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# Genetic Basis of Atherosclerosis: Insights from Mice and Humans

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## Abstract

Atherosclerosis is a complex and heritable disease involving multiple cell types and the interactions of many different molecular pathways. The genetic and molecular mechanisms of atherosclerosis have in part been elucidated by mouse models; at least 100 different genes have been shown to influence atherosclerosis in mice. Importantly, unbiased genome-wide association studies have recently identified a number of novel loci robustly associated with atherosclerotic coronary artery disease (CAD). Here we review the genetic data elucidated from mouse models of atherosclerosis, as well as significant associations for human CAD. Furthermore, we discuss in greater detail some of these novel human CAD loci. The combination of mouse and human genetics has the potential to identify and validate novel genes that influence atherosclerosis, some of which may be candidates for new therapeutic approaches.

### Keywords

CAD; Lipids; Mice; GWAS; Genome-wide

## Introduction

The process of atherosclerosis has been the topic of substantial investigation over many decades. Atherosclerosis is a complex process which has a strong heritable component, and involves a number of cellular processes and molecular mechanisms. Exploiting genetic manipulation in mice and natural genetic variation in humans has the potential to inform our understanding of the pathophysiology of atherosclerosis and identify novel targets for therapeutic intervention. In this article, we first review the data involving deletion of specific genes in mice and the effect on atherosclerosis, as well as unbiased approaches to discovery of genetic loci associated with atherosclerosis in mice. Then we review the current status of human genetic variation and its association with coronary artery disease.

### Genetics of atherosclerosis in mice

The most widely used *in vivo* model for human atherosclerosis is currently the mouse. Wild-type mice on a chow diet are not susceptible to atherosclerosis, and this has led investigators over the years to develop three primary mouse models for examining atherosclerosis: *1; The*

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*cholesterol-cholate diet* is a high fat (15%) cholesterol (1.25%) and cholate (0.5% cholic acid) based diet, known as the "Paigen Diet", and is primarily used to induce atherosclerosis in wild-type mice. The combination of cholesterol and cholate facilitates cholesterol and fat absorption, suppresses the conversion of cholesterol to bile acid, which reduces cholesterol clearance, resulting in increased plasma cholesterol.[1] The cholate also affects gene expression of lipid, lipoprotein, and inflammatory genes, and the net result is increased atherosclerosis in mice.[2,3] However, lesion sizes in mice maintained solely on the Paigen Diet remain small,[4] and therefore this strategy has not been as extensively employed as the other two models. *2; Low density lipoprotein receptor knockout (KO) mice (Ldlr$^{-/-}$)* lack the primary receptor for LDL cholesterol uptake, causing a modest increase in plasma LDL cholesterol levels,[5] however to induce atherogenesis *Ldlr*$^{-/-}$ mice must have their plasma cholesterol levels increased further through the feeding of a "Western type diet (WTD)"[6] or crossing with another model such as the *Apobec1* knockout mouse. *3; Apolipoprotein-E KO mice (Apoe$^{-/-}$)* lack the primary lipoprotein required for the uptake of lipoproteins through the hepatic receptors, leading to even greater plasma cholesterol increase than the *Ldlr*$^{-/-}$ mice, and consequently atherosclerosis can be observed in *Apoe*$^{-/-}$ mice maintained on a regular chow diet, with advanced disease observed when the mice are maintained on a WTD (Figure 1A).[5,7,8]

**Candidate gene approaches in mice—**In a candidate gene loss-of-function approach, a KO mouse model for the specific gene is interrogated using the models outlined above. If the Paigen diet is used, no backcrossing is required, however generally double KO (dKO) mice are generated by crossing the candidate KO with either *Ldlr*$^{-/-}$ or *Apoe*$^{-/-}$ mice. Using these approaches, approximately 100 genes have been reported to robustly and significantly affect atherosclerosis in mice with at a significance threshold of $p<0.01$. Of these 100 genes, approximately 60% of initial studies were performed using the *Apoe*$^{-/-}$ background, 25% using the *Ldlr*$^{-/-}$, 5% tested both backgrounds, and 10% using the Paigen diet. Of the 100 genes, deletions of 65 were shown to decrease atherosclerosis, while deletion of 35 increased atherosclerosis. The 100 genes generally fall into two categories, those that affect atherosclerosis by influencing plasma lipids (n=33, Table 1), and those that do not substantially influence plasma lipids and therefore presumably work through other pathways (n=67, Table 2).

In a candidate gene gain-of-function approach, the generation of over-expression transgenic mice in the *Apoe*$^{-/-}$ or *Ldlr*$^{-/-}$ background has been applied. This approach has several advantages; it allows the examination of genes when knockouts are embryonic lethal, and it allows for the examination of human specific genes, such as cholesteryl ester transfer protein (CETP), which does not have a mouse ortholog.[9] Additional methods for probing the role of specific genes in mouse atherosclerosis include bone-marrow transplantation to show the effects on atherosclerosis from hematopoetic-expressed genes (such as with *Abcg1*[10]) antibody-inhibition studies,[11] and small molecule pharmacologic studies[12], however those studies are not reviewed here in the interest of space.

Many genes that were tested have no or minimal effect on atherosclerosis, or have not been replicated. On several occasions, genes have been reported to have an effect only under certain conditions, such as in the *Icam1*$^{-/-}$ mouse studies where atherosclerosis is affected on the *Apoe*$^{-/-}$ background,[13] but not in the *Ldlr*$^{-/-}$ background.[14]

**Unbiased mapping approaches in mice—**In addition to testing specific genes for their effects on atherosclerosis, mice have also been used to identify atherosclerosis genes using unbiased mapping approaches specifically through the use of quantitative trait locus (QTL) analysis. Thus far, 43 significant mouse QTL have been mapped in mice for atherosclerosis (Table 3).[15] QTL mapping typically involving an F2 generation from two

progenitor strains still requires a pro-atherogenic model in order to map atherosclerosis loci. Of the 43 loci identified, 19 have been mapped using progenitor strains that had the *Apoe*$^{-/-}$ gene introduced, 12 were mapped using strains with *Ldlr*$^{-/-}$, and an additional 12 QTL were mapped simply by maintaining the F2 mapping population on the Paigen diet.

The nature of QTL analysis makes identifying causal genes extremely difficult, as the mapped loci (confidence intervals) typically include hundreds of genes with dozens of plausible candidates, even after applying advanced mapping strategies and bioinformatics.[16–24] Consequently plausible candidates for just a small number of atherosclerosis QTL have been successfully mapped. *Artles1* was the first atherosclerosis QTL to be positionally cloned as the gene arachidonate 5-lipoxygenase (*Alox5*),[25] and the atherosclerosis phenotype was confirmed in *Alox5*$^{-/-}$ mice,[26] although other investigators did not see the same effect.[27] Historically, many KO mice have been generated with the use of embryonic stem (ES) cells derived from the "129" strain, subsequently backcrossed to the more standardized "C57BL/6 (B6)" strain. However, no matter how many backcrosses are performed to B6, a significant proportion surrounding the locus of the KO gene will continue to remain from the 129 strain due to linkage, the so called "passenger gene region".[28] These genes will contain polymorphisms between the ES donor strain and the backcrossed recipient strain, and could affect the phenotype being examined leading to a false conclusion that the knocked-out gene is solely responsible for the QTL effect.[28,29] As we summarize below, *ALOX5* has not been convincingly proven in human genetic studies to be associated with CAD, however, *CXCL12* which is significantly associated with human CAD, maps to the orthologous mouse chromosome (Chr) 6 at 117.1 million bases (Mb) from the acromere, less than 1Mb away from *Alox5* (116.3Mb), and within the so called "passenger gene" region of the *Alox5*$^{-/-}$ strain. Consequently, polymorphisms between 129 alleles in *Cxcl12* and B6 control mice may be a significant contributor to the *Artles1* QTL.

A causal gene was also reported for *Ath1*, one of the first atherosclerosis QTL ever mapped in mice, which is located on distal mouse Chr1.[30] The gene was identified as tumor necrosis factor (ligand) superfamily member 4 (*Tnfsf4,* also known as *Ox40l*). *Tnfsf4*$^{-/-}$ mice showed decreased atherosclerosis, and two human populations that were examined reported SNPs having marginal significance for MI ($p<0.05$).[31] However, other investigators did not observe the significance of those SNPs to MI in their human populations,[32] and as presented later, there is currently no genome-wide association locus reported near the human ortholog *TNFSF4* at the syntenic human location (Chr1 at 173Mb). A third QTL, a disintegrin and metalloproteinase 17 (*ADAM17*) was proposed as the causal gene for an atherosclerosis QTL on mouse Chr 12, however the effect in *Adam17*$^{-/-}$ has not yet been reported.[33,34]

Mice have proven extremely powerful in identifying genes and loci that affect atherosclerosis. More than 100 gene deletion mouse models have revealed detailed biological processes leading to atherosclerosis, crucial insights into the nature of specific causal mechanisms affected by lipid metabolism, inflammation, and the pathogenesis of atherosclerosis itself. It is also interesting to note that many of these genes have shown large effect sizes, typically 20 – 50%. It is therefore likely that deletion of more than one of these genes would not have an additive effect. It is possible that many of the genes act in common pathways leading to atherosclerosis. These genes may be under a large selection pressure in humans preventing null mutations from arising in the general population which may partly explain why few of these genes have been robustly shown to affect CAD in humans, but nonetheless could be relevant to human CAD pathology.

A further point that might explain the large number of mouse atherosclerosis genes that have not been convincingly validated in humans could be the differences in pathogenesis and phenotyping of atherosclerosis between mouse and human (Figure 1). The most important

clinical consequences of atherosclerosis in humans arise from lesions in the coronary, carotid, and cerebral arteries, whereas the focus in mice is on the aorta and proximal great vessels. The size, structure, hydrodynamics, embryonic origin and abundance of the smooth muscle cells, and the elasticity of the arteries differ considerably between mouse and humans.[35] Furthermore, while plaque disruption and thrombosis is a major cause of cardiovascular events in humans, similar events have not been convincingly demonstrated in mice. Perhaps then it is not surprising that translation of the genetic discoveries in mice to human CAD susceptibly has been slow and unconvincing; but this has not necessarily been due solely to the limitations in the mouse model.

Human genetics has until recently been considerably underpowered to identify significant genetic associations with CAD. Indeed, as human studies continue to increase in power, more of the genes and loci identified in the mouse may be replicated in humans. Nonetheless, recent human genetic susceptibility loci, as we discuss below, have been identified in genes and loci that could not have been extrapolated from the accumulated knowledge of these mouse studies. This leads to the conclusion that current mouse model strategies for studying atherosclerosis, relevant to human genetics and biology, may need to be revised.

## Genetics of atherosclerosis in humans

The relationship of genetic variation to atherosclerotic cardiovascular disease in humans has the potential to provide important information on the pathophysiology of atherosclerosis in humans. However, the ability to identify causal genes in human studies has until recently been limited by low sample sizes, and heterogeneity in predictive subclinical phenotypes (Figure 1B).[36,37] The expectation is that there would be numerous genes underlying the susceptibility to atherosclerosis in the general population, and that each would have small effects, similar to all complex traits.[38] There have been hundreds of candidate gene studies and multiple linkage studies. While some of these studies identified “significant” genetic associations with particular genes and polymorphisms, numerous other studies failed to replicate those associations, and specific replication studies have showed that most of those loci could not be replicated.[39] More recently genome-wide association studies (GWAS) has unearthed multiple loci significantly associated with CAD, many of which have been replicated numerous times independently and across ethnic groups. Here, we briefly review the candidate gene and human linkage studies, and then focus primarily on the new developments related to GWAS of CAD.

## Candidate gene studies in humans

Using the candidate gene approach, polymorphisms in specific genes with plausible biological relevance are genotyped to determine association with CAD. The candidate gene approach has revealed some loci with significant and convincing effects on atherosclerosis.[40,41] However, overall the traditional candidate gene approach has yielded a slew of negative studies, or weak associations that could not be replicated. The candidate gene approach for CAD took a more high-throughput approach several years ago with the development of the cardiovascular gene-centric 50K SNP array.[42] This array was designed specifically to examine variants in CAD candidate genes, and a recent meta-analysis involving > 30,000 cases and > 75,000 controls revealed several new genes highly significantly associated with CAD.

## Linkage studies

Although traditional risk factors such as age, gender, and family history are still better predictors of CAD than genetic markers and genetic scores, twin-studies demonstrate a strong heritable component of genetic susceptibility to atherosclerosis. In rare instances

atherosclerosis can appear as a Mendelian disorder, such as in familial hypercholesterolemia (FH), where mutations in the LDL-receptor significantly increase plasma LDL cholesterol and consequently atherosclerosis susceptibility.[43] However, even in FH, there is wide a variation in atherosclerosis. Family based linkage studies have been deployed to identify atherosclerosis loci in an unbiased approach, and such linkage studies can be applied in two general ways; by examining multiple large families in a QTL type approach, or by examining a single very large family under a Mendelian inheritance hypothesis. As with the mouse QTL mapping, the linkage regions using either approach are typically too large to identify plausible causal genes.[44] More than 40 loci have been identified using human linkage studies for different measures of human CAD (MI, acute coronary syndrome, coronary calcification, carotid intimal-medial thickness and peripheral arterial occlusive disease), although very few of the loci have been replicated between studies. In several instances, strong candidate genes were identified including; lipoprotein receptor-related protein 6 (*LRP6*) at 12q13.2,[45] arachidonate 5-lipoxygenase-activating protein (*ALOX5AP*) at 13q12-13,[46] and myocyte enhancer factor 2A (*MEF2A*) at 15q26.3. [47] Atherosclerosis screening in mouse models has not yet been reported for these genes, and the new GWAS loci discussed later map outside of the original confidence intervals which identified *LRP6* and *ALOX5AP*, indicating these may be distinct loci. *MEF2A* is more controversial than the other two genes,[44,48] and maps just 20Mb away from *ADAMTS7* (discussed below) on chromosome 15 which may represent linkage of *MEF2A* to a broader region that includes *ADAMTS7*. Like mouse QTL analysis, family based linkage studies have been very successful in identifying loci, but have yielded a limited a number of convincing genes that affect atherosclerosis.

## Genome-wide association studies (GWAS)

Human genome wide association studies (GWAS) examine millions of polymorphisms simultaneously to examine association to a phenotype in a large unrelated but ethnically similar population, and the phenotype is either treated as a continuous variable, or a case-control binary population comparison. As there are a large number of tests performed simultaneously, the currently accepted threshold for genome-wide significance is $p<5\times10^{-8}$.[49] For GWAS of CAD the case-control approach has been the most commonly reported, and this has yielded multiple loci with highly significant associations to myocardial infarction (MI) and coronary artery disease (CAD) (Table 4). In 2007, this approach successfully identified a locus at chromosome 9p21.3 that was highly associated with risk of MI and CAD.[50–52] Concurrently, the Wellcome Trust Case Control Consortium (WTCCC)[53] reported seven additional novel genome-wide significant loci for MI. Further studies and meta-analyses have added additional significant loci.[50,54–58] The most recent and extensive findings come from two global consortia, CARDIoGRAM[59] and C4D,[60] and bring the total number of genome-wide significant loci for MI/CAD to 34 (Table 4). The CARDIoGRAM consortium pooled the data from 14 different GWAS for a total of 140,000 patients, and reported 13 new loci that are genome-wide significant for CAD, while the C4D consortium examined 70,000 patients focusing on South Asians and Europeans and identified four further loci. Beyond the 34 current loci, there are many hundreds of other SNPs that are nominally significant ($5\times10^{-8}>p<0.05$). These may harbor important genes that will reach significance in larger meta-analyzes, and further information gained from expression-QTL and bioinformatics [16] may provide reason to investigate some of these nominally significant loci more urgently. Information from many of the genes derived from mouse atherosclerosis studies that have nominally significant human associations to CAD may also provide impetus to investigate those genes further.

Several of the CAD loci are significantly associated with LDL cholesterol levels (Table 4), while three quarters of all the CAD loci are completely novel and were not previously

suspected to be involved in atherosclerosis or MI. Indeed the majority of the loci have not even been shown to be significantly associated with other CAD risk factors such as diabetes mellitus, hypertension, or BMI. Conversely, many lipid genes, inflammatory genes, and genes previously shown to affect other CAD risk factors have not yet been 'validated' by unbiased human GWAS studies, at least by the high bar of being genome-wide significant.[42] Notably, several novel CAD loci are associated with lipids (*SORT1, TRIB1,* and *LPA*) and others are related to blood pressure and hypertension,[61] suggesting that these risk factors lie in the causal pathway for these particular genes. However, it appears highly likely that the majority of CAD loci will remain unassociated with known risk factors. Furthermore, little is known about the biology of most of the genes at these loci and the mechanisms by which they may influence atherosclerosis or MI.

## Examples of novel CAD loci identified by GWAS and implications for pathophysiology of atherosclerosis

### 9p21(CDKN2A-B/ANRIL/MTAP)

The 9p21 locus was the first CAD locus discovered using GWAS, and has been reliably reproduced, remaining the strongest association with CAD in the human genome.[54] This locus has long been known to be involved in cancer susceptibility,[62] however there are no associations with known risk factors of CAD such as hyperlipidemia or hypertension.[56] The SNPs associated with CAD are all located in intergenic locations, rather than in coding or gene regulatory regions such as un-translated regions (UTRs) or promoter regions (Figure 2A). Consequently, identifying and characterizing the causal variant and gene has been challenging. Nonetheless, several studies have begun to characterize the functional aspects of this locus, focusing on the nearest genes: cyclin-dependent kinase inhibitor 2A (*CDKN2A*), the homologue *CDKN2B*,[63,64] and the neighboring non-coding transcripts.

The two primary genes *CDKN2A* and *2B* are present on the same strand, and encode several different splice variants; *CDKN2B* encodes the p15 protein, while *CDKN2A* encodes the p16 protein as well as the p14/ARF protein (p19/ARK in mice), although due to alternative splicing p16 and p14 share no homology at the amino acid level.[65] More recently, an additional antisense (relative to *CDKN2B*) non-coding RNA was identified and termed *ANRIL*. The first exon of *ANRIL* is in the promoter of p14 (*CDKN2A*) and overlaps with two exons of p15 (*CDKN2B*), and is now referred to as *CDKN2B*-antisense (*CDKN2B-AS*).[66] Due to the increased attention at this locus, additional non-coding antisense transcripts on the '+ strand' have been identified that overlap with these sequences. Furthermore the gene coding for methylthioadenosine phosphorylase (*MTAP*) has been shown to have multiple alternative transcripts, both coding and non-coding. Two of the non-coding *MTAP* transcripts have shared exons with *ANRIL*. Finally, there is also a new small protein-coding gene called *C9ORF53*, which encodes a 79 amino acid protein and remains largely uncharacterized.

Although it is still unclear which of the genes at this locus is specifically responsible for the CAD association and what the mechanism may be, functional studies have implicated enhancer activity for the neighboring genes.[63,64] One study examining mRNA expression of the genes at the locus from peripheral blood mononuclear cells, with follow up in a much smaller sample size of atherosclerosis plaque tissue, suggested that transcript levels of *ANRIL* (*CDKN2B-AS*), but not *CDKN2A, 2B, C9ORF53* and *MTAP* are associated with atherosclerosis.[67] However, *CDKN2B-AS/ANRIL* has not yet been identified in mice which will make *in vivo* characterization of such an effect difficult. Indeed, mice and humans differ significantly at this region for two reasons, 1) there are significantly more transcripts identified for all the genes in the region in humans compared to mice, and 2) much of the

region that is significantly associated with CAD in humans is either missing, or is not yet convincingly sequenced in mice (Figure 2B).

Despite this, a mouse strain with a targeted deletion of 70kb in the orthologous region on mouse Chr 4, where *CDKN2B-AS/ANRIL* should be ($Chr4^{\Delta 70kb/\Delta 70kb}$), significantly affects cardiac expression of the neighboring genes and the proliferation properties of vascular cells. Cardiac expression of *Cdkn2a* and *Cdkn2b* is reduced in $Chr4^{\Delta 70kb/\Delta 70kb}$ mice, indicating that the locus may be a long range regulator for genes that affect CAD through cardiac and vascular cell proliferation, possibly via *CDKN2A* and *CDKN2B*.[64] Studies using human cells of defined genotype showed that lymphoblastoid cells homozygous for the 'protective' haplotype showed binding of STAT1 to an enhancer in this region whereas cells homozygous for the 'risk' haplotype had no STAT1 binding. Interferon-γ stimulation and STAT1 binding was shown to regulate *CDKN2B* and *CDKN2B-AS* expression in human vascular endothelial cells. Thus genetic variation within enhancers at the 9p21 locus may influence vascular cells responses to inflammatory stimuli, resulting in effects on atherogenesis.[68]

## ADAMTS7

The ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family of proteases is comprised of 19 discrete proteins that are zinc metalloproteases. These proteins are secreted and interact with, and degrade components of, the extracellular matrix. Some ADAMTS family members have partially defined biological functions. ADAMTS13 is the protease that cleaves von Willebrand factor, and mutations in ADAMTS13 cause thrombotic thrombocytopenic purpura. ADAMTS2, 3, and 14 regulate the maturation of procollagen into mature collagen via cleavage of an N-terminal preprotein region, and thus these proteins are collectively known as the procollagen-*n*-proteinases.[69] Finally, many other ADAMTS proteins are known to bind and cleave numerous proteoglycans such as aggrecan, versican, and brevican.[70]

There are multiple lines of evidence linking the ADAMTS family of metalloproteases with the pathogenesis of atherosclerosis. The observation that multiple ADAMTS (ADAMTS1, 4, and 9) proteins can cleave versican, a proteoglycan both highly expressed in regions of the vasculature prone to plaque formation[71] and associated with adult cardiovascular disease,[72] suggests a role for these proteins in plaque formation. Multiple ADAMTS proteins are expressed in human carotid lesions.[73] Specifically, ADAMTS1 localizes with vascular smooth muscle cells (VSMCs) within lesions and its expression is higher in migrating and proliferating VSMCs.[74] ADAMTS4 localizes with macrophages in atherosclerotic lesions, and demonstrates higher levels of expression during plaque development in atherosclerotic mouse models.[73] Additionally, a SNP in *ADAMTS1* has been associated with a nearly two-fold increase in cardiovascular disease.[75]

In a recent GWAS meta-analysis involving patients with (n=12,393) and without (n=7,383) CAD, as ascertained by coronary angiographic phenotyping, the SNP most highly associated with CAD lies in an intron of the *ADAMTS7* gene (p-value=$5.0\times10^{-13}$).[76] This finding was replicated by the CARDIoGRAM consortium.[55] The linkage disequilibrium block that this SNP lies in is completely encompassed by the *ADAMTS7* coding region, strongly implicating *ADAMTS7* as the causal gene. ADAMTS7 can bind and cleave the cartilage oligomeric matrix protein (COMP), an interaction thought to play a role in the progression of arthritis.[77] More recently, *ADAMTS7* over-expression was shown to increase neointimal formation post-injury in a rat carotid artery balloon-injury model.[78] Subsequent knock down of *ADAMTS7* expression by topical application of siRNAs decreased post-injury neointimal formation. Over- and under-expression of *ADAMTS7* also increased and decreased primary VSMC migration, respectively,[78] while exogenous expression of COMP decreased both

post-injury neointimal formation as well as primary VSMC migration. The statistical analyses in human cohorts combined with *in vivo* model observations suggest that *ADAMTS7* is likely to play a causal role in atherogenesis, presumably through enhanced VSMC infiltration and migration in plaques. These results also make ADAMTS7 an exciting target for future studies and potential therapeutic intervention.

### CXCL12 (chemokine (C-X-C motif) ligand 12)

Most of the CAD GWAS loci do not harbor classical inflammatory genes (Table 4). One exception is the 10q11 locus near the gene *CXCL12*, previously known as stromal cell derived factor 1 (*SDF-1*). The most significant SNPs at this locus are in fact in a gene desert located between two non-coding uncharacterized transcripts with *CXCL12* being the nearest gene located ~100,000 bases away. *CXCL12* is a complex gene with two common splice variants (α and β), and up to six additional coding variants. CXCL12 is known to have a major role in angiogenesis and is a key regulator of endothelial cell responses, as well as having anti-inflammatory properties by modulating the accumulation of leukocytes and bone marrow derived stem cells in inflamed tissue.[79]

Additional evidence that *CXCL12* is the causal gene for atherosclerosis at this locus was recently reported in a clinical study examining two CAD populations. The risk allele for the SNP (rs1746048) was shown to be associated with increased atherosclerosis and higher *CXCL12* mRNA transcript levels, particularly for the α-isoform in human liver and natural killer cells.[80] In addition, the risk allele was reported to confer increased plasma protein levels of CXCL12,[80] indicating that higher plasma CXCL12 might result in increased atherosclerosis. However, in a smaller human study, CXCL12 levels were lower in subjects with unstable angina.[81] Additionally, knock-out mouse data (*Cxcl12*$^{-/-}$) indicates that deficiency of CXCL12 is likely to be detrimental to health as it is required for B-cell lymphopoiesis, myelopoiesis, correct formation of the ventricular septum,[82,83] and T-cell development.[84] The *Cxcl12*-α variant in mice has also been shown to confer protection against myocardial ischemia/reperfusion injury.[85] Additional studies to over-express *Cxcl12* in mice would be a useful in clarifying the biological effects of increased CXCL12 but it is possible that differential tissue specific roles may be involved, that the mouse response may differ from human, and that acute vascular injury models may differ from chronic atherosclerosis models.

### ABO (ABO blood group, transferase A, alpha 1–3-N-acetylgalactosaminyltransferase, transferase B, alpha 1–3-galactosyltransferase)

The ABO blood groups were associated with plasma cholesterol levels by the Framingham Study more than 35 years ago.[86] The same study linked ABO blood groups with Intermittent claudication[86] and various other studies at that time also drew links to ischemic heart disease,[87,88] atherosclerosis obliterans,[87,89] and venous thromboembolism.[87,88] Despite these early significant discoveries, the mechanism regarding how different ABO groups affect lipids and cardiovascular disease remain unknown. GWAS studies have recently *'rediscovered'* the ABO locus to be both genome-wide significant for LDL-C cholesterol,[90] as well as with myocardial infarction (MI), whereby the *O* blood group affords protections from MI in patients with angiographic CAD.[76] The specific mechanisms by which the ABO gene locus influences multiple cardiovascular risk factors and MI remain unclear. One reason for the lack of progress is that studying glycoconjugates is considerably more difficult than simply studying nucleic acids or proteins,[91] and because there is a distinct lack of an appropriate *in vivo* animal and specifically mouse models for the human ABO locus.[92]

## Conclusions & Summary

Our review of the mouse model literature reveals a large list of genes that have been shown to affect atherosclerosis in mice. However, very few of these have shown up in human genetic studies to be genome-wide significantly associated with CAD, although some of these mouse atherosclerosis genes may become significant with larger human genetic studies. The gene-centric cardiovascular genotyping array (IBC 50K CAD Consortium) was designed to include many CAD candidate genes that arose from mouse studies, and this approach has been successful in adding several unique associations to the current list of 34 genome-wide significant loci.[42] Targeting more of the genes identified from mouse studies through gene-centric approaches and re-sequencing could identify yet more genes that affect human CAD. Nonetheless, currently there remains substantial "missing genetic heritability" for human CAD.[93]

Mouse QTL for atherosclerosis may have some overlap with the recent human GWAS loci; however most of these QTL remain large and even with novel bioinformatic approaches identifying candidate genes from these QTL remains difficult. Denser genotyping in mouse crosses provides little extra power due to the relatedness of the strains and the limited recombination events. The future 'Collaborative Cross', which is generating hundreds of densely genotyped recombinant-inbred strains, may help generate more finite QTL intervals, although this may prove difficult for atherosclerosis given that if the new strains are not prone to atherosclerosis each will have to be crossed to *Apoe*$^{-/-}$ or *Ldlr*$^{-/-}$ strains.[94–96]

It is also possible that some of the associations of these genes with murine atherosclerosis are false positives, arising due to variants in nearby causal "passenger genes", or to biology which is specific to the common mouse atherosclerosis models, predominantly *Apoe*$^{-/-}$ and *Ldlr*$^{-/-}$ background mice. Indeed the limitations of mouse models may be much more substantial and pernicious than previously recognized. It is apparent from recent human GWAS that there is almost no overlap with the rodent KO models, and that the rodent QTL have not been sufficiently specific to demonstrate overlap, even after at least 34 genome-wide significant loci for human CAD have been described. It is therefore important to illustrate the potential limitations of the commonly used mouse CAD models so that they can be avoided or minimized in future functional studies. The key issues include; (1) current models utilize extreme hypercholesterolemia to induce atherosclerosis – this may be a particularly non-physiological model for the study of non-lipid candidate genes which appear to be more abundant than lipid genes based on recent human GWAS. (2) there is a lack of homology between mouse and human for key genes of interest; for example, CETP is not expressed in mouse, the 9p21 locus is markedly different between human and mouse, and the ABO variants are substantially different between mouse and human.

Moving forward we can expect a more human-translational strategy with mouse studies focused on validating the recent human loci and genes. This will require reasonable genetic homology between mouse and human, but more importantly, there must be a renewed effort to apply new and improved mouse models, particularly with less extreme lipid disturbance for loci with no impact on lipids themselves.

The human heritability of CAD is estimated to be between 30–60%.[97] The recent large-scale meta-analysis of human GWAS data reveals 34 significant loci, and the accumulation of these loci explains just 10% of the heritability of CAD.[98] Many reasons have been provided as to why the detected human genetic variance for complex traits is so low; GWA studies only examine SNPs and neglect much of the other forms of genomic variation; deletions, insertions, inversions, duplications, copy number variants, as well as imprinting/epigenetics, epistasis (gene-by-gene and gene-by-environment), and that there is lack of statistical power

to assess rare variants.[93] However, even though only 10% of human CAD variation is currently explained, it is explained by mostly novel loci that have not yet been investigated. Each of these loci may contain therapeutically targetable genes that may go a long way to reducing CAD incidence, and certainly there remains a lot of work to be done to uncover the functional biology of these novel genes and the mechanisms by which they are related to atherosclerosis.

In terms of human studies, traditional risk factors such as age, sex, smoking, and a family history of premature coronary heart disease are still more predictive of CAD that human genetic markers and genetic scores. Aging in particular affects all metabolic processes and has a profound effect on atherosclerosis, and we do not yet fully understand the impact of aging at the cellular level. However, it is intriguing that some of the new GWAS loci contain genes involved in immunity and cell growth since aging is known to affect these crucial mechanisms. Future more detailed stratified meta-analyses and assessment of interaction effects may yield important gene-by-environment interactions, and help aid in deciphering the causal mechanism.

Overall, mouse models of atherosclerosis, in particular the candidate gene based approaches, have helped us discover and understand many intricacies of the disease and have provided some insight, albeit biased, into the biology of the disease. Recent human GWAS have elucidated a substantial number of novel loci and genes, indicating that we still have some way to go before we fully understand the genetic mechanisms and biological pathways causally involved in human atherosclerosis.

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## List of nonstandard abbreviations

| | |
|---|---|
| **B6** | C57BL/6 |
| **C4D** | The Coronary Artery Disease (C4D) Genetics Consortium Study |
| **CARDIoGRAM** | The Coronary Artery Disease Genome-Wide Replication and Meta-Analysis study |
| **Chr** | Chromosome |
| **CKD** | Chronic kidney disease. |
| **dKO** | Double knock-out |
| **ES** | Embryonic stem |
| **FH** | Familial hypercholesterolemia |
| **GWAS** | Genome-wide association studies |
| **GWSA** | Genome-wide significantly associated |
| **Kb** | Kilo bases |
| **Mb** | Million bases |
| **MGD** | Mouse Genome Database |
| **NCBIM37** | National Center for Biotechnology Information mouse version 37 |
| **QTL** | Quantitative trait locus |

| | |
|---|---|
| **UTRs** | Un-translated regions |
| **VSMCs** | Vascular smooth muscle cells |
| **WTCCC** | Wellcome Trust Case Control Consortium |
| **WTD** | Western type diet |

## Citations


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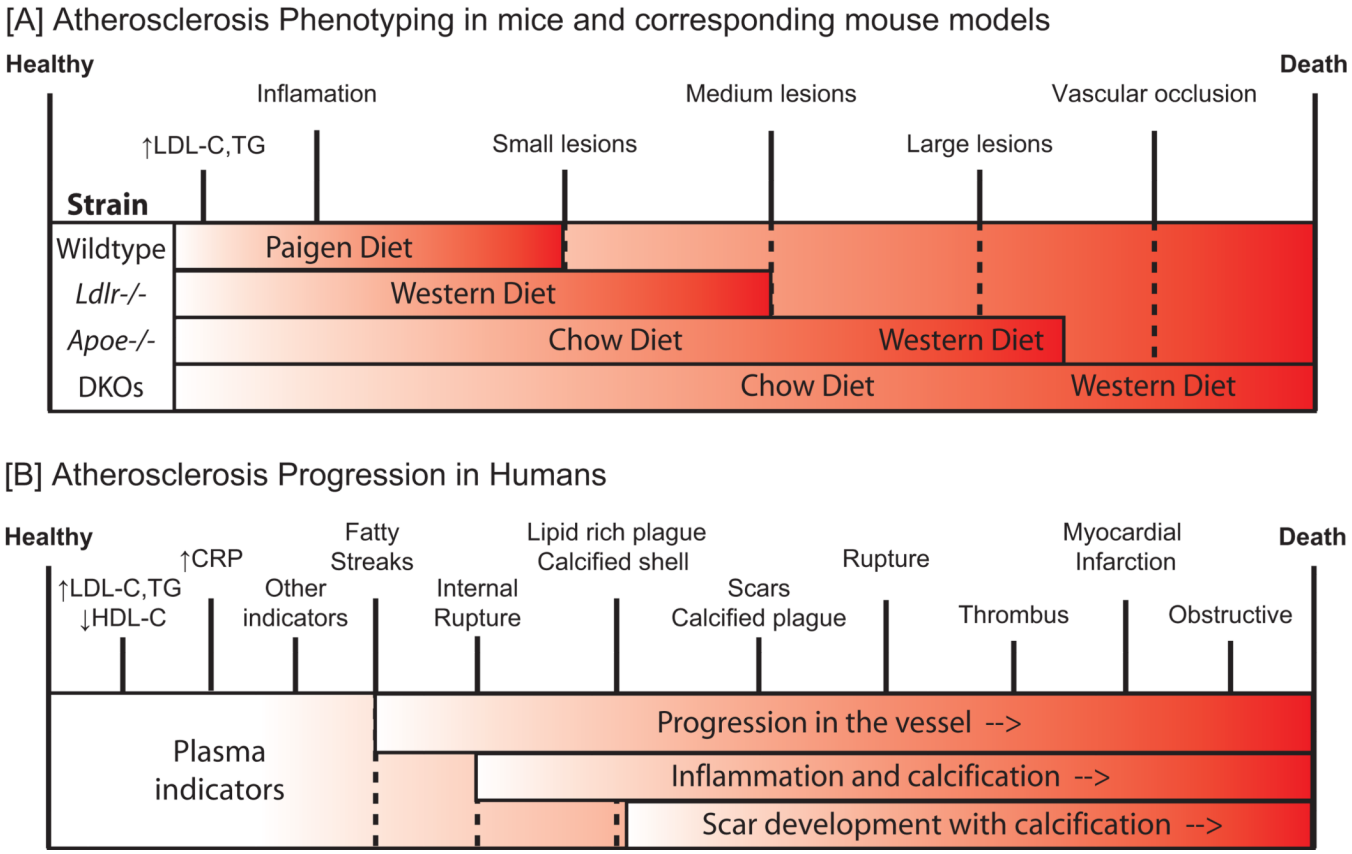


**Figure 1. Phenotypic Progression of Atherosclerosis in mouse and humans**

[A] Approximate progression of observable atherosclerosis in mouse models, noting that double knockouts (DKOs) on either the *Ldlr−/−* or *Apoe−/−* backgrounds can have decrease as well as increased atherosclerosis. [B] An approximate illustration of clinical characterization of atherosclerosis in humans.

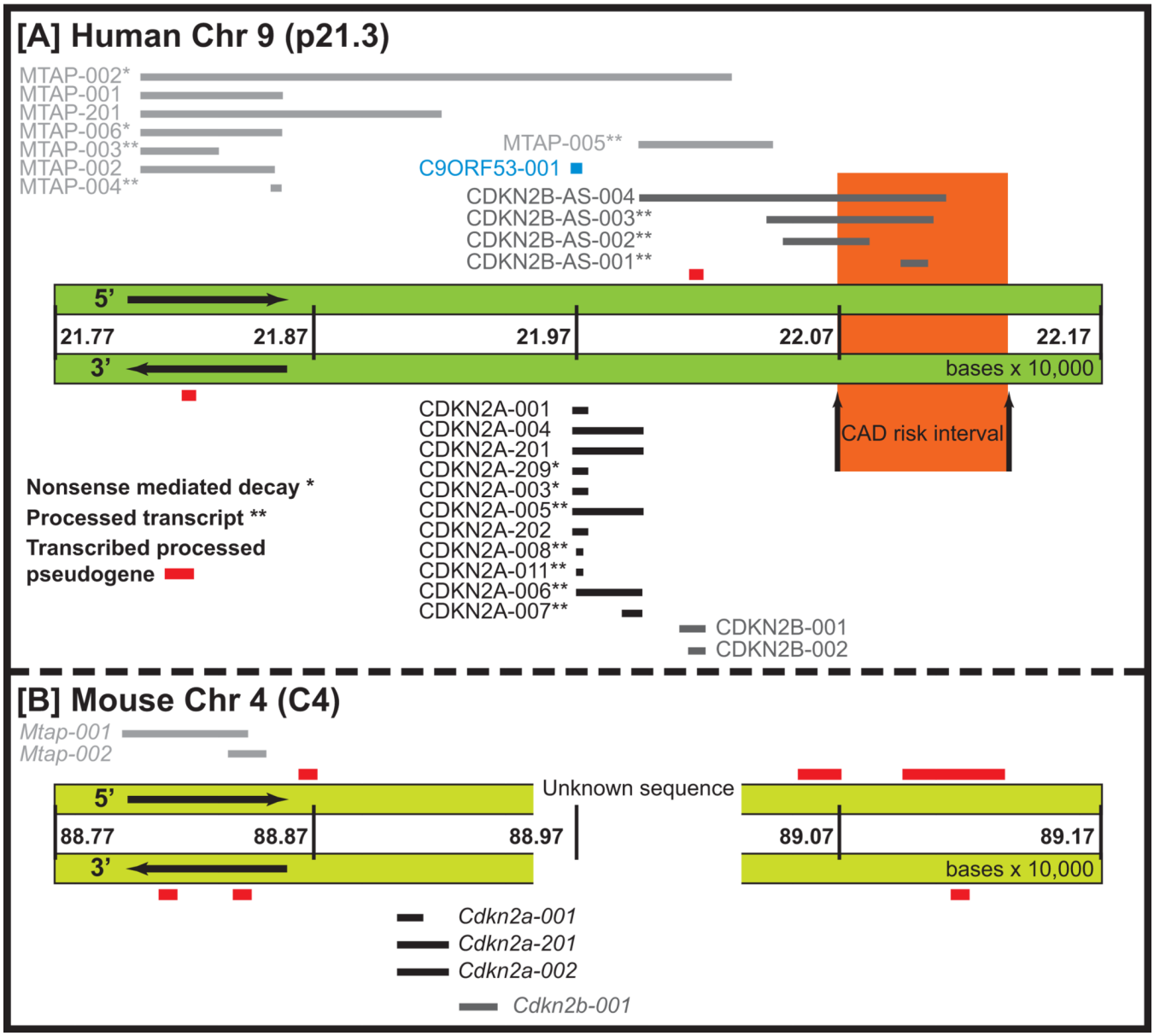


**Figure 2. The 9p21 human CAD locus and the orthologous mouse region**

Horizontal lines indicate the full contiguous length of the labeled transcript. **[A]** 400,000 bases near the 9p21 CAD locus. The "CAD risk interval" indicates the region containing the most GWSA SNPs for CAD. **[B]** 400,000 bases surrounding the orthologous mouse region of the CAD locus on human 9p21. A recent update of the mouse genome at this locus (Assembly NCBIM37, Gene build Jan 2011) indicates that there is a region lacking overlapping sequenced contigs (designated "Unknown sequence") which may be as large as 50,000 bases. The sequenced contigs flanking this region are themselves small and may indicate a region of excessive repetitive DNA preventing the ability to confidently sequence the region.

**Table 1**

Genes affecting atherosclerosis in mice primarily via influencing plasma cholesterol levels[1]

| | | | | Effect in the dKO on: | | |
|---|---|---|---|---|---|---|
| Chr | Mb | Candidate Gene[2] | Background | Atherosclerotic | Plasma Cholesterol[3] | Ref |
| 1 | 71.63 | *Fn1* | *Apoe−/−* | Decrease | Decrease | 99 |
| 1 | 132.95 | *Mapkapk2* | *Ldlr−/−* | Decrease | Increase | 100 |
| 1 | 158.36 | *Soat1* | *Apoe−/− and Ldlr−/−* | Decrease | Decrease | 101 |
| 1 | 163.33 | *Tnfsf4* | *Ldlr−/−* | Decrease | Increase | 31 |
| 1 | 172.98 | *Fcgr3* | *Ldlr−/−* | Decrease | Increase | 102 |
| 2 | 84.98 | *Aplnr* | *Apoe−/−* | Decrease | Increase | 103 |
| 2 | 126.42 | *Hdc* | *Apoe−/−* with Paigen diet | Decrease | Increase | 104 |
| 2 | 148.70 | *Cst3* | *Apoe−/−* | Increase | Increase | 105 |
| 3 | 10.01 | *Fabp5* | *Apoe−/−* | Decrease | Decrease | 106 |
| 3 | 10.20 | *Fabp4* | *Apoe−/−* | Decrease | Decrease | 107 |
| 3 | 96.63 | *Pdzk1* | *Apoe−/−* | Increase | Increase | 108 |
| 3 | 107.54 | *Csf1* | *Apoe−/−* | Decrease | Increase | 109 |
| 4 | 53.04 | *Abca1* | *Apoe−/− and Ldlr−/−* | Increase[4] | Decrease | 110 |
| 4 | 98.69 | *Angptl3* | *Apoe−/−* | Decrease | Decrease | 111 |
| 5 | 17.29 | *Cd36* | *Apoe−/−* | Decrease[5] | Decrease | 112 |
| 5 | 30.34 | *Il6* | *Apoe−/−* | Increase | Increase | 113 |
| 5 | 125.76 | *Scarb1* | *Apoe−/−* | Increase | Increase | 114 |
| 6 | 5.21 | *Pon2* | Paigen diet | Increase | Decrease | 115 |
| 6 | 17.26 | *Cav1* | *Apoe−/−* | Decrease | Increase | 116 |
| 6 | 29.01 | *Lep* | *Ldlr−/−* | Increase | Increase | 117 |
| 6 | 122.53 | *Apobec1* | *Ldlr−/−* | Increase | Increase | 118 |
| 6 | 129.44 | *Olr1* | *Ldlr−/−* | Decrease | Increase | 119 |

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| | | | | Effect in the dKO on: | | |
|---|---|---|---|---|---|---|
| Chr | Mb | Candidate Gene [2] | Background | Atherosclerotic | Plasma Cholesterol [3] | Ref |
| 8 | 40.69 | *Msr1* | *Apoe−/−* | Decrease | Increase | 120 |
| 8 | 108.46 | *Lcat* | *Apoe−/− and Ldlr−/−* | Decrease | Decrease | 121 |
| 9 | 46.04 | *Apoa1* | *Ldlr−/−* | Decrease [6] | Decrease | 122 |
| 9 | 68.50 | *Rora* | Paigen diet | Increase | Decrease | 123 |
| 9 | 70.64 | *Lipc* | *Apoe−/−* | Decrease | Increase | 124 |
| 10 | 19.31 | *Ifngr1* | *Apoe−/−* | Decrease | Increase | 125 |
| 10 | 88.92 | *Nr1h4* | *Apoe−/−* | Increase | Increase | 126 |
| 15 | 101.98 | *Soat2* | *Apoe−/−* | Decrease | Increase | 127 |
| 17 | 33.91 | *Angptl4* | *Apoe−/−* | Decrease | Decrease | 128 |
| 18 | 75.10 | *Lipg* | *Apoe−/−* | Decrease | Increase | 129 |
| 19 | 34.37 | *Fas* | *Apoe−/−* | Increase | Decrease | 130 |

[1] Only studies with a significant difference in atherosclerosis with a minimum significant level of $p<0.01$ are given when compared to controls. A number of gene names and symbols have changed several time and we have attempted to use the most up to date gene symbol according to the Mouse Genome Database (MGD) (http://www.informatics.jax.org).

[2] Full gene names can be obtained from the MGD. Multiple genes have been tested in both *Apoe*$^{-/-}$ and *Ldlr*$^{-/-}$, we report the earliest study to show significance and in several of these studies both backgrounds were examined. Genes were identified by interrogating the MGD and NCBI.

[3] The threshold for a significant difference in plasma cholesterol was set to $p<0.05$.

[4] No changes in whole dKO mice, only in bone macrophage derived transplant experiments from the dKO mice.

[5] Large significant decrease in VLDL-TG.

[6] Female specific effect. Chr, chromosome, Mb, millions of bases from the acromere.

**Table 2**

Genes affecting atherosclerosis in mice without affecting plasma cholesterol levels

| Chr | Mb | Candidate Gene[1] | Background | Atherosclerosis in the dKO | Ref |
|---|---|---|---|---|---|
| 1 | 40.28 | *Il1r1* | *Apoe*−/− with Paigen diet | Decrease [2] | 131 |
| 1 | 132.92 | *Il10* | *Ldlr*−/− | Increase | 132 |
| 1 | 166.04 | *Selp* | *Apoe*−/− | Decrease | 133 |
| 2 | 25.28 | *Fut7* | *Apoe*−/− | Decrease | 134 |
| 2 | 75.51 | *Nfe2l2* | *Apoe*−/− | Decrease | 135 |
| 2 | 164.77 | *Mmp9* | *Apoe*−/− | Increase | 136 |
| 3 | 27.08 | *Nceh1* | *Apoe*−/− | Increase | 137 |
| 3 | 86.80 | *Cd1d1* | *Apoe*−/− | Decrease [2] | 138 |
| 3 | 87.16 | *Cd5l* | *Ldlr*−/− | Decrease | 139 |
| 3 | 95.30 | *Ctss* | *Ldlr*−/− | Decrease | 140 |
| 3 | 96.84 | *Gja5* | *Apoe*−/− | Increase [2] | 141 |
| 3 | 115.81 | *Vcam1* | *Ldlr*−/− | Decrease | 14 |
| 3 | 151.46 | *Ptgfr* | *Ldlr*−/− | Decrease | 142 |
| 4 | 19.94 | *Ttpa* | *Apoe*−/− | Increase | 143 |
| 4 | 66.49 | *Tlr4* | *Apoe*−/− | Decrease | 144 |
| 5 | 23.87 | *Nos3* | *Apoe*−/− | Increase | 145 |
| 5 | 91.32 | *Cxcl1* | *Ldlr*−/− | Decrease | 146 |
| 5 | 92.78 | *Cxcl10* | *Apoe*−/− | Decrease | 147 |
| 5 | 104.86 | *Spp1* | *Apoe*−/− | Decrease | 148 |
| 5 | 112.77 | *Hps4* | Paigen diet | Decrease [2] | 149 |
| 5 | 134.70 | *Ncf1* | *Apoe*−/− | Decrease | 150 |
| 6 | 5.12 | *Pon1* | Paigen diet | Increase | 151 |
| 6 | 116.36 | *Alox5* | *Ldlr*−/− and Paigen diet | Decrease | 26 |
| 6 | 125.50 | *Vwf* | *Ldlr*−/− | Decrease | 152 |

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| Chr | Mb | Candidate Gene[1] | Background | Atherosclerosis in the dKO | Ref |
|---|---|---|---|---|---|
| 7 | 54.02 | *Hps5* | Paigen diet | Decrease [2] | 149 |
| 8 | 23.76 | *Ikbkb* | *Ldlr−/−* | Increase | 153 |
| 8 | 46.48 | *Tlr3* | *Apoe−/−* | Increase [2] | 154 |
| 8 | 97.30 | *Cx3cl1* | *Apoe−/−* | Decrease | 155 |
| 8 | 108.04 | *Hsd11b2* | *Apoe−/−* | Increase | 156 |
| 8 | 108.67 | *Pla2g15* | *Apoe−/−* | Increase | 157 |
| 9 | 7.34 | *Mmp12* | *Apoe−/−* | Decrease | 136 |
| 9 | 7.45 | *Mmp3* | *Apoe−/−* | Increase | 136 |
| 9 | 14.55 | *Fut4* | *Apoe−/−* | Decrease | 134 |
| 9 | 20.82 | *Icam1* | *Apoe−/−* | Decrease | 13 |
| 9 | 108.24 | *Gpx1* | *Apoe−/−* | Increase | 158 |
| 9 | 119.96 | *Cx3cr1* | *Apoe−/−* | Decrease | 159 |
| 9 | 124.02 | *Ccr2* | *Apoe−/−* | Decrease | 160 |
| 10 | 19.65 | *Bax* | *Apoe−/−* with Paigen diet | Increase | 161 |
| 10 | 117.88 | *Ifng* | *Ldlr−/−* | Decrease | 162 |
| 10 | 126.97 | *Lrp1* | *Ldlr−/−* | Increase [3] | 163 |
| 11 | 49.66 | *Mapk9* | *Apoe−/−* | Decrease | 164 |
| 11 | 70.16 | *Alox15* | *Apoe−/−* | Decrease | 165 |
| 11 | 70.27 | *Cxcl16* | *Ldlr−/−* | Increase | 166 |
| 11 | 70.47 | *Pfn1 (+/−)* | *Ldlr−/−* | Decrease | 167 |
| 11 | 78.73 | *Nos2* | *Apoe−/−* | Decrease | 168 |
| 11 | 81.85 | *Ccl2* | *Ldlr−/−* | Decrease | 169 |
| 11 | 87.61 | *Mpo* | *Ldlr−/−* | Increase | 170 |
| 11 | 96.96 | *Tbx21* | *Ldlr−/−* | Decrease | 171 |
| 11 | 104.47 | *Itgb3* | *Apoe−/− and Ldlr−/−* | Decrease | 172 |
| 11 | 105.82 | *Ace (+/−)* | *Apoe−/−* | Decrease | 173 |

| Chr | Mb | Candidate Gene[1] | Background | Atherosclerosis in the dKO | Ref |
|---|---|---|---|---|---|
| 11 | 106.52 | *Pecam1* | *Ldlr−/−* | Increase | 174 |
| 12 | 16.54 | *Lipin1* | Paigen diet | Increase | 175 |
| 12 | 32.86 | *Pik3cg* | *Apoe−/−* | Decrease | 176 |
| 12 | 114.09 | *Gpr132* | *Ldlr−/−* | Decrease | 177 |
| 14 | 47.99 | *Lgals3* | *Apoe−/−* | Decrease | 178 |
| 14 | 56.38 | *Ltb4r1* | *Apoe−/−* | Decrease | 179 |
| 14 | 66.59 | *Clu* | *Apoe−/−* | Decrease | 180 |
| 15 | 4.68 | *C6* | *Apoe−/−* | Decrease [2] | 34 |
| 15 | 54.08 | *Tnfrsf11b* | *Apoe−/−* | Increase | 181 |
| 16 | 17.33 | *Serpind1* | *Apoe−/−* | Increase | 182 |
| 17 | 12.57 | *Plg* | *Apoe−/−* | Increase | 183 |
| 17 | 29.23 | *Cdkn1a* | *Apoe−/−* | Decrease | 184 |
| 17 | 35.82 | *Ddr1* | *Ldlr−/−* | Decrease | 185 |
| 18 | 35.02 | *Egr1* | *Apoe−/−* | Decrease | 186 |
| 19 | 42.83 | *Hps1* | Paigen diet | Increase [2] | 149 |
| 19 | 46.08 | *Hps6* | Paigen diet | Decrease [2] | 149 |
| X | 160.58 | *Ace2* | *Apoe−/−* | Increase | 187 |

See Table 1 for extended legend.

[1] Candidate genes are homozygous KO unless otherwise indicates by as heterozygous by '(+/−)'.

[2] Lipid data not reported.

[3] Conditional KO.

**Table 3**

Mouse atherosclerosis quantitative trait loci (QTL) [1]

| Chr | Peak location or interval Chr (Mb)[2] | Model[3] | QTL name [4] | Ref | Proven Gene | Ref |
|---|---|---|---|---|---|---|
| 1 | | Paigen diet | *Ath1* | 188 | *Tnfsf4* | 31 |
| 1 | | *Apoe−/−* | *Ath30* | 189 | | |
| 1 | 105.4 | *Apoe−/−* | *QTL-#* | 190 | | |
| 1 | 166.3 | *Apoe−/−* | *QTL-#* | 190 | | |
| 1 | 176.6 | *Apoe−/−* | *Ath9* | 191 | | |
| 2 | | Paigen diet | *Ath2* | 192 | | |
| 2 | | *Apoe−/−* | *Ath28* | 193 | | |
| 2 | 148.5 | *Ldlr−/−* | *Athla1* | 194 | | |
| 3 | | *Apoe−/−* | *Ath23* | 193 | | |
| 3 | 115.5 | *Ldlr−/−* | *Ascla4* | 34 | | |
| 3 | 147.8 | *Ldlr−/−* | *Ascla3* | 34 | | |
| 4 | 137.4 – 150.9 | *Ldlr−/−* | *Athsq1* | 195 | | |
| 4 | 45.7 – 105.0 | Paigen diet, *Apoe−/−* | *Ath8* | 196,197 | | |
| 5 | | *Apoe−/−* | *Ath24* | 193 | | |
| 6 | | *Ldlr−/−* | *Artles* | 25,26 | *Alox5* | 29 |
| 6 | | *Ldlr−/−* | *Ath38* | 25 | | |
| 6 | | *Ldlr−/−* | *Athsq2* | 195 | | |
| 6 | 116.6 – 128.5 | *Ldlr−/−* | *Ath37* | 29 | | |
| 7 | 57.0 | Paigen diet | *Aorls2* | 198 | | |
| 7 | | Paigen diet | *Ath3* | 199 | | |
| 7 | | *Apoe−/−* | *Ath31* | 189 | | |
| 9 | 65.3 | *Apoe−/−* | *Ath29* | 189,197,200 | | |

| Chr | Peak location or interval Chr (Mb)[2] | Model[3] | QTL name [4] | Ref | Proven Gene | Ref |
|---|---|---|---|---|---|---|
| 10 | 82.1 | Paigen diet | *Aorls1* | 198,201 | | |
| 10 | | *Apoe−/−* | *Ath11* | 191 | | |
| 10 | 20.1 | Paigen diet | *Ath20* | 201 | | |
| 10 | 67.7 | Paigen diet | *Ath17* | 201 | | |
| 10 | 18.5 | *Ldlr−/−* | *Ascla2* | 34 | | |
| 10 | 21.4 | *Ldlr−/−* | *Ascla1* | 34 | | |
| 11 | 108.6 | Paigen diet | *Ath19* | 201 | | |
| 12 | | Paigen diet | *Ath21* | 201 | | |
| 12 | | Paigen diet | *Ath6* | 202–204 | | |
| 12 | 35.9 | Paigen diet | *Ath18* | 201 | | |
| 12 | 14.3 | *Ldlr−/−* | *Ascla5* | 34 | *Adam17* | 33 |
| 12 | 55.1 | *Ldlr−/−* | *Ascla6* | 34 | | |
| 12 | | *Apoe−/−* | *Cath1* | 205 | | |
| 13 | | *Apoe−/−* | *Ath25* | 193 | | |
| 13 | | *Apoe−/−* | *Ath32* | 189 | | |
| 14 | 51.9 – 165.9 | *Apoe−/−* | *Ath13* | 191 | | |
| 15 | | *Apoe−/−* | *Ath22* | 193 | | |
| 15 | | *Apoe−/−* | *Ath33* | 189 | | |
| 17 | | *Apoe−/−* | *Ath26* | 193, 189 | | |
| 18 | | *Apoe−/−* | *Ath27* | 193 | | |
| 19 | 38.5 | *Apoe−/−* | *Ath16* | 191 | | |

[1] Data sourced from the Mouse Genome Database (MGD) (http://www.informatics.jax.org).

[2] If positions are not listed this indicates they were not reported in the publication.

[3] QTL crosses performed with different progenitor inbred strains which may have had Ldlr−/− or Apoe−/− introduced into the backgrounds of the strains.

[4]QTL-# indicates that no QTL name has yet been assigned. Chr Chromosome, Mb millions of base pairs from acromere.

**Table 4**

Genome wide significantly associated CAD loci in humans ($p<5\times10^{-8}$)

| # | SNP | Band | Mb | Genetic elements in region (+/− 50,000 from reported SNP) | Most likely Causal gene | Related Associations |
|---|---|---|---|---|---|---|
| 1 | rs11206510 | 1p32.3 | 55.50 | *TMEM61, RP11-12C17.2, BSND, PCSK9, USP24* | ***PCSK9*** | Lipids |
| 2 | rs17114036 | 1p32.2 | 56.96 | *PPAP2B, RP11-213P13.1* | ***PPAP2B*** | |
| 3 | rs599839 | 1p13.3 | 109.82 | *SARS, CELSR2, PSRC1, MYBPHL, SORT1* | ***SORT1*** | Lipids |
| 4 | rs17465637 | 1q41 | 222.82 | *MIA3, RP11-378J18.6, RP11-378J18.5, AIDA* | | |
| 5 | rs4299376* | 2p21 | 44.07 | *DYNC2LI1, ABCG5, ABCG8, LRPPRC* | ***ABCG5/8*** | Lipids |
| 6 | rs6725887 | 2q33.1 | 203.75 | *ICA1L, AC010900.1, WDR12, ALS2CR8, AC010900.2* | | |
| 7 | rs2306374 | 3q22.3 | 138.12 | *MRAS, ESYT3* | | |
| 8 | rs2706399* | 5q31.1 | 31.87 | *IRF1, IL5, RAD50* | ***IL5*** | |
| 9 | rs12526453 | 6p24.1 | 12.93 | *PHACTR1* | ***PHACTR1*** | |
| 10 | rs6903956 | 6p24.1 | 11.77 | *C6orf105* | ***C6orf105*** | |
| 11 | rs17609940 | 6p21.31 | 35.03 | *ANKS1A, RP11-527B17.2* | ***ANKS1A*** | |
| 12 | rs12190287 | 6q23.2 | 134.21 | *RP3-323P13.2, RP4-662A9.2, TCF21* | ***TCF21*** | |
| 13 | rs3798220 | 6q25.3 | 160.96 | *LPAL2,AL591069.1, LPA* | ***LPA*** | Lipids |
| 14 | rs10953541 | 7q22.3 | 107.24 | *DUS4L, BCAP29* | | |
| 15 | rs11556924 | 7q32.2 | 129.66 | *RP11-306G20.1, ZC3HC1, 5S_rRNA.114, KLHDC10* | | |
| 16 | rs17321515* | 8q24.13 | 126.49 | *TRIB1, RP11-136O12.2* | ***TRIB1*** | Lipids |
| 17 | rs4977574 | 9p21.3 | 22.10 | *CDKN2A,CDKN2B* | ***CDKN2A,CDKN2B*** | Glaucoma, Diabetes |
| 18 | rs7025486 | 9q33 | 124.42 | *DAB2IP* | ***DAB2IP*** | |
| 19 | rs579459 | 9q34.2 | 136.15 | *ABO, Y_RNA.342, LCN1P2, SURF6* | ***ABO*** | Lipids |
| 20 | rs2505083 | 10p11.23 | 30.34 | *KIAA1462* | ***KIAA1462*** | |
| 21 | rs1746048 | 10q11.21 | 44.78 | *RP11-20J15.2, RP11-20J15.3* | ***CXCL12*** | Inflammatory diseases |
| 22 | rs1412444 | 10q23.31 | 91.00 | *CH25H, LIPA* | ***LIPA*** | |
| 23 | rs12413409 | 10q24.32 | 104.72 | *CNNM2, AL356608.1* | | BP |
| 24 | rs974819 | 11q22.3 | 103.66 | *RP11-563P16.1, PDGFD* | ***PDGFD*** | |
| 25 | rs964184 | 11q23.3 | 116.65 | *BUD13, AP006216.10, AP006216.11, ZNF259, APOA5, AP006216.5, APOA4, APOA1* | ***APOA5-A4-C3-A1*** | Lipids |
| 26 | rs3184504 | 12q24.12 | 111.88 | *SH2B3, ATXN2* | | CKD, BP, Diabetes |
| 27 | rs4773144 | 13q34 | 110.96 | *COL4A1, AL161773.1, COL4A2* | | |

| # | SNP | Band | Mb | Genetic elements in region (+/− 50,000 from reported SNP) | Most likely Causal gene | Related Associations |
|---|---|---|---|---|---|---|
| 28 | rs2895811 | 14q32.2 | 100.13 | *AL160313.1, HHIPL1, CYP46A1* | | |
| 29 | rs3825807 | 15q25.1 | 79.09 | *AC022748.1, ADAMTS7, MORF4L1* | ***ADAMTS7*** | |
| 30 | rs216172 | 17p13.3 | 2.13 | *SMG6, AC090617.1, AC130689.5, AL450226.2* | | |
| 31 | rs12936587 | 17p11.2 | 17.54 | *PEMT, SMCR2, RAI1* | ***PEMT*** | |
| 32 | rs46522 | 17q21.32 | 46.99 | *CALCOCO2, RP11-463M16.4, SNORA68.3, RP11-463M16.5, ATP5G1, UBE2Z* | | |
| 33 | rs1122608 | 19p13.2 | 11.16 | *SMARCA4, AC011442.1, LDLR* | ***LDLR*** | Lipids |
| 34 | rs9982601 | 21q22.11 | 35.60 | *AP000318.2, C21orf82* | | |

SNP: this indicates the most commonly reported SNP for the locus, however there may be multiple genome-wide significant SNPs in the locus in independent linkage disequilibrium spanning thousands of bases. Band: Chromosome, arm and chromatin band of the locus.

*SNP associations made in the IBC 50K SNP array where a lower threshold is required for genome-wide significance due to fewer tests being performed ($p<1\times10^{-6}$). Mb: indicates the location of the reported SNP in millions of bases from the proximal end of the chromosome, assembly: NCBIM37 2011. “Related Associations” indicates that the locus, typical the same SNP listed above, has been reported as genome-wide significant for a phenotype known to affect CAD. BP indicates blood pressure, CKD indicates chronic kidney disease.

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