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Beyond GWASs: The usefulness of mouse genetics in understanding the complex etiology of atherosclerosis

Carrie L. Welch
Division of Molecular Medicine, Columbia University, NY, NY 10032

Abstract

The development of population-based genome-wide association studies (GWASs) has led to the rapid identification of large numbers of genetic variants associated with coronary artery disease (CAD) and related traits. Together with large-scale gene-centric studies, at least 35 loci associated with CAD *per se* have been identified with replication. The majority of these associations are with common single nucleotide polymorphisms (SNPs) exhibiting modest effects on relative risk. The modest nature of the effects, coupled with ethical/practical constraints associated with human sampling, makes it difficult to answer important questions beyond gene/locus localization and allele frequency via human genetic studies. Questions related to gene function, disease-causing mechanism(s), and effective interventions will likely require studies in model organisms. The use of the mouse model for further detailed studies of GWAS-identified CAD-associated loci is highlighted herein.

Keywords

atherosclerosis; coronary artery disease; mouse genetics; genome-wide association study

Introduction

The development of population-based genome-wide association studies (GWASs) has led to the rapid identification of large numbers of genetic variants associated with coronary artery disease (CAD)/ myocardial infarction (MI) and related traits such as plasma LDL-cholesterol, HDL-cholesterol, triglycerides, obesity and hypertension (reviewed in[1–7]). The majority of these associations are with common single nucleotide polymorphisms (SNPs) exhibiting modest effects on relative risk. The use of combined analyses, or meta-analyses, increases the power to detect modest associations.[3, 8, 9] Currently, at least 35 loci associated with CAD *per se* have been identified and, importantly, replicated in at least one independent study (Table 1). While some of the loci are associated with traditional risk factors, many of the loci likely affect atherogenesis via non-traditional mechanisms.

Notably, the CAD loci identified by GWAS thus far have been estimated to explain only ~10% of the additive genetic variance of human CAD.[8] Several human genetic approaches towards detecting loci representing the unexplained variance have been discussed. These include approaches for detecting rare SNPs[10, 11] or copy number variants[12] associated with disease. However, as the list of new disease loci grows, it will be important to establish the clinical or public health importance of the identified loci.

Corresponding author phone: 212-342-9098 fax: 212-305-5052, cbw13@columbia.edu.

Disclosures
None.

Model organisms provide useful tools for obtaining data related to clinical relevance. Due to the modest size effects of SNP variants and ethical/practical constraints associated with human sampling, questions regarding gene function and disease causing mechanism(s) can be assessed more definitively in model organisms. Further, effective interventions and potential modifiers of SNP-disease associations can be tested in model organisms prior to the design of clinical trials in humans. The mouse has become the model of choice due to small size, breeding efficiency, availability of genetic manipulation technologies, and high degree of genome similarity. Human-mouse genomic homologies have been identified for most SNP association loci identified to date (Table 1). Although some CAD-associated variants have been found in gene-poor regions or regions of unknown biological relevance, the candidate causal variants in these cases may function by regulating expression of neighboring genes. Thus, genetic studies of mice exhibiting altered expression *or* function of CAD SNP-residing or neighboring genes may be relevant. Mutant models – including transgenic, knock-outs derived by gene-targeting or gene trap technologies, chemical- or radiation induced mutagenesis, sub-chromosomal locus deletion, and spontaneous mutation – are available for many of the human CAD-associated loci identified to date but few have been queried for atherosclerosis susceptibility/resistance (Table 1). Further, more than 9000 conditional targeted alleles in mouse embryonic stem cells have recently become available.[13] Lastly, random genetic variation among different inbred strains of mice can lead to the identification of novel genes underlying atherosclerosis.

Mendelian disease genes exhibiting common associations

Some of the CAD loci underlying common susceptibility to disease were previously identified in relationship to rare Mendelian forms of hypercholesterolemia/premature CAD. These include *LDLR*, *APOE*, *PCSK9*, *ABCG8*, and *LIPA*. Importantly, gene-specific mutant mouse models displayed effects on atherogenesis and related traits (i.e. plasma cholesterol levels, plant sterol levels, xanthomatosis, lipase deficiency) similar to that observed in humans (Table 1). These provide “positive controls” indicating that the use of mutant mouse models can be relevant to the study of human CAD loci.

The disease causing mechanism for Mendelian disease genes is at least partly established. While clearance of circulating lipoproteins is a common mechanism underlying disease pathogenesis for *LDLR*, *APOE*, and *PCSK9*, new studies in mouse models are revealing additional roles in inflammation (*Apoe*),[14, 15] and apoB secretion (*Pcsk9*).[16] Common variants of *ABCG8* are associated with both plasma phytosterol as well as LDL levels.[17] Detailed studies in mice have outlined the role of *Abcg8* in dietary cholesterol absorption[18] and intestinal cholesterol excretion[19] but the role of plant sterols in atherogenesis remains unresolved. *LIPA* encodes a lysosomal acid lipase involved in the breakdown of cholesterol esters and triglycerides. The *LIPA* risk allele is associated with increased lipase expression but not altered lipid levels, suggesting a novel pathogenic mechanism. Thus, even the Mendelian-associated genes have the potential to reveal new pathogenic mechanisms!

New genes/loci associated with traditional risk factors

A few of the newly identified loci are associated with known risk factors for CAD, suggesting disease-causing mechanisms. For example, *SORT1* and *TRIB1* are associated with lipoprotein levels in human association studies. Functional validation of these associations was obtained via gene-specific over- and under-expression of these genes in genetically uniform mouse models of atherosclerosis.[20, 21] Furthermore, *Sort1* and *Trib1* were shown to modulate hepatic VLDL secretion and production, respectively, from primary hepatocytes in mice.[20, 21] These data suggest that modulation of two novel regulatory pathways for lipoprotein metabolism may alter susceptibility to CAD/MI in humans. The

ABO gene is associated with multiple CAD-related traits: LDL levels, thrombosis, inflammatory gene expression and plant sterol levels.[8, 22, 23] Further studies are required to delineate the relative role of each pathway in the pathogenesis of CAD.

New genes/loci underlying novel pathogenic mechanisms for CAD/MI

The majority of the loci listed in Table 1 have some degree of known protein function but no known role in CAD/MI pathogenesis. For these loci, basic knowledge of directional effects and tissue relevance can be sorted out in mouse models. Directional effects (i.e. for regulatory variants, whether *increased* or *decreased* gene expression is associated with disease) can be confirmed/established using general knockout or transgenic models crossed onto an *Apoe*$^{-/-}$ or *Ldlr*$^{-/-}$ proatherogenic background. In some cases, existing congenic,[24] spontaneous, chemically-, or radiation-induced mutants may be queried (Table 1). Tissue relevance (i.e. the specific tissue type affecting disease pathogenesis) can be assessed using bone marrow (BM) transplantation or tissue-specific knockouts. Reciprocal BM experiments utilizing a chromosome 4 congenic model harboring the 9p21 region of homology, and exhibiting decreased expression of macrophage *Cdkn2a*, indicated that BM-derived cells, but not resident vascular cells, were sufficient to confer the pro-atherosclerotic phenotype of the congenic mouse.[24, 25] Direct testing of the candidate gene showed that BM-derived cells from *Cdkn2a*$^{+/-}$ mice were sufficient to confer accelerated atherogenesis in the *Ldlr*$^{-/-}$ background.[24] Of note, tissue macrophages and mixed monocyte/macrophage populations, but not circulating monocytes, were implicated in the study.[24] This study suggests that macrophage deficiency of *CDKN2A* may partly explain the association of 9p21 with CAD/MI in humans. The data are consistent with human studies reporting lack of association of the 9p21 risk allele with *CDKN2A* expression in circulating monocytes[26] or resident vascular cells,[27] but significant association with decreased levels in T lymphocytes.[28] Studies in human macrophages have not been reported.

Genetic variants of *Anril* have been implicated at the 9p21 human CAD/MI locus. *ANRIL* is a non-coding RNA implicated in both long-range *cis*-acting as well as *trans*-acting transcriptional control of syntenic tumor suppressor genes, *CDKN2A* (encoding *p16*^{INK4a}, *p14*^{ARF}) and *CDKN2B* (encoding *p15*^{INK4b}). Multiple *ANRIL* splice variants are present in human tissues, complicating genetic association studies of the structural gene.[29] A murine deletion mutant covering the homologous region exhibited decreased expression of the neighboring tumor suppressor genes, supporting the hypothesis of an *ANRIL* regulatory variant underlying the 9p21 locus.[30] A potential effect of the variant on atherosclerosis was not observed in the highly athero-resistant model tested. However, testing of the deletion in a more athero-susceptible model has not been carried out as yet.

Two of the CAD-associated loci listed in Table 1 were identified as open reading frames or cDNA clones via annotation efforts of the Human Genome Project (c6orf105) or the RIKEN Genome Science Lab (KIAA1462) but have no known biological function. C6orf105 exhibits ethnic-specific CAD association among Chinese Han populations[31] but KIAA1462 exhibits association in both European and Chinese populations, with similar allele frequencies and size effects.[9] Both loci have homologous DNA sequences in the mouse genome and, thus, targeted deletion or transcriptional disruption may shed light on the biological functions of novel proteins.

Additional mechanistic data including stage of lesion development, genetic background effects, potential effects on lesion regression, and overlapping roles of CAD loci in multiple diseases can be assessed using unique strains and experimental designs. Stage of lesion development can be tested in dietary time course studies of gene-specific knock-out or transgenic mice bred onto standard mouse models of atherosclerosis, or with conditional

knock-outs induced before or after lesion development. Genetic background effects can be tested using different inbred strains of mice (exhibiting differences in susceptibility to atherosclerosis), different engineered models of atherosclerosis, or mutant mice carrying mutations in more than one CAD locus. The Reversa mouse[32, 33] is a model of atherosclerosis regression which may be useful for differentiating hyperlipidemia from other genetic effects on lesion regression. Finally, introduction of CAD-associated mutations into mouse models of diabetes, hypertension, obesity and metabolic syndrome may shed light on shared points of regulation among multiple disease phenotypes.

New discovery of atherosclerosis susceptibility genes

As mentioned above, the CAD loci identified by human GWAS thus far have been estimated to explain only a fraction of the genetic variance of human CAD.[8] Mouse genetic/mapping approaches provide a means of identifying new genes, perhaps untractable by human genetic approaches because of modest effect. While mouse linkage studies pinpoint disease susceptibility loci to relatively large genomic intervals containing large numbers of genes, several techniques have been applied to narrow the list of disease causal candidate genes. Refined mapping of loci can be obtained through the generation of interval-specific congenic strains. A cross between B6-*Apoe*$^{-/-}$ and the more athero-resistant strain FVB-*Apoe*$^{-/-}$ revealed two intervals contributing to atherosclerosis susceptibility; one locus was narrowed to 7 genes, the other to 21 genes.[34] Similarly, the congenic mapping efforts in a cross between B6-*Ldlr*$^{-/-}$ and a wild-derived MOLF strain revealed two atherosclerosis loci on chromosome 4.[24] *Cdkn2a* was identified as a disease-causing gene in one of the intervals but mapping of the distal locus is still underway. Combining a congenic mapping approach with gene expression profiling, Lusis and colleagues identified *Zhx2*[35] as a novel regulator of plasma lipid metabolism.[35] Copy number variants can also be applied to mouse mapping studies. In a cross between B6 and C3H, gene expression levels and several metabolic traits mapped to three unique copy number variants, suggesting novel loci involved in regulation of plasma lipoprotein levels, glucose and body weight.[36] Recently, a hybrid mouse panel was developed for high-resolution association studies in mice. This approach aims to provide refined mapping and increased sensitivity compared to linkage studies. Together, these studies have the potential to reveal new genes and pathways underlying atherosclerosis susceptibility.

Limitations of the mouse model

Many of the loci listed in Table 1 were discovered based on case-control studies of MI. While atherogenesis precedes MI, not all cases of atherosclerosis lead to acute complications. This suggests that different pathologies underlie these clinical phenotypes. Furthermore, the *ABO* gene was specifically associated with MI in the presence of coronary atherosclerosis.[22] Currently available mouse models are susceptible to atherosclerosis but resistant to acute complications. Thus, studies of genes affecting plaque rupture may be limited in the mouse. *ABO* is associated with thrombosis,[22] and at least one spontaneous mutation in mice leads to atherothrombosis.[37] In addition, murine plaques exhibit features of human vulnerable plaques, a precursor to plaque rupture and infarction. These can be assessed by qualitative changes in plaque morphology.[38, 39] Thus, although plaque rupture/MI may not be amenable to study *per se* in murine models, pathogenic mechanisms leading to clinical consequences may be queried.

The identification of phenotypically causal variants underlying CAD susceptibility is important for the delineation of biological genotype-phenotype relationships as well as discovering potential predictors of disease. Lead association SNPs may represent causal variants or may be associated by circumstance alone (ie. exhibiting strong linkage

disequilibrium with the lead SNP). In most cases, disease-causing variants will not be the same in human and mouse. In particular, regulatory variants in non-coding regions may not be conserved. For example, the putative causal variant at *SORT1* is human specific. The causal allele creates a binding site for the CEBP family of transcription factors that does not exist in the mouse.[20] However, data supporting the role of a regulatory variant can be gained from studies in mice. For example, the lead SNP identified for *TRIB1*, a triglyceride-, LDL- and CAD-associated locus, is located downstream of the coding sequence and suggested a regulatory effect on gene expression.[3, 17, 40] Subsequent studies in *Trib1*-overexpressing and -deficient mice showed decreased and increased plasma triglyceride levels, respectively.[21] Demonstration of regulatory effects stemming from an allele-specific mutant construct will be necessary to solidify the genotype-phenotype relationship.

Most disease-associated SNPs exhibit modest effects on relative risk. Thus, the relevance of complete gene knockout and highly-expressing transgenic mice comes into question. Several genetic methods exist for testing modest effects. Mice carrying heterozygous deficiency of a particular gene will likely demonstrate differences in gene expression more closely mimicking the situation in humans.[24] Secondly, BAC transgenic mice generally express only 1–3 copies of a transgene. Thirdly, spontaneous, radiation- and chemically-induced mutants usually harbor point mutations. Some of these models are available for the human CAD-associated loci (Table 1) and can be tested for differences in atherosclerosis susceptibility or plaque morphology.

Summary/Conclusions

Although recent human genetic studies have met with remarkable success in terms of identifying CAD/MI-associated loci, many details regarding the underlying genes/mechanisms remain unanswered. The high degree of genomic similarity between humans and mice, along with the wide array of genetic tools available, indicate that much can be learned from parallel studies of mice and human.

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References

1. Peden JF, Farrall M. Thirty-five common variants for coronary artery disease: The fruits of much collaborative labour. Hum Mol Genet. 2011; 20:R198–R205. [PubMed: 21875899]
2. Schunkert H, Erdmann J, Samani NJ. Genetics of myocardial infarction: A progress report. Eur Heart J. 2010; 31:918–925. [PubMed: 20219748]
3. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W,

Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, Konig IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Doring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2010; 466:707–713. [PubMed: 20686565]

4. Weissglas-Volkov D, Pajukanta P. Genetic causes of high and low serum hdl-cholesterol. J Lipid Res. 2010; 51:2032–2057. [PubMed: 20421590]
5. Johansen CT, Kathiresan S, Hegele RA. Genetic determinants of plasma triglycerides. J Lipid Res. 2011; 52:189–206. [PubMed: 21041806]
6. Choquet H, Meyre D. Genetics of obesity: What have we learned? Curr Genomics. 2011; 12:169–179. [PubMed: 22043165]
7. Franceschini N, Reiner AP, Heiss G. Recent findings in the genetics of blood pressure and hypertension traits. Am J Hypertens. 2011; 24:392–400. [PubMed: 20948529]
8. Schunkert H, Konig IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AF, Barbalic M, Gieger C, Absher D, Aherrahrou Z, Allayee H, Altshuler D, Anand SS, Andersen K, Anderson JL, Ardissino D, Ball SG, Balmforth AJ, Barnes TA, Becker DM, Becker LC, Berger K, Bis JC, Boekholdt SM, Boerwinkle E, Braund PS, Brown MJ, Burnett MS, Buysschaert I, Carlquist JF, Chen L, Cichon S, Codd V, Davies RW, Dedoussis G, Dehghan A, Demissie S, Devaney JM, Diemert P, Do R, Doering A, Eifert S, Mokhtari NE, Ellis SG, Elosua R, Engert JC, Epstein SE, de Faire U, Fischer M, Folsom AR, Freyer J, Gigante B, Girelli D, Gretarsdottir S, Gudnason V, Gulcher JR, Halperin E, Hammond N, Hazen SL, Hofman A, Horne BD, Illig T, Iribarren C, Jones GT, Jukema JW, Kaiser MA, Kaplan LM, Kastelein JJ, Khaw KT, Knowles JW, Kolovou G, Kong A, Laaksonen R, Lambrechts D, Leander K, Lettre G, Li M, Lieb W, Loley C, Lotery AJ, Mannucci PM, Maouche S, Martinelli N, McKeown PP, Meisinger C, Meitinger T, Melander O, Merlini PA, Mooser V, Morgan T, Muhleisen TW, Muhlestein JB, Munzel T, Musunuru K, Nahrstaedt J, Nelson CP, Nothen MM, Olivieri O, Patel RS, Patterson CC, Peters A, Peyvandi F, Qu L, Quyyumi AA, Rader DJ, Rallidis LS, Rice C, Rosendaal FR, Rubin D, Salomaa V, Sampietro ML, Sandhu MS, Schadt E, Schafer A, Schillert A, Schreiber S, Schrezenmeir J, Schwartz SM, Siscovick DS, Sivananthan M, Sivapalaratnam S, Smith A, Smith TB, Snoep JD, Soranzo N, Spertus JA, Stark K, Stirrups K, Stoll M, Tang WH, Tennstedt S, Thorgeirsson G, Thorleifsson G, Tomaszewski M, Uitterlinden AG, van Rij AM, Voight BF, Wareham NJ, Wells GA, Wichmann HE, Wild PS, Willenborg C, Witteman JC, Wright BJ, Ye S, Zeller T, Ziegler A, Cambien F, Goodall AH, Cupples LA, Quertermous T, Marz W, Hengstenberg C, Blankenberg S, Ouwehand WH, Hall AS, Deloukas P, Thompson JR, Stefansson K, Roberts R, Thorsteinsdottir U, O'Donnell CJ, McPherson R, Erdmann J, Samani NJ. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat Genet. 2011; 43:333–338. [PubMed: 21378990]
9. Peden J, Hopewell JC, Saleheen D, Chambers JC, Hager J, Soranzo N, Collins R, Danesh J, Elliott P, Farrall M. A genome-wide association study in europeans and south asians identifies five new loci for coronary artery disease. Nat Genet. 2011; 43:339–344. [PubMed: 21378988]
10. Johansen CT, Wang J, Lanktree MB, Cao H, McIntyre AD, Ban MR, Martins RA, Kennedy BA, Hassell RG, Visser ME, Schwartz SM, Voight BF, Elosua R, Salomaa V, O'Donnell CJ, Dallinga-Thie GM, Anand SS, Yusuf S, Huff MW, Kathiresan S, Hegele RA. Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridemia. Nat Genet. 2010; 42:684–687. [PubMed: 20657596]

11. Gusev A, Kenny EE, Lowe JK, Salit J, Saxena R, Kathiresan S, Altshuler DM, Friedman JM, Breslow JL, Pe'er I. Dash: A method for identical-by-descent haplotype mapping uncovers association with recent variation. Am J Hum Genet. 2011; 88:706–717. [PubMed: 21620352]
12. Grayson BL, Smith ME, Thomas JW, Wang L, Dexheimer P, Jeffrey J, Fain PR, Nanduri P, Eisenbarth GS, Aune TM. Genome-wide analysis of copy number variation in type 1 diabetes. PLoS One. 2010; 5:e15393. [PubMed: 21085585]
13. Skarnes WC, Rosen B, West AP, Koutsourakis M, Bushell W, Iyer V, Mujica AO, Thomas M, Harrow J, Cox T, Jackson D, Severin J, Biggs P, Fu J, Nefedov M, de Jong PJ, Stewart AF, Bradley A. A conditional knockout resource for the genome-wide study of mouse gene function. Nature. 2011; 474:337–342. [PubMed: 21677750]
14. Murphy AJ, Akhtari M, Tolani S, Pagler T, Bijl N, Kuo CL, Wang M, Sanson M, Abramowicz S, Welch C, Bochem AE, Kuivenhoven JA, Yvan-Charvet L, Tall AR. Apoe regulates hematopoietic stem cell proliferation, monocytosis, and monocyte accumulation in atherosclerotic lesions in mice. J Clin Invest. 2011; 121:4138–4149. [PubMed: 21968112]
15. Gaudreault N, Kumar N, Posada JM, Stephens KB, de Mochel NS, Eberle D, Olivas VR, Kim RY, Harms MJ, Johnson A, Messina LM, Rapp JH, Raffai RL. Apoe suppresses atherosclerosis by reducing lipid accumulation in circulating monocytes and the expression of inflammatory molecules on monocytes and vascular endothelium. Arterioscler Thromb Vasc Biol. 2011
16. Herbert B, Patel D, Waddington SN, Eden ER, McAleenan A, Sun XM, Soutar AK. Increased secretion of lipoproteins in transgenic mice expressing human d374y pcsk9 under physiological genetic control. Arterioscler Thromb Vasc Biol. 2010; 30:1333–1339. [PubMed: 20448210]
17. Butterworth AS, Braund PS, Farrall M, Hardwick RJ, Saleheen D, Peden JF, Soranzo N, Chambers JC, Sivapalaratnam S, Kleber ME, et al. Large-scale gene-centric analysis identifies novel variants for coronary artery disease. PLoS Genet. 2011; 7:e1002260. [PubMed: 21966275]
18. Wang J, Grishin N, Kinch L, Cohen JC, Hobbs HH, Xie XS. Sequences in the nonconsensus nucleotide-binding domain of abcg5/abcg8 required for sterol transport. J Biol Chem. 2011; 286:7308–7314. [PubMed: 21209088]
19. Brufau G, Kuipers F, Lin Y, Trautwein EA, Groen AK. A reappraisal of the mechanism by which plant sterols promote neutral sterol loss in mice. PLoS One. 2011; 6:e21576. [PubMed: 21738715]
20. Musunuru K, Strong A, Frank-Kamenetsky M, Lee NE, Ahfeldt T, Sachs KV, Li X, Li H, Kuperwasser N, Ruda VM, Pirruccello JP, Muchmore B, Prokunina-Olsson L, Hall JL, Schadt EE, Morales CR, Lund-Katz S, Phillips MC, Wong J, Cantley W, Racie T, Ejebe KG, Orho-Melander M, Melander O, Kotelianski V, Fitzgerald K, Krauss RM, Cowan CA, Kathiresan S, Rader DJ. From noncoding variant to phenotype via sort1 at the 1p13 cholesterol locus. Nature. 2010; 466:714–719. [PubMed: 20686566]
21. Burkhardt R, Toh SA, Lagor WR, Birkeland A, Levin M, Li X, Robblee M, Fedorov VD, Yamamoto M, Satoh T, Akira S, Kathiresan S, Breslow JL, Rader DJ. Trib1 is a lipid- and myocardial infarction-associated gene that regulates hepatic lipogenesis and vldl production in mice. J Clin Invest. 2010; 120:4410–4414. [PubMed: 21084752]
22. Reilly MP, Li M, He J, Ferguson JF, Stylianou IM, Mehta NN, Burnett MS, Devaney JM, Knouff CW, Thompson JR, Horne BD, Stewart AF, Assimes TL, Wild PS, Allayee H, Nitschke PL, Patel RS, Martinelli N, Girelli D, Quyyumi AA, Anderson JL, Erdmann J, Hall AS, Schunkert H, Quertermous T, Blankenberg S, Hazen SL, Roberts R, Kathiresan S, Samani NJ, Epstein SE, Rader DJ. Identification of adamts7 as a novel locus for coronary atherosclerosis and association of abo with myocardial infarction in the presence of coronary atherosclerosis: Two genome-wide association studies. Lancet. 2011; 377:383–392. [PubMed: 21239051]
23. Teupser D, Baber R, Ceglarek U, Scholz M, Illig T, Gieger C, Holdt LM, Leichtle A, Greiser KH, Huster D, Linsel-Nitschke P, Schafer A, Braund PS, Tiret L, Stark K, Raaz-Schrauder D, Fiedler GM, Wilfert W, Beutner F, Gielen S, Grosshennig A, Konig IR, Lichtner P, Heid IM, Kluttig A, El Mokhtari NE, Rubin D, Ekici AB, Reis A, Garlichs CD, Hall AS, Matthes G, Wittekind C, Hengstenberg C, Cambien F, Schreiber S, Werdan K, Meitinger T, Loeffler M, Samani NJ, Erdmann J, Wichmann HE, Schunkert H, Thiery J. Genetic regulation of serum phytosterol levels and risk of coronary artery disease. Circ Cardiovasc Genet. 2010; 3:331–339. [PubMed: 20529992]

24. Kuo CL, Murphy AJ, Sayers S, Li R, Yvan-Charvet L, Davis JZ, Krishnamurthy J, Liu Y, Puig O, Sharpless NE, Tall AR, Welch CL. Cdkn2a is an atherosclerosis modifier locus that regulates monocyte/macrophage proliferation. Arterioscler Thromb Vasc Biol. 2011; 31:2483–2492. [PubMed: 21868699]
25. Seidelmann SB, Kuo C, Pleskac N, Molina J, Sayers S, Li R, Zhou J, Johnson P, Braun K, Chan C, Teupser D, Breslow JL, Wight TN, Tall AR, Welch CL. Athsq1 is an atherosclerosis modifier locus with dramatic effects on lesion area and prominent accumulation of versican. Arterioscler Thromb Vasc Biol. 2008; 28:2180–2186. [PubMed: 18818413]
26. Jarinova O, Stewart AF, Roberts R, Wells G, Lau P, Naing T, Buerki C, McLean BW, Cook RC, Parker JS, McPherson R. Functional analysis of the chromosome 9p21.3 coronary artery disease risk locus. Arterioscler Thromb Vasc Biol. 2009; 29:1671–1677. [PubMed: 19592466]
27. Folkersen L, Kyriakou T, Goel A, Peden J, Malarstig A, Paulsson-Berne G, Hamsten A, Hugh W, Franco-Cereceda A, Gabrielsen A, Eriksson P. Relationship between cad risk genotype in the chromosome 9p21 locus and gene expression. Identification of eight new anril splice variants. PLoS One. 2009; 4:e7677. [PubMed: 19888323]
28. Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Mohlke KL, Ibrahim JG, Thomas NE, Sharpless NE. Ink4/arf transcript expression is associated with chromosome 9p21 variants linked to atherosclerosis. PLoS One. 2009; 4:e5027. [PubMed: 19343170]
29. Cunnington MS, Keavney B. Genetic mechanisms mediating atherosclerosis susceptibility at the chromosome 9p21 locus. Curr Atheroscler Rep. 2011; 13:193–201. [PubMed: 21487702]
30. Visel A, Zhu Y, May D, Afzal V, Gong E, Attanasio C, Blow MJ, Cohen JC, Rubin EM, Pennacchio LA. Targeted deletion of the 9p21 non-coding coronary artery disease risk interval in mice. Nature. 2010; 464:409–412. [PubMed: 20173736]
31. Wang F, Xu CQ, He Q, Cai JP, Li XC, Wang D, Xiong X, Liao YH, Zeng QT, Yang YZ, Cheng X, Li C, Yang R, Wang CC, Wu G, Lu QL, Bai Y, Huang YF, Yin D, Yang Q, Wang XJ, Dai DP, Zhang RF, Wan J, Ren JH, Li SS, Zhao YY, Fu FF, Huang Y, Li QX, Shi SW, Lin N, Pan ZW, Li Y, Yu B, Wu YX, Ke YH, Lei J, Wang N, Luo CY, Ji LY, Gao LJ, Li L, Liu H, Huang EW, Cui J, Jia N, Ren X, Li H, Ke T, Zhang XQ, Liu JY, Liu MG, Xia H, Yang B, Shi LS, Xia YL, Tu X, Wang QK. Genome-wide association identifies a susceptibility locus for coronary artery disease in the chinese han population. Nat Genet. 2011; 43:345–349. [PubMed: 21378986]
32. Lieu HD, Withycombe SK, Walker Q, Rong JX, Walzem RL, Wong JS, Hamilton RL, Fisher EA, Young SG. Eliminating atherogenesis in mice by switching off hepatic lipoprotein secretion. Circulation. 2003; 107:1315–1321. [PubMed: 12628954]
33. Feig JE, Parathath S, Rong JX, Mick SL, Vengrenyuk Y, Grauer L, Young SG, Fisher EA. Reversal of hyperlipidemia with a genetic switch favorably affects the content and inflammatory state of macrophages in atherosclerotic plaques. Circulation. 2011; 123:989–998. [PubMed: 21339485]
34. Wolfrum S, Rodriguez JM, Tan M, Chen KY, Teupser D, Breslow JL. The mouse atherosclerosis locus at chromosome 10 (ath11) acts early in lesion formation with subcongenic strains delineating 2 narrowed regions. Arterioscler Thromb Vasc Biol. 2010; 30:1583–1590. [PubMed: 20466976]
35. Gargalovic PS, Erbilgin A, Kohannim O, Pagnon J, Wang X, Castellani L, LeBoeuf R, Peterson ML, Spear BT, Lusis AJ. Quantitative trait locus mapping and identification of zhx2 as a novel regulator of plasma lipid metabolism. Circ Cardiovasc Genet. 2010; 3:60–67. [PubMed: 20160197]
36. Orozco LD, Cokus SJ, Ghazalpour A, Ingram-Drake L, Wang S, van Nas A, Che N, Araujo JA, Pellegrini M, Lusis AJ. Copy number variation influences gene expression and metabolic traits in mice. Hum Mol Genet. 2009; 18:4118–4129. [PubMed: 19648292]
37. Welch CL, Sun Y, Arey BJ, Lemaitre V, Sharma N, Ishibashi M, Sayers S, Li R, Gorelik A, Pleskac N, Collins-Fletcher K, Yasuda Y, Bromme D, D'Armiento JM, Ogletree ML, Tall AR. Spontaneous atherothrombosis and medial degradation in apoe−/−, npc1−/− mice. Circulation. 2007; 116:2444–2452. [PubMed: 17984379]
38. Heeneman S, Lutgens E, Schapira KB, Daemen MJ, Biessen EA. Control of atherosclerotic plaque vulnerability: Insights from transgenic mice. Front Biosci. 2008; 13:6289–6313. [PubMed: 18508661]

39. Thorp E, Tabas I. Mechanisms and consequences of efferocytosis in advanced atherosclerosis. J Leukoc Biol. 2009; 86:1089–1095. [PubMed: 19414539]

40. Waterworth DM, Ricketts SL, Song K, Chen L, Zhao JH, Ripatti S, Aulchenko YS, Zhang W, Yuan X, Lim N, Luan J, Ashford S, Wheeler E, Young EH, Hadley D, Thompson JR, Braund PS, Johnson T, Struchalin M, Surakka I, Luben R, Khaw KT, Rodwell SA, Loos RJ, Boekholdt SM, Inouye M, Deloukas P, Elliott P, Schlessinger D, Sanna S, Scuteri A, Jackson A, Mohlke KL, Tuomilehto J, Roberts R, Stewart A, Kesaniemi YA, Mahley RW, Grundy SM, McArdle W, Cardon L, Waeber G, Vollenweider P, Chambers JC, Boehnke M, Abecasis GR, Salomaa V, Jarvelin MR, Ruokonen A, Barroso I, Epstein SE, Hakonarson HH, Rader DJ, Reilly MP, Witteman JC, Hall AS, Samani NJ, Strachan DP, Barter P, van Duijn CM, Kooner JS, Peltonen L, Wareham NJ, McPherson R, Mooser V, Sandhu MS. Genetic variants influencing circulating lipid levels and risk of coronary artery disease. Arterioscler Thromb Vasc Biol. 2010; 30:2264–2276. [PubMed: 20864672]

41. Kathiresan S, Voight BF, Purcell S, Musunuru K, Ardissino D, Mannucci PM, Anand S, Engert JC, Samani NJ, Schunkert H, Erdmann J, Reilly MP, Rader DJ, Morgan T, Spertus JA, Stoll M, Girelli D, McKeown PP, Patterson CC, Siscovick DS, O'Donnell CJ, Elosua R, Peltonen L, Salomaa V, Schwartz SM, Melander O, Altshuler D, Merlini PA, Berzuini C, Bernardinelli L, Peyvandi F, Tubaro M, Celli P, Ferrario M, Fetiveau R, Marziliano N, Casari G, Galli M, Ribichini F, Rossi M, Bernardi F, Zonzin P, Piazza A, Yee J, Friedlander Y, Marrugat J, Lucas G, Subirana I, Sala J, Ramos R, Meigs JB, Williams G, Nathan DM, MacRae CA, Havulinna AS, Berglund G, Hirschhorn JN, Asselta R, Duga S, Spreafico M, Daly MJ, Nemesh J, Korn JM, McCarroll SA, Surti A, Guiducci C, Gianniny L, Mirel D, Parkin M, Burtt N, Gabriel SB, Thompson JR, Braund PS, Wright BJ, Balmforth AJ, Ball SG, Hall AS, Linsel-Nitschke P, Lieb W, Ziegler A, Konig I, Hengstenberg C, Fischer M, Stark K, Grosshennig A, Preuss M, Wichmann HE, Schreiber S, Ouwehand W, Deloukas P, Scholz M, Cambien F, Li M, Chen Z, Wilensky R, Matthai W, Qasim A, Hakonarson HH, Devaney J, Burnett MS, Pichard AD, Kent KM, Satler L, Lindsay JM, Waksman R, Knouff CW, Waterworth DM, Walker MC, Mooser V, Epstein SE, Scheffold T, Berger K, Huge A, Martinelli N, Olivieri O, Corrocher R, McKeown P, Erdmann E, Konig IR, Holm H, Thorleifsson G, Thorsteinsdottir U, Stefansson K, Do R, Xie C, Siscovick D. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet. 2009; 41:334–341. [PubMed: 19198609]

42. Kathiresan S, Melander O, Guiducci C, Surti A, Burtt NP, Rieder MJ, Cooper GM, Roos C, Voight BF, Havulinna AS, Wahlstrand B, Hedner T, Corella D, Tai ES, Ordovas JM, Berglund G, Vartiainen E, Jousilahti P, Hedblad B, Taskinen MR, Newton-Cheh C, Salomaa V, Peltonen L, Groop L, Altshuler DM, Orho-Melander M. 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]

43. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low ldl cholesterol in individuals of african descent resulting from frequent nonsense mutations in pcsk9. Nat Genet. 2005; 37:161–165. [PubMed: 15654334]

44. Rashid S, Curtis DE, Garuti R, Anderson NN, Bashmakov Y, Ho YK, Hammer RE, Moon YA, Horton JD. Decreased plasma cholesterol and hypersensitivity to statins in mice lacking pcsk9. Proc Natl Acad Sci U S A. 2005; 102:5374–5379. [PubMed: 15805190]

45. Frank-Kamenetsky M, Grefhorst A, Anderson NN, Racie TS, Bramlage B, Akinc A, Butler D, Charisse K, Dorkin R, Fan Y, Gamba-Vitalo C, Hadwiger P, Jayaraman M, John M, Jayaprakash KN, Maier M, Nechev L, Rajeev KG, Read T, Rohl I, Soutschek J, Tan P, Wong J, Wang G, Zimmermann T, de Fougerolles A, Vornlocher HP, Langer R, Anderson DG, Manoharan M, Koteliansky V, Horton JD, Fitzgerald K. Therapeutic rnai targeting pcsk9 acutely lowers plasma cholesterol in rodents and ldl cholesterol in nonhuman primates. Proc Natl Acad Sci U S A. 2008; 105:11915–11920. [PubMed: 18695239]

46. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, Barrett JH, Konig IR, Stevens SE, Szymczak S, Tregouet DA, Iles MM, Pahlke F, Pollard H, Lieb W, Cambien F, Fischer M, Ouwehand W, Blankenberg S, Balmforth AJ, Baessler A, Ball SG, Strom TM, Braenne I, Gieger C, Deloukas P, Tobin MD, Ziegler A, Thompson JR, Schunkert H. Genomewide association analysis of coronary artery disease. N Engl J Med. 2007; 357:443–453. [PubMed: 17634449]

47. Kjolby M, Andersen OM, Breiderhoff T, Fjorback AW, Pedersen KM, Madsen P, Jansen P, Heeren J, Willnow TE, Nykjaer A. Sort1, encoded by the cardiovascular risk locus 1p13.3, is a regulator of hepatic lipoprotein export. Cell Metab. 2010; 12:213–223. [PubMed: 20816088]

48. Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, Kwiterovich P, Shan B, Barnes R, Hobbs HH. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent abc transporters. Science. 2000; 290:1771–1775. [PubMed: 11099417]

49. Wilund KR, Yu L, Xu F, Hobbs HH, Cohen JC. High-level expression of abcg5 and abcg8 attenuates diet-induced hypercholesterolemia and atherosclerosis in ldlr−/− mice. J Lipid Res. 2004; 45:1429–1436. [PubMed: 15175362]

50. Wu JE, Basso F, Shamburek RD, Amar MJ, Vaisman B, Szakacs G, Joyce C, Tansey T, Freeman L, Paigen BJ, Thomas F, Brewer HB Jr, Santamarina-Fojo S. Hepatic abcg5 and abcg8 overexpression increases hepatobiliary sterol transport but does not alter aortic atherosclerosis in transgenic mice. J Biol Chem. 2004; 279:22913–22925. [PubMed: 15044450]

51. Basso F, Freeman LA, Ko C, Joyce C, Amar MJ, Shamburek RD, Tansey T, Thomas F, Wu J, Paigen B, Remaley AT, Santamarina-Fojo S, Brewer HB Jr. Hepatic abcg5/g8 overexpression reduces apob-lipoproteins and atherosclerosis when cholesterol absorption is inhibited. J Lipid Res. 2007; 48:114–126. [PubMed: 17060690]

52. Yu L, von Bergmann K, Lutjohann D, Hobbs HH, Cohen JC. Selective sterol accumulation in abcg5/abcg8-deficient mice. J Lipid Res. 2004; 45:301–307. [PubMed: 14657202]

53. Erdmann J, Grosshennig A, Braund PS, Konig IR, Hengstenberg C, Hall AS, Linsel-Nitschke P, Kathiresan S, Wright B, Tregouet DA, Cambien F, Bruse P, Aherrahrou Z, Wagner AK, Stark K, Schwartz SM, Salomaa V, Elosua R, Melander O, Voight BF, O'Donnell CJ, Peltonen L, Siscovick DS, Altshuler D, Merlini PA, Peyvandi F, Bernardinelli L, Ardissino D, Schillert A, Blankenberg S, Zeller T, Wild P, Schwarz DF, Tiret L, Perret C, Schreiber S, El Mokhtari NE, Schafer A, Marz W, Renner W, Bugert P, Kluter H, Schrezenmeir J, Rubin D, Ball SG, Balmforth AJ, Wichmann HE, Meitinger T, Fischer M, Meisinger C, Baumert J, Peters A, Ouwehand WH, Deloukas P, Thompson JR, Ziegler A, Samani NJ, Schunkert H. New susceptibility locus for coronary artery disease on chromosome 3q22.3. Nat Genet. 2009; 41:280–282. [PubMed: 19198612]

54. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M. Genetic variants associated with lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009; 361:2518–2528. [PubMed: 20032323]

55. Lawn RM, Wade DP, Hammer RE, Chiesa G, Verstuyft JG, Rubin EM. Atherogenesis in transgenic mice expressing human apolipoprotein(a). Nature. 1992; 360:670–672. [PubMed: 1465128]

56. Pedersen TX, McCormick SP, Tsimikas S, Bro S, Nielsen LB. Lipoprotein(a) accelerates atherosclerosis in uremic mice. J Lipid Res. 2010; 51:2967–2975. [PubMed: 20584868]

57. Sanan DA, Newland DL, Tao R, Marcovina S, Wang J, Mooser V, Hammer RE, Hobbs HH. Low density lipoprotein receptor-negative mice expressing human apolipoprotein b-100 develop complex atherosclerotic lesions on a chow diet: No accentuation by apolipoprotein(a). Proc Natl Acad Sci U S A. 1998; 95:4544–4549. [PubMed: 9539774]

58. Callow MJ, Stoltzfus LJ, Lawn RM, Rubin EM. Expression of human apolipoprotein b and assembly of lipoprotein(a) in transgenic mice. Proc Natl Acad Sci U S A. 1994; 91:2130–2134. [PubMed: 8134359]

59. Cummings DE, Brandon EP, Planas JV, Motamed K, Idzerda RL, McKnight GS. Genetically lean mice result from targeted disruption of the rii beta subunit of protein kinase a. Nature. 1996; 382:622–626. [PubMed: 8757131]

60. Schreyer SA, Cummings DE, McKnight GS, LeBoeuf RC. Mutation of the riibeta subunit of protein kinase a prevents diet-induced insulin resistance and dyslipidemia in mice. Diabetes. 2001; 50:2555–2562. [PubMed: 11679434]

61. Adams JW, Wang J, Davis JR, Liaw C, Gaidarov I, Gatlin J, Dalton ND, Gu Y, Ross J Jr, Behan D, Chien K, Connolly D. Myocardial expression, signaling, and function of gpr22: A protective

role for an orphan g protein-coupled receptor. Am J Physiol Heart Circ Physiol. 2008; 295:H509–H521. [PubMed: 18539757]

62. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH, Cohen JC. A common allele on chromosome 9 associated with coronary heart disease. Science. 2007; 316:1488–1491. [PubMed: 17478681]
63. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levey AI, Backman VM, Matthiasdottir S, Jonsdottir T, Palsson S, Einarsdottir H, Gunnarsdottir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H, Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science. 2007; 316:1491–1493. [PubMed: 17478679]
64. Consortium. WTC-c. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007; 447:661–678. [PubMed: 17554300]
65. Gonzalez-Navarro H, Abu Nabah YN, Vinue A, Andres-Manzano MJ, Collado M, Serrano M, Andres V. P19(arf) deficiency reduces macrophage and vascular smooth muscle cell apoptosis and aggravates atherosclerosis. J Am Coll Cardiol. 2010; 55:2258–2268. [PubMed: 20381282]
66. George VT, Elston RC, Amos CI, Ward LJ, Berenson GS. Association between polymorphic blood markers and risk factors for cardiovascular disease in a large pedigree. Genet Epidemiol. 1987; 4:267–275. [PubMed: 3478281]
67. Germain M, Saut N, Greliche N, Dina C, Lambert JC, Perret C, Cohen W, Oudot-Mellakh T, Antoni G, Alessi MC, Zelenika D, Cambien F, Tiret L, Bertrand M, Dupuy AM, Letenneur L, Lathrop M, Emmerich J, Amouyel P, Tregouet DA, Morange PE. Genetics of venous thrombosis: Insights from a new genome wide association study. PLoS One. 2011; 6:e25581. [PubMed: 21980494]
68. Barbalic M, Dupuis J, Dehghan A, Bis JC, Hoogeveen RC, Schnabel RB, Nambi V, Bretler M, Smith NL, Peters A, Lu C, Tracy RP, Aleksic N, Heeriga J, Keaney JF Jr, Rice K, Lip GY, Vasan RS, Glazer NL, Larson MG, Uitterlinden AG, Yamamoto J, Durda P, Haritunians T, Psaty BM, Boerwinkle E, Hofman A, Koenig W, Jenny NS, Witteman JC, Ballantyne C, Benjamin EJ. Large-scale genomic studies reveal central role of abo in sp-selectin and sicam-1 levels. Hum Mol Genet. 2010; 19:1863–1872. [PubMed: 20167578]
69. Pare G, Ridker PM, Rose L, Barbalic M, Dupuis J, Dehghan A, Bis JC, Benjamin EJ, Shiffman D, Parker AN, Chasman DI. Genome-wide association analysis of soluble icam-1 concentration reveals novel associations at the nfkbik, pnpla3, rela, and sh2b3 loci. PLoS Genet. 2011; 7:e1001374. [PubMed: 21533024]
70. Kiechl S, Pare G, Barbalic M, Qi L, Dupuis J, Dehghan A, Bis JC, Laxton RC, Xiao Q, Bonora E, Willeit J, Xu Q, Witteman JC, Chasman D, Tracy RP, Ballantyne CM, Ridker PM, Benjamin EJ, Ye S. Association of variation at the abo locus with circulating levels of sicam-1, sp-selectin and se-selectin: A meta-analysis. Circ Cardiovasc Genet. 2011
71. Paterson AD, Lopes-Virella MF, Waggott D, Boright AP, Hosseini SM, Carter RE, Shen E, Mirea L, Bharaj B, Sun L, Bull SB. Genome-wide association identifies the abo blood group as a major locus associated with serum levels of soluble e-selectin. Arterioscler Thromb Vasc Biol. 2009; 29:1958–1967. [PubMed: 19729612]
72. Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, Najjar SS, Zhao JH, Heath SC, Eyheramendy S, Papadakis K, Voight BF, Scott LJ, Zhang F, Farrall M, Tanaka T, Wallace C, Chambers JC, Khaw KT, Nilsson P, van der Harst P, Polidoro S, Grobbee DE, Onland-Moret NC, Bots ML, Wain LV, Elliott KS, Teumer A, Luan J, Lucas G, Kuusisto J, Burton PR, Hadley D, McArdle WL, Brown M, Dominiczak A, Newhouse SJ, Samani NJ, Webster J, Zeggini E, Beckmann JS, Bergmann S, Lim N, Song K, Vollenweider P, Waeber G, Waterworth DM, Yuan X, Groop L, Orho-Melander M, Allione A, Di Gregorio A, Guarrera S, Panico S, Ricceri F, Romanazzi V, Sacerdote C, Vineis P, Barroso I, Sandhu MS, Luben RN, Crawford GJ, Jousilahti P, Perola M, Boehnke M, Bonnycastle LL, Collins FS, Jackson AU, Mohlke KL, Stringham HM, Valle TT, Willer CJ, Bergman RN, Morken MA, Doring A, Gieger C, Illig T, Meitinger T, Org E, Pfeufer A, Wichmann HE, Kathiresan S, Marrugat J, O'Donnell CJ, Schwartz SM, Siscovick DS,

Subirana I, Freimer NB, Hartikainen AL, McCarthy MI, O'Reilly PF, Peltonen L, Pouta A, de Jong PE, Snieder H, van Gilst WH, Clarke R, Goel A, Hamsten A, Peden JF, Seedorf U, Syvanen AC, Tognoni G, Lakatta EG, Sanna S, Scheet P, Schlessinger D, Scuteri A, Dorr M, Ernst F, Felix SB, Homuth G, Lorbeer R, Reffelmann T, Rettig R, Volker U, Galan P, Gut IG, Hercberg S, Lathrop GM, Zelenika D, Deloukas P, Soranzo N, Williams FM, Zhai G, Salomaa V, Laakso M, Elosua R, Forouhi NG, Volzke H, Uiterwaal CS, van der Schouw YT, Numans ME, Matullo G, Navis G, Berglund G, Bingham SA, Kooner JS, Connell JM, Bandinelli S, Ferrucci L, Watkins H, Spector TD, Tuomilehto J, Altshuler D, Strachan DP, Laan M, Meneton P, Wareham NJ, Uda M, Jarvelin MR, Mooser V, Melander O, Loos RJ, Elliott P, Abecasis GR, Caulfield M, Munroe PB. Genome-wide association study identifies eight loci associated with blood pressure. Nat Genet. 2009; 41:666–676. [PubMed: 19430483]

73. Rubin EM, Krauss RM, Spangler EA, Verstuyft JG, Clift SM. Inhibition of early atherogenesis in transgenic mice by human apolipoprotein ai. Nature. 1991; 353:265–267. [PubMed: 1910153]
74. Paszty C, Maeda N, Verstuyft J, Rubin EM. Apolipoprotein ai transgene corrects apolipoprotein e deficiency-induced atherosclerosis in mice. J Clin Invest. 1994; 94:899–903. [PubMed: 8040345]
75. Voyiaziakis E, Goldberg IJ, Plump AS, Rubin EM, Breslow JL, Huang LS. Apoa-i deficiency causes both hypertriglyceridemia and increased atherosclerosis in human apob transgenic mice. J Lipid Res. 1998; 39:313–321. [PubMed: 9507992]
76. Mansouri RM, Bauge E, Gervois P, Fruchart-Najib J, Fievet C, Staels B, Fruchart JC. Atheroprotective effect of human apolipoprotein a5 in a mouse model of mixed dyslipidemia. Circ Res. 2008; 103:450–453. [PubMed: 18658049]
77. Mezdour H, Larigauderie G, Castro G, Torpier G, Fruchart J, Nowak M, Fruchart JC, Rouis M, Maeda N. Characterization of a new mouse model for human apolipoprotein a-i/c-iii/a-iv deficiency. J Lipid Res. 2006; 47:912–920. [PubMed: 16497661]
78. Pennacchio LA, Rubin EM. Apolipoprotein a5, a newly identified gene that affects plasma triglyceride levels in humans and mice. Arterioscler Thromb Vasc Biol. 2003; 23:529–534. [PubMed: 12615678]
79. Baroukh N, Bauge E, Akiyama J, Chang J, Afzal V, Fruchart JC, Rubin EM, Fruchart-Najib J, Pennacchio LA. Analysis of apolipoprotein a5, c3, and plasma triglyceride concentrations in genetically engineered mice. Arterioscler Thromb Vasc Biol. 2004; 24:1297–1302. [PubMed: 15117734]
80. Soranzo N, Spector TD, Mangino M, Kuhnel B, Rendon A, Teumer A, Willenborg C, Wright B, Chen L, Li M, Salo P, Voight BF, Burns P, Laskowski RA, Xue Y, Menzel S, Altshuler D, Bradley JR, Bumpstead S, Burnett MS, Devaney J, Doring A, Elosua R, Epstein SE, Erber W, Falchi M, Garner SF, Ghori MJ, Goodall AH, Gwilliam R, Hakonarson HH, Hall AS, Hammond N, Hengstenberg C, Illig T, Konig IR, Knouff CW, McPherson R, Melander O, Mooser V, Nauck M, Nieminen MS, O'Donnell CJ, Peltonen L, Potter SC, Prokisch H, Rader DJ, Rice CM, Roberts R, Salomaa V, Sambrook J, Schreiber S, Schunkert H, Schwartz SM, Serbanovic-Canic J, Sinisalo J, Siscovick DS, Stark K, Surakka I, Stephens J, Thompson JR, Volker U, Volzke H, Watkins NA, Wells GA, Wichmann HE, Van Heel DA, Tyler-Smith C, Thein SL, Kathiresan S, Perola M, Reilly MP, Stewart AF, Erdmann J, Samani NJ, Meisinger C, Greinacher A, Deloukas P, Ouwehand WH, Gieger C. A genome-wide meta-analysis identifies 22 loci associated with eight hematological parameters in the haemgen consortium. Nat Genet. 2009; 41:1182–1190. [PubMed: 19820697]
81. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Kottgen A, Vasan RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FU, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. Nat Genet. 2009; 41:677–687. [PubMed: 19430479]
82. Zhao Y, Su B, Jacobs RL, Kennedy B, Francis GA, Waddington E, Brosnan JT, Vance JE, Vance DE. Lack of phosphatidylethanolamine n-methyltransferase alters plasma vldl phospholipids and attenuates atherosclerosis in mice. Arterioscler Thromb Vasc Biol. 2009; 29:1349–1355. [PubMed: 19520976]

83. Cole LK, Dolinsky VW, Dyck JR, Vance DE. Impaired phosphatidylcholine biosynthesis reduces atherosclerosis and prevents lipotoxic cardiac dysfunction in apoe−/− mice. Circ Res. 2011; 108:686–694. [PubMed: 21273556]
84. Li Z, Agellon LB, Vance DE. The role of phosphatidylethanolamine methyltransferase in a mouse model of intrahepatic cholestasis. Biochim Biophys Acta. 2011; 1811:278–283. [PubMed: 21292027]
85. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Familial hypercholesterolemia and coronary heart disease: A huge association review. Am J Epidemiol. 2004; 160:421–429. [PubMed: 15321838]
86. Ishibashi S, Goldstein JL, Brown MS, Herz J, Burns DK. Massive xanthomatosis and atherosclerosis in cholesterol-fed low density lipoprotein receptor-negative mice. J Clin Invest. 1994; 93:1885–1893. [PubMed: 8182121]
87. Ishibashi S, Brown MS, Goldstein JL, Gerard RD, Hammer RE, Herz J. Hypercholesterolemia in low density lipoprotein receptor knockout mice and its reversal by adenovirus-mediated gene delivery. J Clin Invest. 1993; 92:883–893. [PubMed: 8349823]
88. Knoblauch H, Bauerfeind A, Krahenbuhl C, Daury A, Rohde K, Bejanin S, Essioux L, Schuster H, Luft FC, Reich JG. Common haplotypes in five genes influence genetic variance of ldl and hdl cholesterol in the general population. Hum Mol Genet. 2002; 11:1477–1485. [PubMed: 12023990]
89. Zhang SH, Reddick RL, Piedrahita JA, Maeda N. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein e. Science. 1992; 258:468–471. [PubMed: 1411543]
90. Plump AS, Smith JD, Hayek T, Aalto-Setala K, Walsh A, Verstuyft JG, Rubin EM, Breslow JL. Severe hypercholesterolemia and atherosclerosis in apolipoprotein e-deficient mice created by homologous recombination in es cells. Cell. 1992; 71:343–353. [PubMed: 1423598]
91. Nakashima Y, Plump AS, Raines EW, Breslow JL, Ross R. Apoe-deficient mice develop lesions of all phases of atherosclerosis throughout the arterial tree. Arterioscler Thromb. 1994; 14:133–140. [PubMed: 8274468]

Table 1

Human-mouse genomic homologies for CAD-associated loci: availability of mutant mouse models.

Human chr	SNP	Gene(s) in region	Related phenotype (human)	Murine homolog(s)	Mouse chr	Mutant models*	Lesion phenotype	Related phenotype (mouse)
1	rs11206510[41]	*PCSK9*	LDL, TC[3, 42, 43]	*Pcsk9*	4	KO, Tg (liver)		LDL, TC[44, 45]
1	rs17114036[8]	*PPAP2B*		*Ppap2b*	4	KO (embryonic lethal)		
1	rs599839[41, 46]	*SORT1*	LDL, TC[3, 42]	*Sort1*	3	KO, Tg		LDL, TC[20, 47]
1	rs17465637[41, 46]	*MIA3*		*Mia3*	1	KO (perinatal lethal)		
2	rs4299376[17]	*ABCG8*	LDL, TC,[3, 48] sitosterolemia[48]	*Abcg8*	17	KO, Tg	↓ B6-*Ldlr*$^{-/-}$, *Abcg8* Tg, WTD[49] -- B6-*Ldlr*$^{-/-}$ or -*Apoe*$^{-/-}$, *Abcg8* liver-specTg, chow[50] ↓ B6-*Ldlr*$^{-/-}$, *Abcg8* liver-specTg, WTD+ezetimibe[51]	LDL, TC, sitosterolemia[49, 52]
2	rs6725887[41]	*WDR12*		*Wdr12*	1	KO (ES cell)		
3	rs2306374[53]	*MRAS*		*Mras*	9	KO		
5	rs2706399[17]	*IL5*		*Il5*	11	KO, Tg		
6	Rs6903956[31]	*C6orf105*		*9530008L14Rik*	13			
6	rs12526453[41]	*PHACTR1*		*Phactr1*	13	KO (ES cell)		
6	rs17609940[8]	*ANKS1A*		*Anks1*	17	KO (perinatal lethal)		
6	rs12190287[8]	*TCF21*		*Tcf21*	10	KO		
6	rs3798220[54] rs10455872[54]	*LPA*	LDL, TC[3] Lp(a)[54]	___	___	huTg	↑ B6xSJL hu*LPA* Tg, HFD[55] ↑ B6 hu*APOB*, *LPA* Tg, WTD[56] -- B6-*Ldlr*$^{-/-}$, hu*APOB*, *LPA* Tg, chow[57]	LDL, TC, Lp(a)[58]
7	rs10953541[9]	*BCAP29* *PRKAR2B* *HBP1* *COG5* *GPR22* *DUS4L*		*Bcap29* *Prkar2b* *Hbp1* *Cog5* *Gpr22* *Dus4l*	12	KO (ES cell) KO KO KO (ES cell) KO KO (ES cell)		body weight[59, 60] insulin resistance[60] heart failure[61]
7	rs11556924[8]	*ZC3HC1*		*Zc3hc1*	6	KO		
8	rs17321515[17]	*TRIB1*	TG, LDL, TC, HDL[3, 42]	*Trib1*	15	KO		LDL, TC, TG[21]

Human chr	SNP	Gene(s) in region	Related phenotype (human)	Murine homolog(s)	Mouse chr	Mutant models*	Lesion phenotype	Related phenotype (mouse)
9	rs4977574[41, 46, 62–64]	*ANRIL* *CDKN2A* (*p16*^{INK4a}, *p14*^{ARF}) *CDKN2B*(*p15*^{INK4b}) *MTAP*		*no contiguous segment)* *Cdkn2a* (*p16*^{Ink4a}, *p19*^{Arf}) *Cdkn2b* (*p15*^{Ink4b}) *Mtap*	4	locus deletion KO, Tg KO, Tg,(promoter), spont mutation	-- 129Sv locus deletion, HFD[30] ↑ B6-*Ldlr*$^{-/-}$, *p16*^{Ink4a}, *p19*^{Arf} BM-specKO, WTD[24] ↑ B6-*Apoe*$^{-/-}$, *p19*^{Arf} KO, HFDb[65]	
9	rs579459[8, 22]	*ABO*	LDL, TC[3, 66] thrombosis[67] inflammation[68–71]	*Abo*	2	KO (ES cell)		
10	rs2505083[9]	*KIAA1462*		*9430020K01Rik*	18	KO (ES cell)		
10	rs1746048[41, 46]	*CXCL12*		*Cxcl12*	6	KO (embryonic lethal) Tg (general, EGFP, endothelial-specific)		
10	rs2246942[9]	*LIPA*		*Lipa*	19	KO		lipase deficiency
10	rs12413409[8]	*CYP17A1* *NT5C2*	blood pressure[72]	*Cyp17a1* *Nt5c2*	19	KO (embryonic lethal) KO (ES cell)		
11	rs974819[9]	*PDGFD*		*Pdgfd*	9	KO		
11	rs964184[8]	*APOA1/C3/A4/A5*	TG, HDL[3, 42]	*Apoa1/c3/a4/a5*	9	KO, Tg (single and compound alleles)	↓ B6-hu*APOA1* Tg, HFD[73] ↓ B6-*Apoe*$^{-/-}$, hu*APOA1* Tg, chow[74] ↑ B6,mixed-hu*APOBTg*, *Apoa1*$^{-/-}$, WTD[75] ↓ B6-*Apoe2 knock-in*, hu*Apoa5* Tg, WTD[76] -- 129/OlaxB6-*Apoa1/c3/a4*$^{-/-}$ KO, WTD[77]	HDL, LDL, TC, TG[73, 77–79]
12	rs3184504[80]	*SH2B3*	blood pressure[81]	*Sh2b3*	5	KO		
13	rs4773144[8]	*COL4A1/A2*		*Col4a1/a2*	8	KO, chem/rad-induced		
14	rs2895811[8]	*HHIPL1*		*Hhipl1*	12	KO (ES cell)		
15	rs3825807[8, 9, 22]	*ADAMTS7*		*Adamtsl7*	9	KO (ES cell)		
17	rs216172[8]	*SMG6* *SRR*		*Smg6* *Srr*	11	KO KO, Tg (EGFP), chem-induced		
17	rs12936587[8]	*PEMT*		*Pemt*	11	KO, spont mutation	↓ B6-*Ldlr*$^{-/-}$, *Pemt*$^{-/-}$, HF/HC[82] ↓ B6-*Apoe*$^{-/-}$, *Pemt*$^{-/-}$, chow[83]	TG, LDL, VLDL, TC,[82, 83] intrahepatic cholestasis[84]

Human chr	SNP	Gene(s) in region	Related phenotype (human)	Murine homolog(s)	Mouse chr	Mutant models*	Lesion phenotype	Related phenotype (mouse)
17	rs46522	*GIP* *SNF8* *UBE2Z* *ATP5G1*		*Gip* *Snf8* *Ube2z* *Atp5g1*	11	KO (ES cell) KO KO (ES cell) KO (ES cell)		
19	rs1122608[41]	*LDLR*	LDL, TC, FH[3, 85]	*Ldlr*	9	KO, Tg, chem.-induced	↑ B6x129Sv-*Ldlr*$^{-/-}$, HFD[86]	LDL, TC, xanthomatosis[87]
19	rs2075650[17]	*APOE*	LDL, TC, HDL[3, 42, 88]	*Apoe*	7	KO, Tg, rad-induced, spont mutation	↑ B6x129Sv-*Apoe*$^{-/-}$, chow[89] ↑ B6x129Sv-*Apoe*$^{-/-}$, chow and WTD[90, 91]	LDL, TC, HDL, xanthomatosis[89, 90]
21	rs9982601[41]	*MRPS6*		*Mrps6*	16	KO (cell line)		

Chr, chromosome; SNP, lead disease-associated single nucleotide polymorphism; KO, knock-out allele(s); Tg, transgenic allele(s); EGFP, enhanced green fluorescent protein; chem-induced, chemically-induced mutant allele(s); rad-induced, radiation-induced mutant allele(s); spont mutation, spontaneous mutant allele(s); FH, familial hypercholesterolemia.

Diets: WTD, Western-type diet (0.15% cholesterol, 21% fat); HFD, high-fat diet (1.25% cholesterol/15% fat/0.5% sodium cholate); HFDb, high-fat diet (10.8% total fat, 0.75% cholesterol without sodium cholate); HF/HC, high-fat/ high cholesterol diet (1.25% cholesterol, 20% olive oil.)

* Mutant alleles listed at www.informatics.jax.org, www.sanger.ac.uk, www.mmrrc.org, and www.fimre.org.