *WWOX* has demonstrated both function in allele-specific binding to HepG2 cell nuclear extract and association with low-plasma HDL-C levels [27]. *WWOX* is also subject to positive selection based on the iHS test (Table 1).

For myocardial infarction and CHD, GWAS have identified 22 loci in European populations, of which four (18%) are likely adaptive genetic variants. Interestingly, for heart attack (late and early onset), only nine genes/ regions have been identified by GWAS [38,45], of which three likely experienced positive selection: *SORT1*/ *CELSR2*/*PSRC1*, *PCSK9* and *PHACTR1*. Some of these genetic variants contribute to heart disease risk through the lipid metabolism pathway, whereas some do so via unknown mechanisms. Variants of *SORT1*/*CELSR2*/ *PSRC1*, *PCSK9* and *MMP3* probably affect heart disease through lipid metabolism pathways, whereas the mechanisms by which *CD36* and *PHACTR1* cause heart disease remain to be illustrated.

Positive selection and risk of obesity

Several GWAS and other recent findings have described SNPs that associate with obesity phenotypes of BMI, waist circumference and weight. We find that seven (21%) of these 31 variants are under putative positive selection by any of a variety of tests (Table 2) [46–52,53•,54••,55,56•,57,58]. Notably, five separate studies [46–50] report that variants of *NEGR1*, encoding a neuronal growth regulator involved in cell adhesion, associate with obesity. At least four reports [47–50] identify *MTCH2*, which codes for a factor involved in mitochondrial transport and apoptosis, and its variants as associating with obesity. In addition, the *CLOCK* gene encodes an integral component of the circadian regulatory system. Variants of this gene and other circadian genes are receiving increased attention for roles in obesity. *CLOCK* variants associate with waist circumference only when saturated fat intake is high [56•]. These and many other newly described obesity loci are under positive selection (Table 2). In total, 14 putative genes/regions under positive selection that contribute to risk of obesity are listed.

Adaptive genetic variants: function and environmental interaction

An important aspect of identified adaptive genetic variants is that they likely represent functional variants, which contribute to disease risk. At *PCSK9*, eight non-synonymous SNPs and one insertion were found within a 28 kbp region in African–American and European American populations [22••]. Among those variants, three displayed significant positive selection signals by REHH. In addition, adaptation was detected by iHS. A common haplotype containing one of these SNPs (rs505151) is associated with increased LDL-C and higher risk of CHD [59]. Protein structure analysis elucidates the nature of naturally occurring *PCSK9* loss-of-function mutants. Three mutations (L82X, Y142X and C679X) result in truncated versions of *PCSK9* that disrupt proper folding and secretion of this convertase, which regulates LDL receptor degradation [39]. Two of those mutations associated with 30–40% reduction in plasma LDL-C in African–Americans [60].

A polymorphism at *MMP3*, at binding sites for ZNF148 and NFKB1, was identified as under positive selection by Fst [34]. Haplotypes containing this variant displayed significantly increased risk of CHD in a Chinese population [35]. The *APOA5* variant rs662799, mapping 1123 bp upstream of the transcription start site, is in strong linkage disequilibrium with a 5′-untranslated region SNP thought to affect translation efficiency. SNP rs662799 has been associated with both triglyceride and total cholesterol levels modified by dietary fat [31]. The *APOA5* gene also harbors signals of recent positive selection (Table 1). It is well known that functional variants or variants in high linkage disequilibrium with a functional variant display more consistent associations. Thus, it should be emphasized that positive selection variants associated with disease phenotypes in one population should also display consistent associations with similar diseases and related phenotypes in other populations. This assumes no epistasis and a similar environment, regardless whether that variant is under positive selection in other populations.

On the contrary, as environmental attributes drive beneficial alleles to high frequencies or fixation, it follows that those adaptive variants, which associate with disease status, are apt to be sensitive to environmental factors, especially dietary and lifestyle. Thus, the importance of gene–environment interactions in disease risk is probably fairly understated. Some examples are provided here of epidemiological evidence of gene–environment interactions in determining lipid and obesity-related phenotypes involving genes and their variants under positive selection. It is anticipated that for many other adaptive variants associating with phenotypes of blood lipids and obesity, there exist gene–environment interactions awaiting characterization.

The *APOA2* gene and its encoded protein have demonstrated roles in adiposity and insulin resistance [61]. A polymorphism in the gene control region, −265T>C or rs5082, exemplifies a SNP under positive selection and interacting with a dietary factor, as it contributes to the susceptibility of obesity. Although several studies have shown association of −265T>C with obesity, the most recent has reported that the *APOA2*–saturated fat interaction modulates the association with BMI in cross-sectional, follow-up and case–control analyses in three independent populations and confirms the importance of this SNP [54••]. Computational analysis of the −265 region of human *APOA2* strongly suggests allele-specific binding of the transcription factor CCAAT/enhancer-binding protein alpha, which participates in adipogenesis [54••,62]. Furthermore, significant positive selection has been ascribed to this polymorphism [12] (Table 2). Several other examples of genes whose variants both associate with phenotypes relevant to obesity, dyslipidemia and heart disease in a manner modulated by dietary or other environmental factors and are under putative positive selection are listed in Tables 1 and 2.

Limitations of studies of positive selection variation

Detection of positive selection is often complicated by the fact that adaptive selection could be confounded by recombination, and/or demographic distribution of genetic variants. Although there are many methods to detect positive selection, no one method detects all genetic variants under natural selection. Each method has its strengths to detect a particular adaptive footprint [11], and accurate detection of all adaptive variants requires use of a suite of methods. In addition, most genome scans for positive selection that are based on SNP genotypes suffer from ascertainment biases. The solution to this problem requires whole-genome resequencing. Further, as adaptive variants are driven by environmental factors, it is thus anticipated that such variants would interact with environmental factors to give rise to disease risk. Most GWAS analyses, however, have not considered genotype by environment interaction. Thus, adaptive genetic variants that are associated with disease risk are likely under-represented by variants identified by GWAS.

Future perspectives

Continued advances in reducing barriers to resequence the human genome will better identify positive selection. Recognition of the role of variants under positive selection in progression of human disease as modified by environmental factors will become widespread. Because differences in environment between populations can hinder replication efforts, it is critical that accurate measures of a full breadth of environmental factors, including dietary intake, physical activity, alcohol and tobacco use, drug treatment and sleep, should be taken in order to fully characterize the role of positive selection in disease. Functional characterization of putative adaptive variants will permit a better understanding of the development of diseases and provide an effective strategy for disease prevention and treatment. Refined approaches to identify adaptive variants, such as the recently described composite of multiple signals [63], sharpen the classification of variants, often to those that are functional.

Conclusion

It is evident that genetic variants under positive selection make important contributions to obesity and heart disease risk. In addition, we believe that adaptive variants interacting with environmental factors modulate disease susceptibility. The degree to which adaptive variants contribute to dyslipidemia and obesity and how environmental factors modulate the genetic association remain to be fully determined. Availability of genome sequence data from a diverse panel of humans will enable better detection of adaptive variants. We suggest that

identifying interactions between adaptive variants and environmental factors such as dietary intake underlying disease phenotypes empower both GWAS and the understanding of the correlation between adaptive variants and the obese and dyslipidemic conditions. Then, applying systems biology approaches of network analysis to the full repertoire of gene–gene and gene–environment interactions will provide a comprehensive means to better understand how environmental factors modulate those genotype–phenotype associations pertinent to human afflictions such as dyslipidemia and obesity.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 148–149).

1. Sabeti PC, Reich DE, Higgins JM, et al. Detecting recent positive selection in the human genome from haplotype structure. Nature. 2002; 419:832–837. [PubMed: 12397357]
2. Sabeti PC, Schaffner SF, Fry B, et al. Positive natural selection in the human lineage. Science. 2006; 312:1614–1620. [PubMed: 16778047]
3. Biswas S, Akey JM. Genomic insights into positive selection. Trends Genet. 2006; 22:437–446. [PubMed: 16808986]
4. Jensen JD, Wong A, Aquadro CF. Approaches for identifying targets of positive selection. Trends Genet. 2007; 23:568–577. [PubMed: 17959267]
5. Bersaglieri T, Sabeti PC, Patterson N, et al. Genetic signatures of strong recent positive selection at the lactase gene. Am J Hum Genet. 2004; 74:1111–1120. [PubMed: 15114531]
6. Williams CM, Ordovas JM, Lairon D, et al. The challenges for molecular nutrition research 1: linking genotype to healthy nutrition. Genes Nutr. 2008; 3:41–49. [PubMed: 18850186]
7. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. Gastroenterology. 2007; 132:2087–2102. [PubMed: 17498505]
8. Qi L, Cho YA. Gene–environment interaction and obesity. Nutr Rev. 2008; 66:684–694. [PubMed: 19019037]
9. Lyon HN, Hirschhorn JN. Genetics of common forms of obesity: a brief overview. Am J Clin Nutr. 2005; 82:215S–217S. [PubMed: 16002823]
10. Neel JV. Diabetes mellitus: a ‘thrifty’ genotype rendered detrimental by ‘progress’? Am J Hum Genet. 1962; 14:353–362. [PubMed: 13937884]
11. Nielsen R, Hellmann I, Hubisz M, et al. Recent and ongoing selection in the human genome. Nat Rev Genet. 2007; 8:857–868. [PubMed: 17943193]
12. Voight BF, Kudaravalli S, Wen X, Pritchard JK. A map of recent positive selection in the human genome. PLoS Biol. 2006; 4:e72. [PubMed: 16494531]
13. Holsinger KE, Weir BS. Genetics in geographically structured populations: defining, estimating and interpreting F_{ST}. Nat Rev Genet. 2009; 10:639–650. [PubMed: 19687804]
14. Sabeti PC, Varilly P, Fry B, et al. Genome-wide detection and characterization of positive selection in human populations. Nature. 2007; 449:913–918. [PubMed: 17943131]

15. Wallace C, Newhouse SJ, Braund P, et al. Genome-wide association study identifies genes for biomarkers of cardiovascular disease: serum urate and dyslipidemia. Am J Hum Genet. 2008; 82:139–149. [PubMed: 18179892]

16. Aulchenko YS, Ripatti S, Lindqvist I, et al. Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts. Nat Genet. 2009; 41:47–55. [PubMed: 19060911]

17. Willer CJ, Sanna S, Jackson AU, et al. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. Nat Genet. 2008; 40:161–169. [PubMed: 18193043]

18. Kathiresan S, Melander O, Guiducci C, et al. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. Nat Genet. 2008; 40:189–197. [PubMed: 18193044]

19. Sandhu MS, Waterworth DM, Debenham SL, et al. LDL-cholesterol concentrations: a genome-wide association study. Lancet. 2008; 371:483–491. [PubMed: 18262040]

20. Kathiresan S, Willer CJ, Peloso GM, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. Nat Genet. 2009; 41:56–65. [PubMed: 19060906]

21. Sabatti C, Service SK, Hartikainen AL, et al. Genome-wide association analysis of metabolic traits in a birth cohort from a founder population. Nat Genet. 2009; 41:35–46. [PubMed: 19060910]

22••. Ding K, Kullo IJ. Molecular population genetics of PCSK9: a signature of recent positive selection. Pharmacogenet Genomics. 2008; 18:169–179. *PCSK9*, which was not previously detected as under positive selection with HapMap genotype data, was indeed subjected to recent positive selection using several methods based on resequencing data, underscoring the importance of identifying positive selection signals with whole-genome sequence instead of genotype data. [PubMed: 18300938]

23. Burkhardt R, Kenny EE, Lowe JK, et al. Common SNPs in HMGCR in micronesians and whites associated with LDL-cholesterol levels affect alternative splicing of exon13. Arterioscler Thromb Vasc Biol. 2008; 28:2078–2084. [PubMed: 18802019]

24•. Talmud PJ, Drenos F, Shah S, et al. Gene-centric association signals for lipids and apolipoproteins identified via the HumanCVD BeadChip. Am J Hum Genet. 2009; 85:628–642. This study together with other GWAS reported on major loci that contribute to genetic variation of lipid traits in European populations. Ironically, these loci only account for less then 15% of the total phenotype variation of any given lipid trait. [PubMed: 19913121]

25. Love-Gregory L, Sherva R, Sun L, et al. Variants in the CD36 gene associate with the metabolic syndrome and high-density lipoprotein cholesterol. Hum Mol Genet. 2008; 17:1695–1704. [PubMed: 18305138]

26. Madden J, Carrero JJ, Brunner A, et al. Polymorphisms in the CD36 gene modulate the ability of fish oil supplements to lower fasting plasma triacyl glycerol and raise HDL cholesterol concentrations in healthy middle-aged men. Prostaglandins Leukot Essent Fatty Acids. 2008; 78:327–335. [PubMed: 18550349]

27. Lee JC, Weissglas-Volkov D, Kyttälä M, et al. WW-domain-containing oxidor-eductase is associated with low plasma HDL-C levels. Am J Hum Genet. 2008; 83:180–192. [PubMed: 18674750]

28. Kooner JS, Chambers JC, Aguilar-Salinas CA, et al. Genome-wide scan identifies variation in MLXIPL associated with plasma triglycerides. Nat Genet. 2008; 40:149–151. [PubMed: 18193046]

29. Pollin TI, Damcott CM, Shen H, et al. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. Science. 2008; 322:1702–1705. [PubMed: 19074352]

30. Cardona F, Guardiola M, Queipo-Ortuño MI, et al. The -1131T>C SNP of the APOA5 gene modulates response to fenofibrate treatment in patients with the metabolic syndrome: a postprandial study. Atherosclerosis. 2009; 206:148–152. [PubMed: 19344899]

31. Mattei J, Demissie S, Tucker KL, Ordovas JM. Apolipoprotein A5 polymorphisms interact with total dietary fat intake in association with markers of metabolic syndrome in Puerto Rican older adults. J Nutr. 2009; 139:2301–2308. [PubMed: 19828688]

32. Pickrell JK, Coop G, Novembre J, et al. Signals of recent positive selection in a worldwide sample of human populations. Genome Res. 2009; 19:826–837. [PubMed: 19307593]

33. Myles S, Davison D, Barrett J, et al. Worldwide population differentiation at disease-associated SNPs. BMC Med Genomics. 2008; 1:22. [PubMed: 18533027]
34. Rockman MV, Hahn MW, Soranzo N, et al. Positive selection on MMP3 regulation has shaped heart disease risk. Curr Biol. 2004; 14:1531–1539. [PubMed: 15341739]
35. Wu N, Lu X, Hua Y, et al. Haplotype analysis of the stromelysin-1 (MMP3) and gelatinase B (MMP9) genes in relation to coronary heart disease. Ann Hum Genet. 2009; 73 (Pt 4):404–410. [PubMed: 19438845]
36. Arnett DK, Li N, Tang W, et al. Genome-wide association study identifies single-nucleotide polymorphism in KCNB1 associated with left ventricular mass in humans: the HyperGEN Study. BMC Med Genet. 2009; 10:43. [PubMed: 19454037]
37. Vasan RS, Glazer NL, Felix JF, et al. Genetic variants associated with cardiac structure and function: a meta-analysis and replication of genome-wide association data. JAMA. 2009; 302:168–178. [PubMed: 19584346]
38. Kathiresan S, Voight BF, Purcell S, et al. Myocardial Infarction Genetics Consortium. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet. 2009; 41:334–341. [PubMed: 19198609]
39. Lambert G, Charlton F, Rye KA, Piper DE. Molecular basis of PCSK9 function. Atherosclerosis. 2009; 203:1–7. [PubMed: 18649882]
40. Fasano T, Cefalù AB, Di Leo E, et al. A novel loss of function mutation of PCSK9 gene in white subjects with low-plasma low-density lipoprotein cholesterol. Arterioscler Thromb Vasc Biol. 2007; 27:677–681. [PubMed: 17170371]
41••. Ding K, Kullo IJ. Evolutionary genetics of coronary heart disease. Circulation. 2009; 119:459–467. This review summarized the methods of detecting natural selection and recent hypothesis about the potential relevance of genetic variants under positive selection in contributing to CHD in humans. [PubMed: 19171868]
42. Delgado-Lista J, Perez-Jimenez F, Ruano J, et al. Effects of variations in the APOA1/C3/A4/A5 gene cluster on different parameters of postprandial lipid metabolism in healthy young men. J Lipid Res. 2010; 51:63–73. [PubMed: 19592705]
43. Shanker J, Perumal G, Rao VS, et al. Genetic studies on the APOA1-C3-A5 gene cluster in Asian Indians with premature coronary artery disease. Lipids Health Dis. 2008; 7:33. [PubMed: 18801202]
44. Jang Y, Paik JK, Hyun YJ, et al. The apolipoprotein A5-1131T>C promoter polymorphism in Koreans: association with plasma APOA5 and serum triglyceride concentrations, LDL particle size and coronary artery disease. Clin Chim Acta. 2009; 402:83–87. [PubMed: 19159622]
45. Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science. 2007; 316:1491–1493. [PubMed: 17478679]
46. Thorleifsson G, Walters GB, Gudbjartsson DF, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet. 2009; 41:18–24. [PubMed: 19079260]
47. Willer CJ, Speliotes EK, Loos RJ, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet. 2009; 41:25–34. [PubMed: 19079261]
48. Renström F, Payne F, Nordström A, et al. Replication and extension of genome-wide association study results for obesity in 4923 adults from northern Sweden. Hum Mol Genet. 2009; 18:1489–1496. [PubMed: 19164386]
49. Southam L, Soranzo N, Montgomery SB, et al. Is the thrifty genotype hypothesis supported by evidence based on confirmed type 2 diabetes-and obesity-susceptibility variants? Diabetologia. 2009; 52:1846–1851. [PubMed: 19526209]
50. Bauer F, Elbers CC, Adan RA, et al. Obesity genes identified in genome-wide association studies are associated with adiposity measures and potentially with nutrient-specific food preference. Am J Clin Nutr. 2009; 90:951–959. [PubMed: 19692490]
51. Johansson A, Marroni F, Hayward C, et al. Linkage and genome-wide association analysis of obesity-related phenotypes: association of weight with the MGAT1 gene. Obesity (Silver Spring). 2009 Epub ahead of print. 10.1038/oby.2009.359

52. Garenc C, Vohl MC, Bouchard C, Pérusse L. LIPE C-60G influences the effects of physical activity on body fat and plasma lipid concentrations: the Quebec Family Study. Hum Genomics. 2009; 3:157–168. [PubMed: 19164092]

53•. Lai CQ, Parnell LD, Arnett DK, et al. WDTC1, the ortholog of Drosophila adipose gene, associates with human obesity, modulated by MUFA intake. Obesity (Silver Spring). 2009; 17:593–600. This gene, initially identified as under positive selection in *Drosophila*, is also a candidate gene under positive selection in humans where variants associated with obesity and interact with dietary fat. [PubMed: 19238144]

54••. Corella D, Peloso G, Arnett DK, et al. APOA2, dietary fat, and body mass index: replication of a gene–diet interaction in 3 independent populations. Arch Intern Med. 2009; 169:1897–1906. This report demonstrated that *APOA2*, a putative gene under positive selection detected by iHS, displayed strong and consistent interactions with dietary fat intake influencing BMI. [PubMed: 19901143]

55. Heard-Costa NL, Zillikens MC, Monda KL, et al. NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. PLoS Genet. 2009; 5:e1000539. [PubMed: 19557197]

56•. Garaulet M, Lee YC, Shen J, et al. CLOCK genetic variation and metabolic syndrome risk: modulation by monounsaturated fatty acids. Am J Clin Nutr. 2009; 90:1466–1475. This intriguing report suggests links between circadian regulators and obesity, modulated by dietary fat intake. Sleep could be an important, if under-reported, phenotype. [PubMed: 19846548]

57. Junyent M, Parnell LD, Lai CQ, et al. ADAM17_i33708A>G polymorphism interacts with dietary n-6 polyunsaturated fatty acids to modulate obesity risk in the Genetics of Lipid Lowering Drugs and Diet Network study. Nutr Metab Cardiovasc Dis. 2009 Epub ahead of print. 10.1016/j.numecd.2009.06.011

58. Cotsapas C, Speliotes EK, Hatoum IJ, et al. Common body mass index-associated variants confer risk of extreme obesity. Hum Mol Genet. 2009; 18:3502–3507. [PubMed: 19553259]

59. Chen SN, Ballantyne CM, Gotto AM Jr, et al. A common PCSK9 haplotype, encompassing the E670G coding single nucleotide polymorphism, is a novel genetic marker for plasma low-density lipoprotein cholesterol levels and severity of coronary atherosclerosis. J Am Coll Cardiol. 2005; 45:1611–1619. [PubMed: 15893176]

60. Cohen J, Pertsemlidis A, Kotowski IK, et al. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet. 2005; 37:161–165. [PubMed: 15654334]

61. Kalopissis AD, Pastier D, Chambaz J. Apolipoprotein A-II: beyond genetic associations with lipid disorders and insulin resistance. Curr Opin Lipidol. 2003; 14:165–172. [PubMed: 12642785]

62. Krempler F, Breban D, Oberkofler H, et al. Leptin, peroxisome proliferator-activated receptor-gamma, and CCAAT/enhancer binding protein-alpha mRNA expression in adipose tissue of humans and their relation to cardiovascular risk factors. Arterioscler Thromb Vasc Biol. 2000; 20:443–449. [PubMed: 10669642]

63. Grossman SR, Shylakhter I, Karlsson EK, et al. A composite of multiple signals distinguishes causal variants in regions of positive selection. Science. 2010 in press. 10.1126/science.1183863

Table 1

Genetic variants under positive selection affecting blood lipids and heart disease

Trait	Gene(s)	Positive selection measure	Environmental factor[a]	Reference
LDL-C	*APOA1* cluster[b]	Tajima D		[15,16]
	CELSR2, PSRC1, SORT1	Fay and Wu H, Tajima D, Fst		[15–21]
	PCSK9	iHS, Fst, long-range haplotype		[17,18,20,22••]
	HMGCR	Tajima D		[16,18,20,2•]
	APOB	Tajima D		[20]
	SH2B3	iHS		[24•]
HDL-C	*LCAT*	Fay and Wu H, Tajima D		[17,20,21]
	CD36	iHS, Tajima D		[25]
			Fish oil	[26]
	WWOX	iHS		[27]
	APOA1 cluster	Tajima D		[20]
Triglycerides	*APOA1* cluster	Tajima D		[16–18,20,28,29]
	APOA5	Tajima D	Fenofibrate	[30]
			Total dietary fat	[31]
	GCKR	Fst		[16–18,20]
	MLXIPL	Fay and Wu H		[16,17,20,28]
	MLXIPL[c]	Fay and Wu H		[18]
	CD36	iHS, Tajima D	Fish oil	[26]
	XKR6, AMAC1L2	iHS, Fay and Wu H, Tajima D, Fst		[20]
		Fay and Wu H, Tajima D		[16]
	BAZ1B	Fay and Wu H, Tajima D		[24•]
Total cholesterol	*APOA1* cluster	Tajima D		[16]
	APOA5	Tajima D	Total dietary fat	[31]
	CELSR2	Fay and Wu H, Tajima D, Fst		[16]
	HMGCR	Tajima D		[16]
Lipid levels, multiple traits	*ADAM17*	XP-EHH		[32]
Coronary artery disease	Chr10: rs10761659	Fst		[33]
Coronary heart disease	*MMP3*	Fst		[34,35]
	CD36	iHS, Tajima D		[36]
	WWOX	iHS		[37]
Myocardial infarction	*CELSR2, PSRC1, SORT1*	Fay and Wu H, Tajima D, Fst		[38]
	PCSK9	iHS		[22••,38]
	PHACTR1	Fay and Wu H, Tajima D, Fst		[38]

Genes and genetic variants identified over the past 2 years as associating with either blood lipid traits or heart disease and noted to be under putative positive selection are listed. When the genotype–phenotype association is known to be modified by an environmental or dietary factor, that factor is also listed. GWAS, genome-wide association studies; HDL-C, HDL-cholesterol; iHS, integrated haplotype score; LDL-C, LDL-cholesterol; *PCSK9*, proprotein convertase subtilisin-like kexin type 9; SNP, single-nucleotide polymorphism.

[a] Environmental factor modifying the SNP–phenotype association; for GWAS, this was not determined.

[b] *APOA1* cluster includes four genes: *APOA1*, *APOC3*, *APOA4* and *APOA5*.

[c] Associations mapped to genes *BCL7B*, *TBL2* and *MLXIPL*.

Table 2

Genetic variants under positive selection affecting obesity traits

Trait	Gene(s)	Positive selection measure	Environmental factor[a]	Reference
Obesity, BMI	*NEGR1*	Tajima D, Fst		[46–49]
	MTCH2	Tajima D, Fst		[47–50]
	TMEM18	Fay and Wu H		[47,51]
	LIPE	Fay and Wu H, Tajima D	Physical activity	[52]
	WDTC1	Fay and Wu H	Monounsaturated fat	[53•]
	Chr1: rs3934834	Tajima D		[51]
	LPP	Fay and Wu H		[51]
	APOA2	iHS	Saturated fat	[54••]
Obesity, waist circumference	*CDH12*	iHS, Fay and Wu H, Tajima D, Fst		[55]
	NEGR1	Tajima D, Fst		[50]
	CLOCK	iHS	Saturated fat	[56•]
Obesity, weight	Chr1: rs1973993	Tajima D		[46]
	NEGR1	Tajima D		[46]
	DUPD1	Tajima D		[51]
	LPP	Fay and Wu H		[51]
Obesity, risk	*ADAM17*	iHS, Fay and Wu H, Tajima D, Fst	n-6 polyunsaturated fat	[57]
Obesity, extreme	*FBN2*	iHS, Fay and Wu H, Tajima D		[58]

Genes and genetic variants reported over the past 2 years as associating with measures of obesity and observed to be under putative positive selection are listed. When the genotype–phenotype association is reported to be modified by an environmental or dietary factor, that factor is also listed. GWAS, genome-wide association studies; iHS, integrated haplotype score; SNP, single-nucleotide polymorphism.

[a]Environmental factor modifying the SNP–phenotype association; for GWAS, this was not tested.